



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 non-invasive neurophysiological measurements of human spinal cord and brainstem activity

Summary

EudraCT number	2019-000755-14
Trial protocol	BE IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	17 September 2023
First version publication date	17 September 2023

Trial information

Trial identification

Sponsor protocol code	IMI2-PainCare-BioPain-RCT2
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sapienza University of Rome
Sponsor organisation address	viale dell'università 30, Rome, Italy,
Public contact	Department of Human Neurosciences, Sapienza University of Rome, +39 0649914758, andrea.truini@uniroma1.it
Scientific contact	Department of Human Neurosciences, Sapienza University of Rome, +39 0649914758, andrea.truini@uniroma1.it

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	19 April 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 RIII flexion reflex area 60 minutes post-drug administration differs in the tapentadol period as compared to the placebo period, at the sensitized limb
2. To test if the percentage reduction of N13 amplitude 60 minutes post-drug administration differs in the tapentadol period as compared to the placebo period, at the sensitized limb

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	16 September 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	Belgium: 4
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed from September 16, 2019 to February 4, 2022 at 4 centers in Belgium, Germany, and Italy. The trial had to be terminated early due operational impact of the Covid19 pandemic during the past 2 years and as the overall timelines of the project did not allow any further extension of the trial

Pre-assignment

Screening details:

Screening details:

We screened 34 subjects, of which 16 were screened in Italy, 6 in Belgium, and 5 in Germany. In total, 24 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	Subject, Investigator, Monitor, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Lacosamide

Arm description: -

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

Dosage and administration details:

Dosage and administration details:

composition: 2x 100 mg lacosamide tablets. Single dose.

Arm title	Pregabalin
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Arm description: -

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:

Dosage and administration details:

2 x 75 mg pregabalin capsules, single dose.

Arm title	Tapentadol
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	Tapentadol
Investigational medicinal product code	
Other name	Palexia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosage and administration details:

2x 50 mg tapentadol immediate release tablet, single dose

Arm title	placebo
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Arm description: -

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

Dosage and administration details:

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	24	22	23
Completed	24	22	23

Number of subjects in period 1	placebo
Started	23
Completed	23

Baseline characteristics

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: -	

Reporting group values	Lacosamide	Pregabalin	Tapentadol
Number of subjects	24	22	23
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)	24	22	23
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	27.1	27.1	27.1
standard deviation	± 4.2	± 4.2	± 4.2
Gender categorical Units: Subjects			
Female	14	13	13
Male	10	9	10

Reporting group values	placebo	Total	
Number of subjects	23	24	
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)	23	24	
From 65-84 years	0	0	

85 years and over	0	0	
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Age continuous Units: years arithmetic mean standard deviation	27.1 ± 4.2	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	9	10	

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	24		
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)	24		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	27.1 ± 4.2		
Gender categorical Units: Subjects			
Female	14		
Male	10		

End points

End points 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: -	
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: co-primary: percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, at the sensitized lower limb.

End point title	co-primary: percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, at the sensitized lower limb.
End point description: To test if the percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, differs in the tapentadol period as compared to the placebo period, at the sensitized lower limb.	
End point type	Primary
End point timeframe: The first measurement post dosing (i.e. around 1 hour after drug administration) relative to the predose measurement (i.e. difference 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	24	22	23	23
Units: area under the curve				
arithmetic mean (standard deviation)	48.07 ($\pm$ 255.61)	-11.42 ($\pm$ 35.21)	-10.23 ($\pm$ 80.11)	58.22 ($\pm$ 290.74)

Statistical analyses

Statistical analysis title	co-primary outcome
Statistical analysis description: To test if the percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, differs in the tapentadol period as compared to the placebo period, at the sensitized lower limb.	
Comparison groups	Tapentadol v placebo

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.047
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	-79.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-157.93
upper limit	-1.16
Variability estimate	Standard error of the mean
Dispersion value	39.61

Notes:

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

Since it is a cross-over study, subjects in the analysis are 23 and not 46.

Statistical analysis title	co-primary outcome (secondary objective)
Statistical analysis description:	
To test if the percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, differs in the lacosamide period as compared to the placebo period, at the sensitized lower limb.	
Comparison groups	Lacosamide v placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.62
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	-19.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-96.98
upper limit	58.01
Variability estimate	Standard error of the mean
Dispersion value	39.16

Notes:

[2] - Since it is a cross-over study, subjects in the analysis are 23 and not 47

Statistical analysis title	co-primary outcome (secondary objective)
Statistical analysis description:	
To test if the percentage of change of the RIII area of the flexion reflex at the time point t60 post-drug administration vs the pre-drug time point, differs in the pregabalin period as compared to the placebo period, at the sensitized lower limb.	
Comparison groups	placebo v Pregabalin

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.072
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	-73.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-153.52
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	40.49

Notes:

[3] - Since it is a cross-over study, subjects in the analysis are 23 and not 45

Primary: co-primary: percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, at the sensitized upper arm.

End point title	co-primary: percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, at the sensitized upper arm.
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End point description:

To test if the percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, differs in the tapentadol period as compared to the placebo period, at the sensitized upper arm.

End point type	Primary
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End point timeframe:

The first measurement post dosing (i.e. around 1 hour after drug administration) relative to the predose measurement (i.e. difference 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	24	22	22 ^[4]	23
Units: amplitude microvolts				
arithmetic mean (standard deviation)	-12.38 (± 44.9)	-10.45 (± 33.26)	19.12 (± 69.37)	6.78 (± 62.15)

Notes:

[4] - Change values. PD values were only available for 22 at both baseline and first postdose PD

Statistical analyses

Statistical analysis title	co-primary outcome
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Statistical analysis description:

To test if the percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, differs in the tapentadol period as compared to the placebo period, at the sensitized upper arm.

Comparison groups	Tapentadol v placebo
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.92
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.21
upper limit	35.65
Variability estimate	Standard deviation
Dispersion value	17.15

Notes:

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

Since it is a cross-over study, subjects in the analysis are 23 and not 45.

Statistical analysis title	co-primary outcome (secondary objective)
Statistical analysis description:	
To test if the percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, differs in the lacosamide period as compared to the placebo period, at the sensitized upper arm.	
Comparison groups	placebo v Lacosamide
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.139
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	-25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.18
upper limit	8.19
Variability estimate	Standard deviation
Dispersion value	16.77

Notes:

[6] - Since it is a cross-over study, subjects in the analysis are 23 and not 47

Statistical analysis title	co-primary outcome (secondary objective)
Statistical analysis description:	
To test if the percentage of change of the N13-SEP amplitude at the time point t60 post-drug administration vs the pre-drug time point, differs in the pregabalin period as compared to the placebo period, at the sensitized upper arm.	
Comparison groups	placebo v Pregabalin

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.27
Method	MMRM model
Parameter estimate	Mean difference (final values)
Point estimate	-19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.92
upper limit	14.91
Variability estimate	Standard deviation
Dispersion value	17.14

Notes:

[7] - Since it is a cross-over study, subjects in the analysis are 23 and not 45.

Secondary: key secondary analysis:percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration

End point title	key secondary analysis:percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration
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End point description:

To test if the percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration vs the pre-drug administration differs in the tapentadol, pregabalin and/or lacosamide periods as compared to the placebo period.

End point type	Secondary
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End point timeframe:

The first measurement post dosing (i.e. around 1 hour after drug administration) relative to the pre-dose measurement (i.e. difference 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	24	22	23	23
Units: % change AUC				
arithmetic mean (standard deviation)	34.4 (± 66.5)	-2.7 (± 68.04)	5 (± 35.18)	11.4 (± 42.7)

Statistical analyses

Statistical analysis title	Key secondary endpoint
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Statistical analysis description:

To test if the percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration vs the pre-drug administration differs in the tapentadol, pregabalin and/or lacosamide periods as compared to the placebo period.

Comparison groups	Lacosamide v placebo
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Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.527
Method	MMRM model
Parameter estimate	Median difference (final values)
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	40.8
Variability estimate	Standard deviation
Dispersion value	15.61

Notes:

[8] - Since it is a cross-over study, subjects in the analysis are 23 and not 47

Statistical analysis title	Key secondary endpoint
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Statistical analysis description:

To test if the percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration vs the pre-drug administration differs in the tapentadol, pregabalin and/or lacosamide periods as compared to the placebo period.

Comparison groups	placebo v Pregabalin
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.131
Method	MMRM model
Parameter estimate	Median difference (final values)
Point estimate	-24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.5
upper limit	7.3
Variability estimate	Standard deviation
Dispersion value	15.87

Notes:

[9] - Since it is a cross-over study, subjects in the analysis are 23 and not 45.

Statistical analysis title	Key secondary endpoint
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Statistical analysis description:

To test if the percentage of change of the R2 recovery cycle at 500 ms interstimulus time interval at the time point T60 post-drug administration vs the pre-drug administration differs in the tapentadol, pregabalin and/or lacosamide periods as compared to the placebo period.

Comparison groups	placebo v Tapentadol
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Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.546
Method	MMRM model
Parameter estimate	Median difference (final values)
Point estimate	-9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.6
upper limit	21.6
Variability estimate	Standard deviation
Dispersion value	15.71

Notes:

[10] - Since it is a cross-over study, subjects in the analysis are 23 and not 46.

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Reporting groups

Reporting group title	Lacosamide
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Reporting group description: -

Reporting group title	Pregabalin
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Reporting group description: -

Reporting group title	Tapentadol
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	Lacosamide	Pregabalin	Tapentadol
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 22 (0.00%)	0 / 22 (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 / 23 (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	Pregabalin	Tapentadol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	4 / 22 (18.18%)	5 / 22 (22.73%)
Cardiac disorders			

Palpitations subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 22 (9.09%) 1	3 / 22 (13.64%) 1
Somnolence subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	0 / 22 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 22 (9.09%) 1	1 / 22 (4.55%) 1
General disorders and administration site conditions			
sweating subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 22 (4.55%) 1
Fatigue subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 22 (4.55%) 1	1 / 22 (4.55%) 1
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	2 / 22 (9.09%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 22 (0.00%) 0	1 / 22 (4.55%) 2

Non-serious adverse events	placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
General disorders and administration site conditions sweating subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Fatigue subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 23 (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:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36064434>

<http://www.ncbi.nlm.nih.gov/pubmed/34756635>

<http://www.ncbi.nlm.nih.gov/pubmed/34715423>

<http://www.ncbi.nlm.nih.gov/pubmed/34675309>

<http://www.ncbi.nlm.nih.gov/pubmed/33759294>