

**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 painful diabetic neuropathy.

Summary

EudraCT number	2012-000400-14
Trial protocol	ES RO
Global end of trial date	04 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-204
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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, +34 934466000, jcebreco@esteva.es
Scientific contact	Study Medical Monitor, Laboratorios del Dr. Esteve, +34 934466000, jcebreco@esteva.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	08 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2014
Global end of trial reached?	Yes
Global end of trial date	04 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the analgesic efficacy of E-52862 in subjects with moderate to severe painful diabetic neuropathy.

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	30 October 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	Romania: 133
Country: Number of subjects enrolled	Spain: 30
Worldwide total number of subjects	163
EEA total number of subjects	163

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)	115
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain and Romania, during 30-Oct-2012 (FSFV) and 4-Dec-2014 (LSLV)

Pre-assignment

Screening details:

Male and female patients ≥ 18 years, with pain due to polyneuropathy caused by DM 1 or DM 2, HbA1c $\leq 10.0\%$. Pain present for ≥ 6 months, but < 5 years, score ≥ 3 on the Michigan Neuropathy Screening Instrument, with a moderate to severe pain intensity measured by a score of ≥ 4 on the NPRS

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
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Arm title	E-52862
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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
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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	85	78
Completed	83	77
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial (overall period)
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Reporting group description:

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Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	163	163	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	58.4 ± 10.4	-	
Gender categorical Units: Subjects			
Female	84	84	
Male	79	79	

Subject analysis sets

Subject analysis set title	Per Protocol analysis set
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects who are deemed to have no major protocol violations that could interfere with the objectives of this study.

Reporting group values	Per Protocol analysis set		
Number of subjects	125		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	59.7 ± 8.55		
Gender categorical Units: Subjects			
Female	72		
Male	53		

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	Per Protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects who are deemed to have no major protocol violations that could interfere with the objectives of this study.	

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	Per Protocol analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	64	125	
Units: numeric (pain rating scale)				
arithmetic mean (standard deviation)	-2.6 (\pm 1.76)	-2.4 (\pm 1.83)	-2.5 (\pm 1.79)	

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	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6815
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.125

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.729
upper limit	0.478

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

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

End point type	Secondary
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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	Per Protocol analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	61	64	125	
Units: numeric (pain rating scale)				
arithmetic mean (standard deviation)	-2.6 (± 1.76)	-2.8 (± 1.96)	-2.7 (± 1.86)	

Statistical analyses

Statistical analysis title	Two-way ANCOVA model
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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
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Number of subjects included in analysis	125
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.5125
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Method	ANCOVA
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Parameter estimate	Mean difference (net)
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Point estimate	0.213
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Confidence interval	
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level	95 %
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sides	2-sided
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lower limit	-0.43
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upper limit	0.857
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Secondary: 50% responders rate

End point title	50% responders rate
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End point description:

End point type	Secondary
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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	61	64		
Units: percent				
number (not applicable)				
Responder	44.3	39.1		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	E-52862
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	E-52862	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 78 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	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	29 / 85 (34.12%)	21 / 78 (26.92%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 85 (8.24%)	5 / 78 (6.41%)	
occurrences (all)	16	10	
Headache			
subjects affected / exposed	3 / 85 (3.53%)	5 / 78 (6.41%)	
occurrences (all)	4	9	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	8 / 85 (9.41%) 15	0 / 78 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	5 / 78 (6.41%) 5	

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: