Clinical trial results:
A randomized, double-blind, placebo-controlled, cross-over, multi-center trial in healthy subjects to investigate the effects of lacosamide, pregabalin and tapentadol on biomarkers of pain processing observed by electro-encephalography (EEG)

Summary

EudraCT number	2019-001204-37
Trial protocol	BE IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	IMI2-PainCare-BioPain-RCT3

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UCLouvain
Sponsor organisation address	Place de l'Université 1, Louvain-la-Neuve, Belgium, 1348
Public contact	Clinical Trials Information, Institute of Neuroscience (IoNS), Université catholique de Louvain, 0032 027645447, andre.mouraux@uclouvain.be
Scientific contact	Clinical Trials Information, Institute of Neuroscience (IoNS), Université catholique de Louvain, 0032 027645447, andre.mouraux@uclouvain.be

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	30 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2022
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To test if the percentage reduction of LEP amplitude 60 minutes post-drug administration differs in the tapentadol period as compared to the placebo period, at the non-sensitized forearm.
2. To test if the percentage reduction of PEP amplitude 60 minutes post-drug administration differs in the tapentadol period as compared to the placebo period, at the sensitized forearm.

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	07 September 2020
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	Belgium: 16
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed from 07.09.2020 to 01.04.2022 at 4 centers in Belgium, Germany, Italy and the UK. No subjects were recruited in the UK and Germany, and the trial had to be terminated early due operational impact of the Covid-19 pandemic during the past 2 years and as the overall timelines of the project did not allow any further extension o

Pre-assignment

Screening details:

We screened 23 subjects, of which 18 were screened in Belgium, 1 in Germany and 4 in Italy. In total, 20 subjects were enrolled/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	Investigator, Subject, Monitor, Data analyst, Assessor

Blinding implementation details:

Lacosamide, pregabalin, tapentadol or placebo were assigned to each subject by a double-blind randomization schedule. The investigator/trial personnel and subjects were blinded to the assignment of pregabalin, tapentadol, lacosamide and placebo (double-blind procedure).

Arms

Are arms mutually exclusive?	No
Arm title	Lacosamide

Arm description:

Lacosamide 200 mg

Arm type	Experimental
Investigational medicinal product name	Lacosamide
Investigational medicinal product code	
Other name	N03AX18, vimpat
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2x 100 mg lacosamide tablets, single dose

Arm title	Pregabalin

Arm description:

Pregabalin 150 mg

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

Dosage and administration details:

2x 75 mg pregabalin capsule , single dose

Arm title	Tapentadol

Arm description:

Tapentadol 100 mg

Arm type	Experimental

Investigational medicinal product name	oTapentadol
Investigational medicinal product code	
Other name	N02AX06
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2x 50 mg tapentadol immediate release tablet, 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 - Deutscher Arzneimittel Codex). Single dose

Number of subjects in period 1	Lacosamide	Pregabalin	Tapentadol
Started	20	20	20
Completed	20	20	20

Number of subjects in period 1	Placebo
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	overall study

Reporting group description: -

Reporting group values	overall study	Total	
Number of subjects	20	20	
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)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	25.7		
standard deviation	± 4.43	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	9	9	

Subject analysis sets

Subject analysis set title	Full analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:
subjects in the ‘all enrolled set’ that have been randomized

Reporting group values	Full analysis Set		
Number of subjects	20		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	20		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	25.7		
standard deviation	± 4.43		
Gender categorical Units: Subjects			
Female	11		
Male	9		

End points

End points reporting groups

Reporting group title	Lacosamide
Reporting group description: Lacosamide 200 mg	
Reporting group title	Pregabalin
Reporting group description: Pregabalin 150 mg	
Reporting group title	Tapentadol
Reporting group description: Tapentadol 100 mg	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: subjects in the 'all enrolled set' that have been randomized	

Primary: First co-primary endpoint (LEP Tapentadol vs Placebo)

End point title	First co-primary endpoint (LEP Tapentadol vs Placebo)[1]
End point description: Comparison of the tapentadol vs placebo effects on the percentage of change in amplitude of the N2-P2 complex of laser-evoked potentials (LEPs), at the non-sensitized forearm.	
End point type	Primary
End point timeframe: The first measurement post dosing (around 1 hour after drug administration) relative to the pre-dose measurement (i.e. change relative to period-specific baseline).	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Different arms are present in order to validate different endpoints. So, all endpoints are not concerning all arms.

End point values	Tapentadol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: %				
arithmetic mean (standard deviation)	-11.18 (± 29.94)	1.83 (± 31.81)		

Statistical analyses

Statistical analysis title	First co-primary outcome
Statistical analysis description: percentage of change in amplitude of the N2-P2 complex of laser-evoked potentials (LEPs) in tapentadol treatment arm vs the placebo treatment arm, at the non-sensitized forearm.	
Comparison groups	Tapentadol v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.025 [2]
Method	Mixed Models for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-19.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.59
upper limit	-3.48
Variability estimate	Standard error of the mean
Dispersion value	8.1

Notes:

[2] - The two co-primary endpoints are tested for their differences between the arms Tapentadol versus Placebo. This is conducted in parallel, splitting the overall α equally between the endpoint tests: each test has a Type I error of α/2 (0.05/2=0.025)

Primary: Second co-primary endpoint (PEP Tapentadol vs Placebo)

End point title	Second co-primary endpoint (PEP Tapentadol vs Placebo)[3]

End point description:

Comparison of the tapentadol vs placebo effects on the percentage of change in amplitude of the N2-P2 complex of pinprick-evoked potentials (PEPs), at the sensitized forearm.

End point type	Primary

End point timeframe:

The first measurement post dosing (around 1 hour after drug administration) relative to the pre-dose measurement (i.e. change relative to period-specific baseline).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Different arms are present in order to validate different endpoints. So, all endpoints are not concerning all arms.

End point values	Tapentadol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: %				
arithmetic mean (standard deviation)	-5.83 (± 24.15)	0.04 (± 45.32)		

Statistical analyses

Statistical analysis title	Second co-primary outcome

Statistical analysis description:

percentage of change in amplitude of the N2-P2 complex of pinprick-evoked potentials (PEPs) in the tapentadol treatment arm vs the placebo treatment arm, at the sensitized forearm.

Comparison groups	Tapentadol v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.025 [4]
Method	Mixed Models for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-5.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.41
upper limit	10.45
Variability estimate	Standard error of the mean
Dispersion value	8.04

Notes:

[4] - The two co-primary endpoints are tested for their differences between the arms Tapentadol versus Placebo. This is conducted in parallel, splitting the overall α equally between the endpoint tests: each test has a Type I error of α/2 (0.05/2=0.025)

Secondary: First key secondary analysis of primary endpoints (LEP)

End point title	First key secondary analysis of primary endpoints (LEP)[5]

End point description:

Comparison of the mean effects of lacosamide & pregabalin vs placebo on the percentage of change in amplitude of the N2-P2 complex of laser-evoked potentials (LEPs), at the non-sensitized forearm.

End point type	Secondary

End point timeframe:

The first measurement post dosing (around 1 hour after drug administration) relative to the pre-dose measurement (i.e. change relative to period-specific baseline).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Different arms are present in order to validate different endpoints. So, all endpoints are not concerning all arms.

End point values	Lacosamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: %				
arithmetic mean (standard deviation)	-15.53 (± 17.02)	1.83 (± 31.81)		

Statistical analyses

Statistical analysis title	First key secondary analysis of primary endpoints

Statistical analysis description:

Mean percentage of change in amplitude of the N2-P2 complex of laser-evoked potentials (LEPs) in the lacosamide & pregabalin treatment arms vs the placebo treatment arm, at the non-sensitized forearm.

Comparison groups	Placebo v Lacosamide

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.02 [6]
Method	Mixed Models for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.7
upper limit	1.88
Variability estimate	Standard error of the mean
Dispersion value	6.96

Notes:

[6] - If any of these two co-primary endpoint tests showed significant differences, key secondary analyses were pre-specified using the α-levels as detailed in Mouraux et al (2021). Trials, 22(1), 404. https://doi.org/10.1186/s13063-021-05272-y

Secondary: Second key secondary analysis of primary endpoints (PEP)

End point title	Second key secondary analysis of primary endpoints (PEP)[7]

End point description:

Comparison of the mean effects of lacosamide & pregabalin vs placebo on the percentage of change in amplitude of the N2-P2 complex of pinprick-evoked potentials (PEPs), at the sensitized forearm.

End point type	Secondary

End point timeframe:

The first measurement post dosing (around 1 hour after drug administration) relative to the pre-dose measurement (i.e. change relative to period-specific baseline).

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Different arms are present in order to validate different endpoints. So, all endpoints are not concerning all arms.

End point values	Lacosamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: %				
arithmetic mean (standard deviation)	-5.20 (± 17.21)	0.04 (± 45.32)		

Statistical analyses

Statistical analysis title	Second key secondary analysis of primary endpoints

Statistical analysis description:

Mean percentage of change in amplitude of the N2-P2 complex of pinprick-evoked potentials (PEPs) in the lacosamide & pregabalin treatment arms vs the placebo treatment arm, at the sensitized forearm.

Comparison groups	Lacosamide v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.004 [8]
Method	Mixed Models for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.55
upper limit	12.19
Variability estimate	Standard error of the mean
Dispersion value	7

Notes:

[8] - If any of these two co-primary endpoint tests showed significant differences, key secondary analyses were pre-specified using the α-levels as detailed in Mouraux et al (2021). Trials, 22(1), 404. https://doi.org/10.1186/s13063-021-05272-y

Secondary: Secondary endpoint (EEG)

End point title	Secondary endpoint (EEG)

End point description:

Differences across all treatment arms (lacosamide, pregabalin, tapentadol and placebo) on the percentage of change in amplitude of theta band oscillations in the resting EEG (eyes open).

End point type	Secondary

End point timeframe:

The first measurement post dosing (around 1 hour after drug administration) relative to the pre-dose measurement (i.e. change relative to period-specific baseline).

End point values	Lacosamide	Pregabalin	Tapentadol	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	19	20	20
Units: %				
arithmetic mean (standard deviation)	21.69 (± 21.22)	6.73 (± 8.45)	2.55 (± 9.87)	6.45 (± 10.51)

Statistical analyses

Statistical analysis title	Key secondary endpoint analysis (theta)

Statistical analysis description:

Mean percentage of change in amplitude of theta oscillations (resting EEG eyes open) compared across all treatment arms (lacosamide, pregabalin, tapentadol and placebo).

Comparison groups	Lacosamide v Pregabalin v Tapentadol v Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0083 [9]
Method	Mixed models analysis

Notes:

[9] - If any of these two co-primary endpoint tests showed significant differences, key secondary analyses were pre-specified using the α-levels as detailed in Mouraux et al (2021). Trials, 22(1), 404. https://doi.org/10.1186/s13063-021-05272-y

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study period 1 to 7-14 days after 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	Pregabaline
Reporting group description: -	
Reporting group title	Tapentadol
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Lacosamide	Pregabaline	Tapentadol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Lacosamide	Pregabaline	Tapentadol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	3 / 20 (15.00%)	3 / 20 (15.00%)
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Eye disorders			

Diplopia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0 0 / 20 (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.

Intermittent interruptions due to COVID-19 lockdown and regulations

Notes: