Clinical trial results:
An exploratory, randomized, double blind, placebo controlled, parallel groups Phase II clinical trial to evaluate the efficacy and safety of E-52862 (400 mg) by oral route, in patients with post-surgical neuropathic pain.

Summary

EudraCT number	2012-000402-30
Trial protocol	ES
Global end of trial date	03 December 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	ESTEVE-SIGM-205

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratorios Dr. Esteve. S.A. (ESTEVE)
Sponsor organisation address	Avda. Mare de Déu de Montserrat, 221, Barcelona, Spain, 08041
Public contact	Study Medical Monitor, Laboratorios del Dr. Esteve. S.A, +34 934466000, jcebrecos@esteve.es
Scientific contact	Study Medical Monitor, Laboratorios del Dr. Esteve. S.A, +34 934466000, jcebrecos@esteve.es

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 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2014
Global end of trial reached?	Yes
Global end of trial date	03 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the analgesic efficacy of repeated doses of E-52862 in subjects with moderate to severe post-surgical neuropathic pain

Protection of trial subjects:

The study will be conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2012
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: 116
Worldwide total number of subjects	116
EEA total number of subjects	116

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)	92
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain during 5-Nov-2012 (FSFV) and 3-Dec-2014 (LSLV)

Pre-assignment

Screening details:

Male and female patients ≥ 18 years with chronic neuropathic pain (DN4 score ≥ 4) of moderate to severe intensity (≥ 4 on the NPRS) caused by a surgery intervention that occurred ≥ 3 months before inclusion in the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	E-52862

Arm description:

Active arm

Arm type	Experimental
Investigational medicinal product name	E-52862
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400 mg once a day

Arm title	Control

Arm description:

Control 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:

1 capsule of placebo once a day

Number of subjects in period 1	E-52862	Control
Started	55	61
Completed	44	55
Not completed	11	6
Consent withdrawn by subject	4	2
Physician decision	-	1
Adverse event, non-fatal	5	2
Other	2	-
Not received study medication	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)
Reporting group description:	
N=115, excluding patient who did not take study medication	

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	116	116	
Age categorical Units: Subjects			

Age continuous			
Excluding patient who did not take study medication			
Units: years			
arithmetic mean	52.55		
standard deviation	± 12.81	-	
Gender categorical Units: Subjects			
Female	79	79	
Male	37	37	

End points

End points reporting groups	
Reporting group title	E-52862
Reporting group description:	
Active arm	
Reporting group title	Control
Reporting group description:	
Control arm	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomised patients who took at least one dose of study medication and with at least one valid baseline and on-treatment efficacy observation	

Primary: NPRS – Average pain – change from baseline to day 28	
End point title	NPRS – Average pain – change from baseline to day 28
End point description:	
End point type	Primary
End point timeframe:	
Time specific change from baseline to day 28 in mean pain intensity in the previous 7 days interval measured by a Numerical Pain Rating Scale (NPRS), included in a patient diary (average 24 hour pain)	

End point values	E-52862	Control	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	55	59	114	
Units: numeric (pain rating scale)				
arithmetic mean (standard deviation)	-1.56 (± 1.91)	-0.89 (± 1.76)	-1.19 (± 1.85)	

Statistical analyses

Statistical analysis title	Two-way ANCOVA model
Statistical analysis description:	
Analysis of variance (ANOVA) model including factors for treatment, center (fixed effects) and baseline value (covariate).	
Comparison groups	E-52862 v Control
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.655
upper limit	-0.091

Secondary: NPRS – Worst pain – change from baseline to day 28

End point title	NPRS – Worst pain – change from baseline to day 28

End point description:

End point type	Secondary

End point timeframe:

Time specific change from baseline to day 28 in mean pain intensity in the previous 7 days interval measured by a Numerical Pain Rating Scale (NPRS), included in a patient diary (worst 24 hour pain)

End point values	E-52862	Control	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	55	59	114	
Units: numeric (pain rating scale)				
arithmetic mean (standard deviation)	-2 (± 2.266)	-1.04 (± 2.092)	-1.47 (± 2.215)	

Statistical analyses

Statistical analysis title	Two-way ANCOVA model

Statistical analysis description:

Analysis of variance (ANOVA) model including factors for treatment, center (fixed effects) and baseline value (covariate).

Comparison groups	E-52862 v Control
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.909
upper limit	-0.07

Secondary: 50% responders rate

End point title	50% responders rate

End point description:

End point type	Secondary

End point timeframe:

Reduction from baseline to day 28 of at least 50% of the 24-hour average pain score (measured by an NPRS included in the patient diary)

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	59		
Units: percent				
number (not applicable)	16.4	8.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first IMP intake up to two weeks after the last IMP administration

Adverse event reporting additional description:

Treatment Emergent Adverse Event are displayed. The AEs that occurred after the first IMP intake are going to be considered as treatment emergent AEs (TEAEs) either serious or not.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	E-52862

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	E-52862	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 55 (5.45%)	4 / 60 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine increased, Blood potassium increased, Blood urea increased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased, Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Procedural pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 55 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 60 (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	E-52862	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 55 (90.91%)	46 / 60 (76.67%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 55 (43.64%)	15 / 60 (25.00%)	
occurrences (all)	43	20	
Headache			
subjects affected / exposed	17 / 55 (30.91%)	13 / 60 (21.67%)	
occurrences (all)	46	29	
Somnolence			
subjects affected / exposed	3 / 55 (5.45%)	2 / 60 (3.33%)	
occurrences (all)	4	2	
General disorders and administration site conditions			

Malaise			
subjects affected / exposed	3 / 55 (5.45%)	3 / 60 (5.00%)	
occurrences (all)	5	3	
Fatigue			
subjects affected / exposed	2 / 55 (3.64%)	4 / 60 (6.67%)	
occurrences (all)	5	6	
Asthenia			
subjects affected / exposed	2 / 55 (3.64%)	3 / 60 (5.00%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 55 (32.73%)	4 / 60 (6.67%)	
occurrences (all)	34	6	
Abdominal pain upper			
subjects affected / exposed	14 / 55 (25.45%)	7 / 60 (11.67%)	
occurrences (all)	33	12	
Vomiting			
subjects affected / exposed	7 / 55 (12.73%)	1 / 60 (1.67%)	
occurrences (all)	9	1	
Dyspepsia			
subjects affected / exposed	6 / 55 (10.91%)	1 / 60 (1.67%)	
occurrences (all)	7	1	
Abdominal discomfort			
subjects affected / exposed	6 / 55 (10.91%)	0 / 60 (0.00%)	
occurrences (all)	6	0	
Dry mouth			
subjects affected / exposed	5 / 55 (9.09%)	1 / 60 (1.67%)	
occurrences (all)	6	2	
Constipation			
subjects affected / exposed	4 / 55 (7.27%)	0 / 60 (0.00%)	
occurrences (all)	4	0	
Flatulence			
subjects affected / exposed	3 / 55 (5.45%)	0 / 60 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			

subjects affected / exposed	3 / 55 (5.45%)	1 / 60 (1.67%)	
occurrences (all)	3	1	
Toothache			
subjects affected / exposed	1 / 55 (1.82%)	3 / 60 (5.00%)	
occurrences (all)	1	6	
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)	3 / 60 (5.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	4 / 55 (7.27%)	0 / 60 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 55 (10.91%)	2 / 60 (3.33%)	
occurrences (all)	10	2	
Insomnia			
subjects affected / exposed	6 / 55 (10.91%)	4 / 60 (6.67%)	
occurrences (all)	6	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 55 (9.09%)	4 / 60 (6.67%)	
occurrences (all)	7	4	
Back pain			
subjects affected / exposed	4 / 55 (7.27%)	2 / 60 (3.33%)	
occurrences (all)	5	5	
Pain in extremity			
subjects affected / exposed	4 / 55 (7.27%)	5 / 60 (8.33%)	
occurrences (all)	4	8	
Neck pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 60 (5.00%)	
occurrences (all)	4	3	
Muscle spasms			
subjects affected / exposed	2 / 55 (3.64%)	5 / 60 (8.33%)	
occurrences (all)	2	5	
Limb discomfort			

subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	3 / 60 (5.00%) 3	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	1 / 60 (1.67%) 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

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

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Notes: