Clinical trial results:
Efficacy and safety of gabapentin versus placebo to prevent the incidence of PostHerpetic Neuralgia

Summary

EudraCT number	2013-000521-31
Trial protocol	ES
Global end of trial date	16 December 2016

Results information

Result version number	v1 (current)
This version publication date	26 November 2017
First version publication date	26 November 2017
Summary attachment (see zip file)	Summary of results (EudraCTdef.docx)

Trial information

Trial identification

Sponsor protocol code	PI12_01813

Additional study identifiers

ISRCTN number	ISRCTN79871784
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gerencia de Atención Primaria Mallorca
Sponsor organisation address	C/ Reina Esclaramunda 9, Palma, Spain, 07005
Public contact	Dr. Joan Llobera Canavés, Research Unit/ Gerencia de Atención Primaria Mallorca, 0034 971175883, jllobera@ibsalut.caib.es
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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	04 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of optimal doses of gabapentin for 5 weeks in the acute phase of herpes zoster in patients>= 50 years with moderate to severe pain added to the usual treatment to reduce the percentage of patients without post-herpetic neuralgia at 12 weeks.

Protection of trial subjects:

This study followed the principles outlined in the Declaration of Helsinki. All patients provided written informed consent, and were told that participation is voluntary and can be withdrawn at any time without any negative consequences concerning their current or future medical treatments.
All participants received specific treatment for Herpes related pain, investigator were asked to follow the WHO three-step pain relief ladder : non-opioids (paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. Use of systemic corticosteroids and tricyclic antidepressants will not be allowed.

Background therapy:

All participants were treated with 1000-mg caplets of valacyclovir hydrochloride 3 times a day for 7 days for Herpes Zoster treatment and all participants received specific treatment for Herpes related pain, investigator were asked to follow the WHO three-step pain relief ladder : non-opioids (paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. Use of systemic corticosteroids and tricyclic antidepressants will not be allowed.

Evidence for comparator:

N/A (placebo was the comparator)

Actual start date of recruitment	14 February 2014
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	Spain: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	49
From 65 to 84 years	45
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

all patients were recruited between 14/02/2014 to 16/09/2016 from 18 primary care health center in Mallorca

Pre-assignment

Screening details:

N/A

Period 1

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

Blinding implementation details:

The Hospital Son Espases central pharmacy packaged the study treatments (placebo or gabapentin) using an unblinded randomization code list. The link between the randomization code and the corresponding treatment remained blinded for all other study team members. During the process of randomization, each subject were assigned a randomization code, and given the treatment package with that code. This sequential randomization were generated in blocks of 6.

Arms

Are arms mutually exclusive?	Yes
Arm title	Gabapentin

Arm description:

Gabapentin were initiated at 300 mg/day and then increased in a stepwise manner according to the instructions for use. The dose weree increased, regardless of whether efficacy is achieved at a lower dose, to a ceiling daily dose of 1800 mg/day. In patients who develop intolerable adverse effects, the dose were reduced. The optimal dose established during the titration period was maintained throughout the remainder of the study and followed by 1 week of dose tapering

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

Dosage and administration details:

Gabapentin were initiated at 300 mg/day and then increased in a stepwise manner according to the instructions for use. The dose were increased, regardless of whether efficacy is achieved at a lower dose, to a ceiling daily dose of 1800 mg/day. In patients who develop intolerable adverse effects, the dose were reduced. The optimal dose established during the titration period were maintained throughout the remainder of the study and followed by 1 week of dose tapering

Arm title	placebo

Arm description:

Placebo arm

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:

placebo initiated at 300 mg/day and then increased in a stepwise manner according to the instructions for use. The dose were increased, regardless of whether efficacy is achieved at a lower dose, to a ceiling daily dose of 1800 mg/day. In patients who develop intolerable adverse effects, the dose were reduced. The optimal dose established during the titration period were maintained throughout the remainder of the study and followed by 1 week of dose tapering

Number of subjects in period 1	Gabapentin	placebo
Started	50	48
Completed	33	42
Not completed	17	6
Consent withdrawn by subject	3	1
Adverse event, non-fatal	3	-
Lost to follow-up	10	5
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Gabapentin
Reporting group description:	
Gabapentin were initiated at 300 mg/day and then increased in a stepwise manner according to the instructions for use. The dose weree increased, regardless of whether efficacy is achieved at a lower dose, to a ceiling daily dose of 1800 mg/day. In patients who develop intolerable adverse effects, the dose were reduced. The optimal dose established during the titration period was maintained throughout the remainder of the study and followed by 1 week of dose tapering	
Reporting group title	placebo
Reporting group description:	
Placebo arm	

Reporting group values	Gabapentin	placebo	Total
Number of subjects	50	48	98
Age categorical Units: Subjects			
50-64	24	23	47
65-84	20	23	43
more than 85	3	1	4
Not recorded	3	1	4
Age continuous Units: years			
arithmetic mean	65.1	66	
standard deviation	± 11.4	± 11.1	-
Gender categorical Units: Subjects			
Female	27	29	56
Male	20	18	38
Not recorded	3	1	4
Herpes Zoster location Units: Subjects			
Torax	26	18	44
Abdominal	5	5	10
extremities	8	12	20
Others	10	13	23
Not recorded	1	0	1
Herpes Zoster vacination Units: Subjects			
yes	9	10	19
no	28	31	59
Not recorded	13	7	20
Body Mass index Units: kg/m2			
arithmetic mean	28.1	27.3	
standard deviation	± 4.7	± 5.7	-
MOS-Sleep (Disturbance) Units: N/A			
arithmetic mean	34.2	36.6	

standard deviation	± 25.8	± 31.4	-
MOS-Sleep (snoring)			
Units: n/a			
arithmetic mean	56.9	44.9	
standard deviation	± 37.2	± 37.9	-
MOS-Sleep (short of breath or headache)			
Units: n/a			
arithmetic mean	10.9	6.1	
standard deviation	± 20.1	± 15.1	-
MOS-Sleep(adequacy)			
Units: n/a			
arithmetic mean	70.4	70.6	
standard deviation	± 31.6	± 30.7	-
MOS-Sleep (somnolence)			
Units: n/a			
arithmetic mean	30.4	31.6	
standard deviation	± 19.7	± 22	-
MOS-Sleep (sleep problems index 6)			
Units: n/a			
arithmetic mean	24.6	25.2	
standard deviation	± 18.3	± 23.3	-
MOS-Sleep (sleep problems index 9)			
Units: n/a			
arithmetic mean	27.4	28	
standard deviation	± 18.6	± 23.3	-
Short form Health survey-12 (role Physical)			
Units: n/a			
arithmetic mean	31.7	32.6	
standard deviation	± 9.1	± 9	-
Short form Health survey-12 (Physical functioning)			
Units: n/a			
arithmetic mean	49.8	51.3	
standard deviation	± 10.8	± 9.5	-
Short form Health survey-12 (bodily pain)			
Units: n/a			
arithmetic mean	30.3	30.4	
standard deviation	± 3.8	± 3.7	-
Short form Health survey-12 (General health)			
Units: n/a			
arithmetic mean	44.5	45.8	
standard deviation	± 9.3	± 9.9	-
Short form Health survey-12 (role emotional)			
Units: n/a			
arithmetic mean	40	42.5	
standard deviation	± 9.6	± 6.8	-
Short form Health survey-12(Mental Health)			
Units: n/a			

arithmetic mean	43.8	43.4	
standard deviation	± 2.7	± 2.1	-
Visual Analogue Scale (VAS) pain balseline			
Units: N/A			
arithmetic mean	67.9	66.2	
standard deviation	± 20.2	± 18.9	-

End points

End points reporting groups

Reporting group title	Gabapentin
Reporting group description:	
Gabapentin were initiated at 300 mg/day and then increased in a stepwise manner according to the instructions for use. The dose weree increased, regardless of whether efficacy is achieved at a lower dose, to a ceiling daily dose of 1800 mg/day. In patients who develop intolerable adverse effects, the dose were reduced. The optimal dose established during the titration period was maintained throughout the remainder of the study and followed by 1 week of dose tapering	
Reporting group title	placebo
Reporting group description:	
Placebo arm	

Primary: Post-Herpetic neuralgia (VAS >1) at 12 weeks

End point title	Post-Herpetic neuralgia (VAS >1) at 12 weeks
End point description:	
Post herpetic neuralgia defined as at least 10 mm in a Visual Analogue Scale of 100 mm for pain at 12 weeks from inclusion	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Gabapentin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	42		
Units: mm				
post-herpetic neuralgia Yes	5	2		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Gabapentin v placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	19.7

Notes:

[1] - P-value =0.144

Secondary: 50 % Pain reduction at 12 weeks

End point title	50 % Pain reduction at 12 weeks

End point description:

Pain reduction of at least 50% from baseline

End point type	Secondary

End point timeframe:

12 weeks

End point values	Gabapentin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	42		
Units: percentage				
50% Pain reduction-Yes	30	42		

Statistical analyses

Statistical analysis title	Secondaru Outcomes/50% Pain reduction at 12 weeks
Comparison groups	Gabapentin v placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	7.72

Notes:

[2] - P-value=0.046

Secondary: Quality of life-SF12-General Health Physical

End point title	Quality of life-SF12-General Health Physical

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Gabapentin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	28		
Units: Sf-12				
arithmetic mean (standard deviation)	52.6 (± 7.2)	48.4 (± 7.2)		

Statistical analyses

Statistical analysis title	Secondary analysis: Sf-12 General Health
Comparison groups	placebo v Gabapentin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05 [3]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.72
upper limit	-1.52

Notes:

[3] - P-Value=0,093

Secondary: Dolor Neuropatique Questionnaire-4

End point title	Dolor Neuropatique Questionnaire-4

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Gabapentin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	37		
Units: Percentage				
DN-4 +	4	4		

Statistical analyses

Statistical analysis title	Secondary analysis:DN-4
Comparison groups	Gabapentin v placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	5.14

Notes:

[4] - p-value=0.827

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Gabapentine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Gabapentine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Lacunar stroke			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Gabapentine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 50 (22.00%)	6 / 48 (12.50%)	
General disorders and administration site conditions			

Dizziness			
subjects affected / exposed	5 / 50 (10.00%)	3 / 48 (6.25%)	
occurrences (all)	5	3	
Somnolence			
subjects affected / exposed	3 / 50 (6.00%)	2 / 48 (4.17%)	
occurrences (all)	33	42	
Abdominal pain/vomits			
subjects affected / exposed	3 / 50 (6.00%)	1 / 48 (2.08%)	
occurrences (all)	3	1	

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

None reported