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, as part of an analgesic therapy balanced with morphine, followed by an open label extension, in the treatment of post-operative pain due to abdominal hysterectomy

Summary

EudraCT number	2011-003302-24
Trial protocol	ES
Global end of trial date	26 September 2013

Results information

Result version number	v1 (current)
This version publication date	03 August 2016
First version publication date	03 August 2016

Trial information

Trial identification

Sponsor protocol code	ESTEVE-SIGM-201

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	Jesus Cebrecos, Laboratorios Dr. Esteve S.A., 34 934466000, jcebrecos@esteve.es
Scientific contact	Jesus Cebrecos, Laboratorios 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	31 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2013
Global end of trial reached?	Yes
Global end of trial date	26 September 2013
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 effect of E-52862 compared to placebo on pain following hysterectomy, measured through the morphine consumption administered by Patient Controlled Analgesia (PCA) during the first 24 post-operative hours, pain at rest and movement-evoked pain.

Protection of trial subjects:

The study has been 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	13 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain, during 13-Feb-2012 (FSFV) and 26-Sep-2013 (LSLV)

Pre-assignment

Screening details:

Female patients aged between 18 and 80 years, scheduled for an elective non-malignant partial or total abdominal hysterectomy (non laparoscopic) under general anaesthesia (patients with cervix carcinoma stage 1 or endometrial carcinoma stage 1 can be also included)

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:

400 mg once a day , during three days.

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:

1 capsule of placebo once a day , during three days.

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	60	61
Completed	52	52
Not completed	8	9
Adverse event, non-fatal	1	1
Suspended surgery	2	2
Prohibited Medication	5	6

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	121	121	
Age categorical Units: Subjects			
Adults (18-64 years)	121	121	
Age continuous Units: years arithmetic mean standard deviation	 46.02 ± 5	 -	
Gender categorical Units: Subjects			
Female	121	121	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who receive at least 1 dose of the study drug. Safety analysis will be performed on the safety set.

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.

Reporting group values	Safety analysis set	Per Protocol analysis set	
Number of subjects	121	104	
Age categorical Units: Subjects			
Adults (18-64 years)	121	104	
Age continuous Units: years arithmetic mean standard deviation	 46.02 ± 5	 46.19 ± 4.95	
Gender categorical Units: Subjects			
Female	121	104	

End points

End points reporting groups

Reporting group title	E-52862
Reporting group description:	
400 mg once a day , during three days.	
Reporting group title	Control
Reporting group description:	
1 capsule of placebo once a day , during three days.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who receive at least 1 dose of the study drug. Safety analysis will be performed on the safety set.	
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: Total morphine consumption administered by PCA (24 hours)

End point title	Total morphine consumption administered by PCA (24 hours)
End point description:	
Total morphine consumption in mg administered by PCA during the 24 hours post-operative period.	
End point type	Primary
End point timeframe:	
24 hours post-operative period.	

End point values	E-52862	Control	Per Protocol analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	52	104	
Units: mg				
arithmetic mean (standard deviation)	27.14 (± 17.57)	24.43 (± 14.22)	25.79 (± 15.96)	

Statistical analyses

Statistical analysis title	Two-way ANOVA model
Statistical analysis description:	
Two-way ANOVA model with treatment and centre as factors.	
Comparison groups	E-52862 v Control

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3892
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.45
upper limit	3.32
Variability estimate	Standard error of the mean
Dispersion value	2.96

Secondary: Total morphine consumption administered by PCA (48 hours)

End point title	Total morphine consumption administered by PCA (48 hours)

End point description:

Total morphine consumption in mg administered by PCA during the 48 hours post-operative period.

End point type	Secondary

End point timeframe:

48 hours post-operative period.

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: mg				
arithmetic mean (standard deviation)	38.42 (± 22.27)	35.11 (± 18.89)		

Statistical analyses

Statistical analysis title	Two- way ANOVA model

Statistical analysis description:

Two-way ANOVA model with treatment and center as factors.

Comparison groups	E-52862 v Control

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.93
upper limit	4.76
Variability estimate	Standard error of the mean
Dispersion value	3.95

Secondary: Total morphine consumption PCA plus subcutaneous (24h)

End point title	Total morphine consumption PCA plus subcutaneous (24h)

End point description:

Total morphine consumption in mg administered by PCA plus subcutaneous injection during the 24 hours post-operative period.

End point type	Secondary

End point timeframe:

24 hours post-operative period.

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: mg				
arithmetic mean (standard deviation)	28.47 (± 18.55)	25.91 (± 14.97)		

Statistical analyses

Statistical analysis title	Two-way ANOVA model

Statistical analysis description:

two-way ANOVA model with treatment and center as factors.

Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4738
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.35
upper limit	3.91
Variability estimate	Standard error of the mean
Dispersion value	3.09

Secondary: Total morphine consumption PCA plus subcutaneous (48h)

End point title	Total morphine consumption PCA plus subcutaneous (48h)

End point description:

Total morphine consumption in mg administered by PCA plus subcutaneous injection during the 48 hours post-operative period.

End point type	Secondary

End point timeframe:

48 hours post-operative period

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: mg				
arithmetic mean (standard deviation)	40.45 (± 23.64)	36.58 (± 19.5)		

Statistical analyses

Statistical analysis title	Two-way ANOVA model

Statistical analysis description:

Two-way ANOVA model with treatment and center as factors

Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.399
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.58
upper limit	4.66
Variability estimate	Standard error of the mean
Dispersion value	4.09

Secondary: Pain intensity at rest (8h)	
End point title	Pain intensity at rest (8h)
End point description:	
Pain intensity at rest during the first 8 hours after the end of surgery.	
End point type	Secondary
End point timeframe:	
8 hours after the end of surgery.	

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: cm				
arithmetic mean (standard deviation)	1.73 (± 1.58)	2.11 (± 1.54)		

Statistical analyses

Statistical analysis title	ANOVA repeated measures mixed model
Statistical analysis description:	
ANOVA repeated measures mixed model, with terms for treatment, time, site and interaction between treatment and time as fixed effects and subject as a random effect.	
Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0465
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.0092
Variability estimate	Standard error of the mean
Dispersion value	0.29

Secondary: Pain intensity at rest (18h)	
End point title	Pain intensity at rest (18h)
End point description:	
Pain intensity at rest during the first 18 hours after the end of surgery.	

End point type	Secondary

End point timeframe:

18 hours after the end of surgery

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: cm				
arithmetic mean (standard deviation)	1.5 (± 1.52)	1.85 (± 1.97)		

Statistical analyses

Statistical analysis title	ANOVA repeated measures mixed model.

Statistical analysis description:

ANOVA repeated measures mixed model, with terms for treatment, time, site and interaction between treatment and time as fixed effects and subject as a random effect.

Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0469
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	-0.0074
Variability estimate	Standard error of the mean
Dispersion value	0.27

Secondary: Pain intensity at rest (24h)

End point title	Pain intensity at rest (24h)

End point description:

Pain intensity at rest during the first 24 hours after the end of surgery.

End point type	Secondary

End point timeframe:

24 hours after the end of surgery.

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: cm				
arithmetic mean (standard deviation)	1.6 (± 1.61)	1.6 (± 1.64)		

Statistical analyses

Statistical analysis title	ANOVA repeated measures mixed model.
Statistical analysis description:	
ANOVA repeated measures mixed model, with terms for treatment, time, site and interaction between treatment and time as fixed effects and subject as a random effect.	
Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0588
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.018
Variability estimate	Standard error of the mean
Dispersion value	0.25

Secondary: Consumption of pain rescue medication

End point title	Consumption of pain rescue medication
End point description:	
Percentage of patients that required pain rescue medication during the first 48 hours after the end of surgery.	
End point type	Secondary
End point timeframe:	
First 48 hours after the end of surgery.	

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	52		
Units: Patients				
Rescue Medication	16	15		
No Rescue Medication	36	37		

Statistical analyses

Statistical analysis title	Chi Square test
Comparison groups	E-52862 v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8303
Method	Chi-squared

Secondary: Long term assessment of post-operative pain	
End point title	Long term assessment of post-operative pain
End point description: Long term assessment of post-operative pain: incidence of pain at 6 months	
End point type	Secondary
End point timeframe: 6 months	

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Patients				
Pain	8	7		
No Pain	45	40		

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	E-52862 v Control
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

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).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

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	7 / 60 (11.67%)	4 / 61 (6.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Anaemia postoperative	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		

subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervix haematoma uterine	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haematoma	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic haematoma	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic	Additional description: This Adverse Event was considered non- related to study medication but related to the surgical procedure itself.		
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (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	41 / 60 (68.33%)	44 / 61 (72.13%)	
Nervous system disorders			
Headache	Additional description: 0 out of 9 were assessed as related to E-52862 and 0 out of 5 were assessed as related to placebo.		
subjects affected / exposed	8 / 60 (13.33%)	5 / 61 (8.20%)	
occurrences (all)	9	5	
Dizziness	Additional description: 1 out of 3 were assessed as related to E-52862 and 0 out of 8 were assessed as related to placebo.		
subjects affected / exposed	3 / 60 (5.00%)	7 / 61 (11.48%)	
occurrences (all)	3	8	
Gastrointestinal disorders			
Nausea	Additional description: 4 out of 19 were assessed as related to E-52862 and 7 out of 26 were assessed as related to placebo.		
subjects affected / exposed	14 / 60 (23.33%)	23 / 61 (37.70%)	
occurrences (all)	19	26	
Vomiting	Additional description: 2 out of 3 were assessed as related to E-52862 and 3 out of 10 were assessed as related to placebo.		
subjects affected / exposed	3 / 60 (5.00%)	9 / 61 (14.75%)	
occurrences (all)	3	10	
Constipation	Additional description: 1 out of 3 were assessed as related to E-52862 and 0 out of 1 were assessed as related to placebo.		
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	
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

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

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Notes: