Clinical trial results:
A randomized, double-blind, controlled with active treatment (tramadol 100 mg) and placebo, parallel groups, Phase II clinical trial to establish the effective dose between 4 strengths of E-58425 for moderate to severe dental pain

Summary

EudraCT number	2011-002778-21
Trial protocol	ES
Global end of trial date	13 February 2013

Results information

Result version number	v1 (current)
This version publication date	15 December 2016
First version publication date	15 December 2016

Trial information

Trial identification

Sponsor protocol code	ESTEVE-SACO4-201

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	Clinical Investigation Department, Laboratorios del Dr. Esteve, S.A, 34 934466000, svidela@esteve.es
Scientific contact	Clinical Investigation Department, Laboratorios del Dr. Esteve, S.A, 34 934466000, svidela@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	27 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2013
Global end of trial reached?	Yes
Global end of trial date	13 February 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to establish the effective dose between 4 strengths of E 58425 for moderate to severe dental pain based on pain intensity (PI), total pain relief (TOTPAR), use of supplementary analgesic medication, time of onset of pain relief (PAR) and overall assessment.

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	10 February 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: 334
Worldwide total number of subjects	334
EEA total number of subjects	334

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)	334
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain during 10-Feb-2012 (FSFV) and 13-Feb-2013 (LSLV)

Pre-assignment

Screening details:

Male and female patients ≥ 18 with Moderate or Severe pain (score of at least 50 mm on VAS) as a result of an oral surgical procedure under local anesthesia and/or sedation. The procedure had to involve the extraction of at least two impacted third molars requiring bone removal.

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-58425 50 mg

Arm description:

Active experimental arm

Arm type	Experimental
Investigational medicinal product name	E-58425
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg, single dose (all treatments were over-encapsulated for treatment blinding)

Arm title	E-58425 100 mg

Arm description:

Active experimental arm

Arm type	Experimental
Investigational medicinal product name	E-58425
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg, single dose (all treatments were over-encapsulated for treatment blinding)

Arm title	E-58425 150 mg

Arm description:

Active experimental arm

Arm type	Experimental

Investigational medicinal product name	E-58425
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
150 mg, single dose (all treatments were over-encapsulated for treatment blinding)

Arm title	E-58425 200 mg

Arm description:
Active experimental arm

Arm type	Experimental
Investigational medicinal product name	E-58425
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
200 mg, single dose (all treatments were over-encapsulated for treatment blinding)

Arm title	Tramadol 100 mg

Arm description:
Active control arm

Arm type	Active comparator
Investigational medicinal product name	Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
100 mg, single dose (all treatments were over-encapsulated for treatment blinding)

Arm title	Placebo

Arm description:
Placebo Control arm

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

Dosage and administration details:
Placebo, single dose (all treatments were over-encapsulated for treatment blinding)

Number of subjects in period 1	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg
Started	55	53	57
Completed	55	53	55
Not completed	0	0	2
Lost to follow-up	-	-	2

Number of subjects in period 1	E-58425 200 mg	Tramadol 100 mg	Placebo
Started	57	58	54
Completed	57	58	54
Not completed	0	0	0
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)

Reporting group description: -

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	334	334	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	24.5		
standard deviation	± 5.63	-	
Gender categorical Units: Subjects			
Female	192	192	
Male	142	142	
Baseline pain intesity			
Moderate baseline pain: VAS = 50-60 mm Severe baseline pain: VAS = >60 mm (data for Per Protocol Analysis Set)			
Units: Subjects			
Moderate	186	186	
Severe	102	102	
Non per protocol set	46	46	

End points

End points reporting groups

Reporting group title	E-58425 50 mg
Reporting group description:	
Active experimental arm	
Reporting group title	E-58425 100 mg
Reporting group description:	
Active experimental arm	
Reporting group title	E-58425 150 mg
Reporting group description:	
Active experimental arm	
Reporting group title	E-58425 200 mg
Reporting group description:	
Active experimental arm	
Reporting group title	Tramadol 100 mg
Reporting group description:	
Active control arm	
Reporting group title	Placebo
Reporting group description:	
Placebo Control arm	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who were randomized and who received study medication, for whom no relevant protocol deviations were documented, at least three valid VAS measurements were available eight hours after receiving the study medication and had not taken rescue medication during the first hour post-dose.

Primary: SPID (0-8 h)

End point title	SPID (0-8 h)

End point description:

The SPID was defined as the sum of PID between time 0 and time t weighted with the time between two consecutive values, i.e., each PIDt value was multiplied with the time interval since the previous evaluation and summed up.
The pain intensity difference (PID) was defined as PIDt = PIt-PI0, where PI0 is the pain intensity (VAS) at t=0 hours and PIt is the pain intensity at specific time points. Positive values therefore correspond to an increase in pain, while negative values correspond to a decrease in pain.
Pain intensity (PI) was assessed using a 100mm VAS. The first pain intensity VAS score of at least 50mm obtained during the 4 hours post-dental extraction will be considered the study baseline pain, and the study medication will be administered immediately. After receiving the dose of study medication, the pain intensity VAS score was gathered at different time intervals.

End point type	Primary

End point timeframe:

Sum of pain intensity difference from 0-8 hours

End point values	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg	E-58425 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	54	46
Units: mm*h				
arithmetic mean (standard deviation)	-21.05 (± 242.985)	-89.53 (± 233.626)	-139.04 (± 226.775)	-172.82 (± 224.241)

End point values	Tramadol 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	47		
Units: mm*h				
arithmetic mean (standard deviation)	22.16 (± 228.242)	70.91 (± 212.612)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

ANOVA with factors treatment and center without interaction

Comparison groups	E-58425 50 mg v E-58425 100 mg v E-58425 150 mg v E-58425 200 mg v Tramadol 100 mg v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANOVA

Notes:

[1] - Overall p-value for treatment

Secondary: TOTPAR (0-8 h)

End point title	TOTPAR (0-8 h)

End point description:

TOTPAR was defined as the sum of PAR between time 0 and time t weighted with the time between two consecutive values, i.e., each PARt value was multiplied with the time interval since the previous evaluation.
Pain relief (PAR) was assessed by a 5-point ordinal scale at the same time points as the pain intensity (excluding baseline). Patients were asked how much pain relief they had experienced since the intake of study medication.

End point type	Secondary

End point timeframe:

Total pain relief from 0-8 hours

End point values	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg	E-58425 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	54	46
Units: Score*Hours				
arithmetic mean (standard deviation)	15.94 (± 8.458)	21.13 (± 10.313)	20.63 (± 10.035)	22.77 (± 9.991)

End point values	Tramadol 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	47		
Units: Score*Hours				
arithmetic mean (standard deviation)	16.55 (± 9.247)	14.72 (± 8.695)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

ANOVA with factors treatment and center without interaction

Comparison groups	E-58425 50 mg v E-58425 100 mg v E-58425 150 mg v E-58425 200 mg v Tramadol 100 mg v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANOVA

Notes:

[2] - Overall p-value for treatment

Secondary: Consumption of rescue medication

End point title	Consumption of rescue medication

End point description:

End point type	Secondary

End point timeframe:

Rate of patients of patients that took at least one dose of rescue medication up to 8 hours after study drug administration

End point values	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg	E-58425 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	54	46
Units: percent				
number (not applicable)				
Yes	73.3	61.7	50	39.1

End point values	Tramadol 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	47		
Units: percent				
number (not applicable)				
Yes	73.5	80.9		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel

Statistical analysis description:

Cochran-Mantel-Haenszel test stratified by center

Comparison groups	E-58425 50 mg v E-58425 100 mg v E-58425 150 mg v E-58425 200 mg v Tramadol 100 mg v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Overall p-value for treatment

Secondary: 50% responders rate

End point title	50% responders rate

End point description:

End point type	Secondary

End point timeframe:

Rate of patients who had a 50% reduction in pain intesity as compared to baseline up to 8 hours after study drug administration

End point values	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg	E-58425 200 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	54	46
Units: percent				
number (not applicable)				
Yes	15.6	31.9	42.6	52.2

End point values	Tramadol 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	47		
Units: percent				
number (not applicable)				
Yes	18.4	12.8		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel

Statistical analysis description:

Cochran-Mantel-Haenszel test stratified by center

Comparison groups	E-58425 50 mg v E-58425 100 mg v E-58425 150 mg v E-58425 200 mg v Tramadol 100 mg v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Overall p-value for treatment

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first IMP intake to follow-up visit (7 days +/- 2 days) or the last scheduled contact with the patient	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	E-58425 50 mg
Reporting group description: -	
Reporting group title	E-58425 100 mg
Reporting group description: -	
Reporting group title	E-58425 150 mg
Reporting group description: -	
Reporting group title	E-58425 200 mg
Reporting group description: -	
Reporting group title	Tramadol 100 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)	0 / 53 (0.00%)	1 / 57 (1.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 53 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 55 (0.00%)	0 / 53 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 55 (0.00%)	0 / 53 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Postoperative abscess			
subjects affected / exposed	1 / 55 (1.82%)	0 / 53 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 55 (0.00%)	0 / 53 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	E-58425 200 mg	Tramadol 100 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	1 / 58 (1.72%)	0 / 54 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Postoperative abscess			

subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 58 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	E-58425 50 mg	E-58425 100 mg	E-58425 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 55 (12.73%)	6 / 53 (11.32%)	9 / 57 (15.79%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 55 (0.00%)	1 / 53 (1.89%)	0 / 57 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 55 (0.00%)	2 / 53 (3.77%)	4 / 57 (7.02%)
occurrences (all)	0	2	4
Nausea			
subjects affected / exposed	1 / 55 (1.82%)	2 / 53 (3.77%)	0 / 57 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	E-58425 200 mg	Tramadol 100 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 57 (29.82%)	17 / 58 (29.31%)	5 / 54 (9.26%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 57 (7.02%)	2 / 58 (3.45%)	1 / 54 (1.85%)
occurrences (all)	4	2	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	12 / 57 (21.05%)	11 / 58 (18.97%)	0 / 54 (0.00%)
occurrences (all)	12	12	0
Nausea			

subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 7	6 / 58 (10.34%) 6	0 / 54 (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.

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Notes: