Clinical trial results:
A randomized, double-blind, placebo-controlled, cross-over trial in healthy subjects to investigate the effects of lacosamide, pregabalin and tapentadol on biomarkers of pain processing observed by functional magnetic resonance imaging (FMRI) of the brain

Summary

EudraCT number	2019-000908-15
Trial protocol	DK FR
Global end of trial date	27 June 2022

Results information

Result version number	v1 (current)
This version publication date	07 December 2024
First version publication date	07 December 2024

Trial information

Trial identification

Sponsor protocol code	IMI2-PainCare-BioPain-RCT4

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University
Sponsor organisation address	Aarhus University, Aarhus, Denmark,
Public contact	Danish Pain Research Center, Aarhus University, +45 93508575, dprc@clin.au.dk
Scientific contact	Danish Pain Research Center, Aarhus University, +45 93508575, dprc@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	26 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2022
Global end of trial reached?	Yes
Global end of trial date	27 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To test if the punctate evoked BOLD response in the posterior insula at 3 hours post-drug administration differs in pregabalin period as compared to the placebo period, at the sensitized leg.
2. To test if the resting state connectivity between SII and thalamus at 3 hours post-drug administration in the presence of sensitization differs in the pregabalin period as compared to the placebo period.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the ICH Good Clinical Practice (GCP) guidelines. Local regulatory requirements were followed. Written informed consent was obtained from all subjects. The information interview was conducted in an office without disturbances and interruptions, and there was enough time to give information and discuss possible questions. The subjects 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	08 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 6
Worldwide total number of subjects	31
EEA total number of subjects	15

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)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed from February 8, 2021 to June 27, 2022 at 3 centers in Denmark, France and the United Kingdom.

Pre-assignment

Screening details:

We screened 39 subjects, of which 20 were screened in the UK, 10 in Denmark, and 9 in France. In total, 31 subjects were enrolled/randomized and 29 completed the study.

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, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Pregabalin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	N03AX16
Other name	Lyrica
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 x 75mg pregabalin capsules, single dose

Arm title	Lacosamide

Arm description: -

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

Dosage and administration details:

2 x 100mg lacosamide capsules, single dose

Arm title	Tapentadol

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tapentadol
Investigational medicinal product code	N02AX06
Other name	Alexia
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 x 50mg tapentadol capsules, single dose

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 x hard gelatine capsules filled with mannitol and colloidal silicon dioxide (DAC - deutchser arzneimittel codex), single dose

Number of subjects in period 1	Pregabalin	Lacosamide	Tapentadol
Started	29	29	29
Completed	29	29	28
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	Placebo
Started	29
Completed	29
Not completed	0
Adverse event, non-fatal	-

Baseline characteristics

Reporting groups

Reporting group title	Overall study (overall period)

Reporting group description: -

Reporting group values	Overall study (overall period)	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	25.6		
standard deviation	± 4.03	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	22	22	

End points

End points reporting groups

Reporting group title	Pregabalin
Reporting group description: -	
Reporting group title	Lacosamide
Reporting group description: -	
Reporting group title	Tapentadol
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Primary endpoint 1: To test if the punctate evoked BOLD response in the posterior insula at 3 hours post-drug administration differs in pregabalin period as compared to the placebo period, at the sensitized leg.

End point title	Primary endpoint 1: To test if the punctate evoked BOLD response in the posterior insula at 3 hours post-drug administration differs in pregabalin period as compared to the placebo period, at the sensitized leg.

End point description:

End point type	Primary

End point timeframe:

The second measurement post dosing (i.e. around 3 hours after drug administration).

End point values	Pregabalin	Lacosamide	Tapentadol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	29	28	29
Units: BOLD response				
arithmetic mean (standard deviation)	0.251 (± 0.1353)	0.293 (± 0.1313)	0.268 (± 0.1436)	0.313 (± 0.1308)

Statistical analyses

Statistical analysis title	Primary endpoint 1: Pregabalin vs. placebo

Statistical analysis description:

To test if the punctate evoked BOLD response in the posterior insula at 3 hours post-drug administration differs in pregabalin period as compared to the placebo period, at the sensitized leg.

Comparison groups	Placebo v Pregabalin

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.134
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	0.016

Notes:

[1] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Additional endpoint: Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.566
Method	Mixed models for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.089
upper limit	0.049

Notes:

[2] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Additional endpoint: Tapentadol vs placebo
Comparison groups	Tapentadol v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.05
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.138
upper limit	0

Notes:

[3] - Note: This is a crossover study so the number of subjects included is 29.

Primary: Primary endpoint 2: To test if the resting state connectivity between SII

and thalamus at 3 hours post-drug administration in the presence of sensitization differs in the pregabalin period as compared to the placebo period.

End point title	Primary endpoint 2: To test if the resting state connectivity between SII and thalamus at 3 hours post-drug administration in the presence of sensitization differs in the pregabalin period as compared to the placebo period.

End point description:

End point type	Primary

End point timeframe:

The second measurement post dosing (i.e. around 3 hours after drug administration).

End point values	Pregabalin	Lacosamide	Tapentadol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	29	28	29
Units: Functional connectivity				
arithmetic mean (standard deviation)	-0.6 (± 0.82)	-0.8 (± 0.72)	-0.7 (± 0.65)	-0.5 (± 0.55)

Statistical analyses

Statistical analysis title	Primary endpoint 2: Pregabalin vs placebo
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.458
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.2

Notes:

[4] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Additional endpoint: Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.047
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0

Notes:

[5] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Additional endpoint: Tapentadol vs placebo
Comparison groups	Tapentadol v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.236
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.1

Notes:

[6] - Note: This is a crossover study so the number of subjects included is 29.

Secondary: Secondary endpoint 1: To test if the punctate evoked BOLD response in the posterior insula at 1 hour post-drug administration differs in at least one analgesic treatment period as compared to the placebo period, at the sensitized leg.

End point title	Secondary endpoint 1: To test if the punctate evoked BOLD response in the posterior insula at 1 hour post-drug administration differs in at least one analgesic treatment period as compared to the placebo period, at the sensitized leg.

End point description:

End point type	Secondary

End point timeframe:

The first measurement post dosing (i.e. around 1 hour after drug administration).

End point values	Pregabalin	Lacosamide	Tapentadol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	28	29
Units: BOLD response				
arithmetic mean (standard deviation)	0.289 (± 0.2046)	0.321 (± 0.1928)	0.289 (± 0.1300)	0.364 (± 0.1519)

Statistical analyses

Statistical analysis title	Secondary endpoint: Pregabalin vs placebo

Statistical analysis description:

To test if the punctate evoked BOLD response in the posterior insula at 1 hour post-drug administration differs in at least one analgesic treatment period as compared to the placebo period, at the sensitized leg.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.033
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.143
upper limit	-0.006

Notes:

[7] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Secondary endpoint: Lacosamide vs placebo

Statistical analysis description:

To test if the punctate evoked BOLD response in the posterior insula at 1 hour post-drug administration differs in at least one analgesic treatment period as compared to the placebo period, at the sensitized leg.

Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.295
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.032

Notes:

[8] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Secondary endpoint: Tapentadol vs placebo
Comparison groups	Tapentadol v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.01
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.092

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.161
upper limit	-0.023

Notes:

[9] - Note: This is a crossover study so the number of subjects included is 29.

Secondary: Secondary endpoint 2: To test if the resting state connectivity between SII and thalamus at 1 hour post-drug administration in the presence of sensitization differs in at least one analgesic treatment session as compared to the placebo session.

End point title	Secondary endpoint 2: To test if the resting state connectivity between SII and thalamus at 1 hour post-drug administration in the presence of sensitization differs in at least one analgesic treatment session as compared to the placebo session.

End point description:

End point type	Secondary

End point timeframe:

The first measurement post dosing (i.e. around 1 hour after drug administration).

End point values	Pregabalin	Lacosamide	Tapentadol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	28	29
Units: Functional connectivity				
arithmetic mean (standard deviation)	-0.5 (± 0.78)	-0.7 (± 0.81)	-0.6 (± 0.59)	-0.3 (± 0.74)

Statistical analyses

Statistical analysis title	Secondary endpoint: Pregabalin vs placebo
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.402
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.2

Notes:

[10] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Secondary endpoint: Lacosamide vs placebo
Comparison groups	Lacosamide v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.045
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0

Notes:

[11] - Note: This is a crossover study so the number of subjects included is 29.

Statistical analysis title	Secondary endpoint: Tapentadol vs placebo
Comparison groups	Tapentadol v Placebo
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.058
Method	Mixed models with repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0

Notes:

[12] - Note: This is a crossover study so the number of subjects included is 29.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study period 1 to 7-14 days after the last study period.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	Lacosamide
Reporting group description: -	
Reporting group title	Pregabalin
Reporting group description: -	
Reporting group title	Tapentadol
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Lacosamide	Pregabalin	Tapentadol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Lacosamide	Pregabalin	Tapentadol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	5 / 29 (17.24%)	11 / 29 (37.93%)
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	4 / 29 (13.79%)	6 / 29 (20.69%)
occurrences (all)	2	4	6
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)	2 / 29 (6.90%)	3 / 29 (10.34%)
occurrences (all)	1	2	3
Headache			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Presyncope	Additional description: light headedness		
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	3 / 29 (10.34%)
occurrences (all)	1	1	3
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Paracusis	Additional description: Auditory hallucination		
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Tinnitus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Diplopia	Additional description: Double vision		
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Nystagmus	Additional description: Horizontal nystagmus		
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 29 (13.79%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Presyncope	Additional description: light headedness		
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
General disorders and administration site conditions			

Nausea			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Paracusis	Additional description: Auditory hallucination		
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Eye disorders			
Diplopia	Additional description: Double vision		
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Nystagmus	Additional description: Horizontal nystagmus		
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 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.

There were intermittent interruptions to data collection due to the COVID-19 pandemic, but these delays did not affect the overall study results or data analysis.

Notes: