Clinical trial results:
A proof-of-concept phase 2, randomized, placebo-controlled, double blind, multicentre clinical trial in 2 parallel groups to evaluate the efficacy and safety of E-52862 for reducing the incidence and severity of oxaliplatin-induced peripheral neuropathy in patients treated for colorectal cancer.

Summary

EudraCT number	2012-000398-21
Trial protocol	ES GR
Global end of trial date	23 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-202

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, svidela@esteve.es
Scientific contact	Study Medical Monitor, 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	17 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2014
Global end of trial reached?	Yes
Global end of trial date	23 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To establish the efficacy of E-52862 to reduce the incidence and the severity of OXL-induced chronic neuropathy in patients treated for colorectal cancer.
-To explore the efficacy of E-52862 to reduce the severity and duration of OXL-induced acute neuropathy.
-To evaluate whether E-52862 can raise the cumulative total dose of OXL than can be delivered without dose-limiting chronic neuropathy.
-To explore the incidence of dose-reduction, dose-delays and discontinuation of oxaliplatin due to symptomatic neuropathy grade 3 or 4.
-To explore the incidence of adverse events by severity, of serious adverse events, of adverse events leading to E 52862 discontinuation and of adverse events related to E-52862 by severity.
-To assess E-52862 plasma exposure associated with the treatment.

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	27 September 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	Greece: 48
Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	Italy: 14
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)	67
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Spain, Greece and Italy, during 27-Sep-2012 (FSFV) and 23-Dec-2014 (LSLV)

Pre-assignment

Screening details:

Male and female patients ≥ 18 to 80 years with colorectal cancer ≤ 2 years, Karnofsky ≥70. Chemotherapy not received with cytotoxic drugs in the past. Starting an adjuvant or palliative 6-month chemotherapy regimen, including OXA at a scheduled dose in the first cycle ≥60 mg/m2 (FOLFOX 4 and FOLFOX 6, with or without cetuximab or bevacizumab).

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 oral single daily administration during the first 5 days of every chemotherapy cycle, starting the day before the cycle, up to a maximum of 12 cycles of OXA

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:

Placebo oral single daily administration during the first 5 days of every chemotherapy cycle, starting the day before the cycle, up to a maximum of 12 cycles of OXA

Number of subjects in period 1	E-52862	Control
Started	62	59
Completed	34	25
Not completed	28	34
Adverse event, non-fatal	16	10
Other	11	23
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (overall period)
Reporting group description: N=121, including only patients who took study medication	

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	121	121	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 61.2 ± 11.3	 -	
Gender categorical Units: Subjects			
Female	46	46	
Male	75	75	

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 expanded
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who were randomized to treatment and received at least one dose of study medication and who had a postbaseline assessment of the quantitative sensory testing of thermal sensitivity.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who were randomized to treatment and received at least one dose of study medication and who had baseline and at least one postbaseline (after at least 4 cycles) TNS assessment	

Primary: Pre-cycle Cold Pain Threshold

End point title	Pre-cycle Cold Pain Threshold
End point description:	
Quantitaive Sensory Testing (QST) parameter: Temperature at which the patient reports that the thermal stimulus is firstly perceived as painful during the progressive reduction of the temperature from the neutral value. - Full analysis set expanded -	
End point type	Primary
End point timeframe:	
Quantitaive Sensory Testing (QST) Pre-cycle assesments performed at 7 timepoints (baseline, pre-cycle cycle 2, pre-cycle cycle 4, pre-cycle cycle 8, pre-cycle cycle 10, pre-cycle cycle 12 and follow-up visits).	

End point values	E-52862	Control	Full analysis set expanded	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	56	114	
Units: Centigrade degrees				
arithmetic mean (standard deviation)				
Cycle 1 (baseline)	17.95 (± 5.81)	18.56 (± 6.61)	18.25 (± 6.2)	
Cycle 2	19.48 (± 6.42)	21.7 (± 4.26)	20.56 (± 5.57)	
Cycle 4	19.86 (± 6.07)	21.51 (± 4.17)	20.71 (± 5.22)	
Cycle 8	20.37 (± 3.89)	20.65 (± 4.95)	20.51 (± 4.41)	
Cycle 10	18.96 (± 5.38)	20.52 (± 5.32)	19.68 (± 5.37)	
Cycle 12	19.01 (± 5.01)	19.45 (± 5.86)	19.2 (± 5.35)	
Follow-up	20.92 (± 4.24)	21.36 (± 4.11)	21.14 (± 4.16)	

Statistical analyses

Statistical analysis title	General linear mixed models

Statistical analysis description:

The values recorded at each cycle were compared between study arms using an analysis for repeated observations based on the maximum or restricted maximum likelihood-based linear mixed model for longitudinal data. All models included the fixed categorical effects of treatment, visit (time points measured), site, the continuous fixed covariate of baseline score, and the patient-nested-within-site blocks as random factor.

Comparison groups	E-52862 v Control
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Mixed models analysis

Primary: Post-cycle Cold Pain Threshold

End point title	Post-cycle Cold Pain Threshold

End point description:

Quantitaive Sensory Testing (QST) parameter: Temperature at which the patient reports that the thermal stimulus is firstly perceived as painful during the progressive reduction of the temperature from the neutral value.

- Full analysis set expanded -

End point type	Primary

End point timeframe:

Quantitaive Sensory Testing (QST) Post-cycle assesments performed at 7 timepoints (baseline, post-cycle cycle 2, post-cycle cycle 4, post-cycle cycle 8, post-cycle cycle 10, post-cycle cycle 12 and follow-up visits).

End point values	E-52862	Control	Full analysis set expanded	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	60	59	119	
Units: centigrade degrees				
arithmetic mean (standard deviation)				
Cycle 1 (baseline)	18.86 (± 7.05)	22.67 (± 3.59)	20.68 (± 5.96)	
Cycle 2	20.73 (± 4.97)	22.08 (± 4.19)	21.4 (± 4.67)	
Cycle 4	20.72 (± 4.57)	22.07 (± 4.8)	21.43 (± 4.72)	
Cycle 8	20.47 (± 4.51)	21.69 (± 3.74)	21.06 (± 4.18)	
Cycle 10	19.64 (± 4.85)	21.55 (± 4.02)	20.5 (± 4.57)	
Cycle 12	19.06 (± 4.79)	20.45 (± 5.37)	19.65 (± 5.04)	
Follow-up	20.92 (± 4.24)	21.36 (± 4.11)	21.14 (± 4.16)	

Statistical analyses

Statistical analysis title	General linear mixed models

Statistical analysis description:

The values recorded at each cycle were compared between study arms using an analysis for repeated observations based on the maximum or restricted maximum likelihood-based linear mixed model for longitudinal data. All models included the fixed categorical effects of treatment, visit (time points measured), site, the continuous fixed covariate of baseline score, and the patient-nested-within-site blocks as random factor

Comparison groups	E-52862 v Control
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed models analysis

Primary: Pre-cycle suprathreshold cold stimulus-evoked pain in the dominant hand

End point title	Pre-cycle suprathreshold cold stimulus-evoked pain in the dominant hand

End point description:

Quantitaive Sensory Testing (QST) parameter: To determine the pain evoked by a suprathreshold cold stimulus, a constant temperature stimulus was applied. The method started with the thermode at a neutral temperature of 32ºC until the patient reported a neutral thermal sensation. Then, it was cooled progressively at a rate of −1.5ºC/s until it reached the suprathreshold temperature, previously determinated for each patient, which was maintained for 5 seconds. After that time, the patient evaluated the intensity of the evoked pain using an 11-point numerical rating scale.

End point type	Primary

End point timeframe:

Quantitaive Sensory Testing (QST) Pre-cycle assesments performed at 7 timepoints (baseline, pre-cycle cycle 2, pre-cycle cycle 4, pre-cycle cycle 8, pre-cycle cycle 10, pre-cycle cycle 12 and follow-up visits).

End point values	E-52862	Control	Full analysis set expanded	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58	56	114	
Units: Numeric (Pain rating scale)				
arithmetic mean (standard deviation)				
Cycle 1 (baseline)	4.21 (± 2.33)	4.36 (± 2.16)	4.28 (± 2.24)	
Cycle 2	4.74 (± 2.55)	5.44 (± 2.01)	5.08 (± 2.32)	
Cycle 4	5.25 (± 2.63)	5.8 (± 2.08)	5.53 (± 2.37)	
Cycle 8	5.43 (± 2.64)	5.77 (± 2.48)	5.59 (± 2.55)	
Cycle 10	5.88 (± 2.72)	6.65 (± 2.31)	6.24 (± 2.55)	
Cycle 12	6.09 (± 2.69)	6.42 (± 2.44)	6.23 (± 2.57)	
Follow-up	5.8 (± 2.22)	6.26 (± 2.31)	6.03 (± 2.27)	

Statistical analyses

Statistical analysis title	General linear mixed models

Statistical analysis description:

The values recorded at each cycle were compared between study arms using an analysis for repeated observations based on the maximum or restricted maximum likelihood-based linear mixed model for longitudinal data. All models included the fixed categorical effects of treatment, visit (time points measured), site, the continuous fixed covariate of baseline score, and the patient-nested-within-site blocks as random factor.

Comparison groups	E-52862 v Control
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Mixed models analysis

Primary: Post-cycle suprathreshold cold stimulus-evoked pain in the dominant hand

End point title	Post-cycle suprathreshold cold stimulus-evoked pain in the dominant hand

End point description:

Quantitaive Sensory Testing (QST) parameter: To determine the pain evoked by a suprathreshold cold stimulus, a constant temperature stimulus was applied. The method started with the thermode at a neutral temperature of 32ºC until the patient reported a neutral thermal sensation. Then, it was cooled progressively at a rate of −1.5ºC/s until it reached the suprathreshold temperature, previously determinated for each patient, which was maintained for 5 seconds. After that time, the patient evaluated the intensity of the evoked pain using an 11-point numerical rating scale.

End point type	Primary

End point timeframe:

Quantitaive Sensory Testing (QST) Post-cycle assesments performed at 7 timepoints (baseline, post-cycle cycle 2, post-cycle cycle 4, post-cycle cycle 8, post-cycle cycle 10, post-cycle cycle 12 and follow-up visits).

End point values	E-52862	Control	Full analysis set expanded	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	60	59	119	
Units: Numeric (Pain rating scale)				
arithmetic mean (standard deviation)				
Cycle 1 (baseline)	4.61 (± 2.08)	5.04 (± 2.19)	4.81 (± 2.13)	
Cycle 2	5.13 (± 2.55)	5.78 (± 2.05)	5.45 (± 2.33)	
Cycle 4	5.49 (± 2.58)	6.04 (± 2.08)	5.78 (± 2.34)	
Cycle 8	5.85 (± 2.52)	6.07 (± 2.53)	5.96 (± 2.51)	
Cycle 10	6.11 (± 2.44)	6.72 (± 2.5)	6.39 (± 2.47)	
Cycle 12	6.44 (± 2.66)	6.44 (± 2.31)	6.44 (± 2.46)	
Follow-up	5.8 (± 2.22)	6.26 (± 2.31)	6.03 (± 2.27)	

Statistical analyses

Statistical analysis title	General linear mixed models

Statistical analysis description:

The values recorded at each cycle were compared between study arms using an analysis for repeated

observations based on the maximum or restricted maximum likelihood-based linear mixed model for longitudinal data. All models included the fixed categorical effects of treatment, visit (time points measured), site, the continuous fixed covariate of baseline score, and the patient-nested-within-site blocks as random factor.

Comparison groups	E-52862 v Control
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Mixed models analysis

Primary: Total neuropathy score 7item 'clinical' variant (cTNS)

End point title	Total neuropathy score 7item 'clinical' variant (cTNS)

End point description:

The TNS is a composite measure of peripheral nerve function that combines subjective and objective information obtained from grading of symptoms, signs, nerveconduction studies and quantitative sensory testing. The 7 'clinical' ítems included were: Sensory symptoms, Motor symptoms, Autonomic symptoms, Pin sensitivity, Vibration sensitivity, Strength and Deep tendon reflexes.

End point type	Primary

End point timeframe:

TNS assessments performed at 6 timepoints (baseline, cycle 4, cycle 8, cycle 10, cycle 12 and follow-up visits).

End point values	E-52862	Control	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	52	55	107	
Units: Score				
arithmetic mean (standard deviation)				
Cycle 1 (baseline)	0.27 (± 1.09)	0.11 (± 0.46)	0.19 (± 0.83)	
Cycle 4	1.19 (± 1.95)	1.45 (± 2.16)	1.33 (± 2.06)	
Cycle 8	2.6 (± 2.83)	1.76 (± 2.2)	2.2 (± 2.58)	
Cycle 10	3.6 (± 3.21)	3.85 (± 2.5)	3.71 (± 2.9)	
Cycle 12	6.97 (± 3.42)	5.46 (± 4.09)	6.29 (± 3.78)	
Follow-up	7.54 (± 3.21)	6.8 (± 4.24)	7.18 (± 3.75)	

Statistical analyses

Statistical analysis title	General linear mixed models

Statistical analysis description:

The values recorded at each cycle were compared between study arms using an analysis for repeated observations based on the maximum or restricted maximum likelihood-based linear mixed model for longitudinal data. All models included the fixed categorical effects of treatment, visit (time points measured), site, the continuous fixed covariate of baseline score, and the patient-nested-within-site blocks as random factor

Comparison groups	E-52862 v Control

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	Mixed models analysis

Primary: Proportion of patients with severe neuropathy (NCI-CTCAE ≥3)

End point title	Proportion of patients with severe neuropathy (NCI-CTCAE ≥3)

End point description:

The grade of treatment-associated neuropathy in the form of peripheral sensory neuropathy was assessed with the 4th version of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) of the US Cancer Institute.
Severe neuropathy is defined as NCI-CTCAE grade ≥3 toxicity at any time during chemotherapy.

Patients with an UNKNOWN value in the following tables are those patients whose NCI-CTCAE assessment is not available at end of treatment cycle (cycle 12 or previous if the patient withdrew the study) and whose previous scheduled NCI-CTCAE assessments were <3). They are excluded from the analysis.

End point type	Primary

End point timeframe:

Assessments obtained at the screening visit, at pre-cycle visits of cycles 2, 4, 8, 10 and 12 (or at the end of chemotherapy, whichever is first), and at the follow-up visit.

End point values	E-52862	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: percent				
number (not applicable)				
Severe Neuropathy	3	18		

Statistical analyses

Statistical analysis title	Comparison of proportions

Statistical analysis description:

Patients with an UNKNOWN value are excluded from the analysis

Comparison groups	E-52862 v Control
Number of subjects included in analysis	68
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.046
Method	Chi-squared corrected

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected from the time of signing the informed consent to the completion of the clinical study (including the follow up visit) or premature patient discontinuation from the clinical study.

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	17.1

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	9 / 62 (14.52%)	9 / 59 (15.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 62 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 62 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 62 (1.61%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 62 (0.00%)	2 / 59 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 59 (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	62 / 62 (100.00%)	58 / 59 (98.31%)	
Nervous system disorders			
Dysesthesia			
subjects affected / exposed	7 / 62 (11.29%)	3 / 59 (5.08%)	
occurrences (all)	34	4	
Dysgeusia			
subjects affected / exposed	19 / 62 (30.65%)	13 / 59 (22.03%)	
occurrences (all)	31	21	
Headache			
subjects affected / exposed	9 / 62 (14.52%)	3 / 59 (5.08%)	
occurrences (all)	10	5	
Hypoesthesia			
subjects affected / exposed	14 / 62 (22.58%)	10 / 59 (16.95%)	
occurrences (all)	15	11	
Neurotoxicity			
subjects affected / exposed	8 / 62 (12.90%)	6 / 59 (10.17%)	
occurrences (all)	28	13	
Paresthesia			
subjects affected / exposed	30 / 62 (48.39%)	27 / 59 (45.76%)	
occurrences (all)	168	143	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	17 / 62 (27.42%)	7 / 59 (11.86%)	
occurrences (all)	26	10	
Neutropenia			
subjects affected / exposed	32 / 62 (51.61%)	23 / 59 (38.98%)	
occurrences (all)	65	35	
Thrombocytopenia			
subjects affected / exposed	25 / 62 (40.32%)	28 / 59 (47.46%)	
occurrences (all)	57	68	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 62 (48.39%)	30 / 59 (50.85%)	
occurrences (all)	146	139	
Chest pain			

subjects affected / exposed	1 / 62 (1.61%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	9 / 62 (14.52%)	5 / 59 (8.47%)	
occurrences (all)	12	8	
Mucosal inflammation			
subjects affected / exposed	21 / 62 (33.87%)	14 / 59 (23.73%)	
occurrences (all)	35	38	
Pyrexia			
subjects affected / exposed	13 / 62 (20.97%)	16 / 59 (27.12%)	
occurrences (all)	18	19	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 62 (3.23%)	8 / 59 (13.56%)	
occurrences (all)	2	13	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 62 (17.74%)	7 / 59 (11.86%)	
occurrences (all)	14	10	
Abdominal pain upper			
subjects affected / exposed	6 / 62 (9.68%)	6 / 59 (10.17%)	
occurrences (all)	7	11	
Aphthosus stomatitis			
subjects affected / exposed	2 / 62 (3.23%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Constipation			
subjects affected / exposed	13 / 62 (20.97%)	4 / 59 (6.78%)	
occurrences (all)	20	4	
Diarrhea			
subjects affected / exposed	25 / 62 (40.32%)	22 / 59 (37.29%)	
occurrences (all)	46	59	
Dyspepsia			
subjects affected / exposed	2 / 62 (3.23%)	4 / 59 (6.78%)	
occurrences (all)	3	5	
Dysphagia			

subjects affected / exposed	4 / 62 (6.45%)	5 / 59 (8.47%)	
occurrences (all)	6	10	
Nausea			
subjects affected / exposed	29 / 62 (46.77%)	23 / 59 (38.98%)	
occurrences (all)	58	65	
Odynophagia			
subjects affected / exposed	3 / 62 (4.84%)	4 / 59 (6.78%)	
occurrences (all)	3	4	
Paresthesia oral			
subjects affected / exposed	17 / 62 (27.42%)	14 / 59 (23.73%)	
occurrences (all)	60	47	
Vomiting			
subjects affected / exposed	10 / 62 (16.13%)	8 / 59 (13.56%)	
occurrences (all)	18	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 62 (9.68%)	8 / 59 (13.56%)	
occurrences (all)	6	8	
Dysphonia			
subjects affected / exposed	9 / 62 (14.52%)	9 / 59 (15.25%)	
occurrences (all)	16	15	
Dyspnea			
subjects affected / exposed	3 / 62 (4.84%)	4 / 59 (6.78%)	
occurrences (all)	4	5	
Epistaxis			
subjects affected / exposed	5 / 62 (8.06%)	8 / 59 (13.56%)	
occurrences (all)	8	11	
Laryngospasm			
subjects affected / exposed	3 / 62 (4.84%)	8 / 59 (13.56%)	
occurrences (all)	7	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 62 (6.45%)	3 / 59 (5.08%)	
occurrences (all)	4	3	
Erythema			

subjects affected / exposed	1 / 62 (1.61%)	4 / 59 (6.78%)	
occurrences (all)	1	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 62 (6.45%)	5 / 59 (8.47%)	
occurrences (all)	4	6	
Insomnia			
subjects affected / exposed	6 / 62 (9.68%)	7 / 59 (11.86%)	
occurrences (all)	11	9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 62 (8.06%)	2 / 59 (3.39%)	
occurrences (all)	5	2	
Joint stiffness			
subjects affected / exposed	9 / 62 (14.52%)	14 / 59 (23.73%)	
occurrences (all)	35	40	
Muscle spasms			
subjects affected / exposed	5 / 62 (8.06%)	6 / 59 (10.17%)	
occurrences (all)	6	10	
Myalgia			
subjects affected / exposed	4 / 62 (6.45%)	1 / 59 (1.69%)	
occurrences (all)	6	1	
Pain in extremity			
subjects affected / exposed	2 / 62 (3.23%)	5 / 59 (8.47%)	
occurrences (all)	2	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 62 (4.84%)	3 / 59 (5.08%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	3 / 62 (4.84%)	3 / 59 (5.08%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 62 (27.42%)	13 / 59 (22.03%)	
occurrences (all)	36	18	

Hyperglycemia			
subjects affected / exposed	4 / 62 (6.45%)	7 / 59 (11.86%)	
occurrences (all)	10	9	
Hyperuricaemia			
subjects affected / exposed	4 / 62 (6.45%)	2 / 59 (3.39%)	
occurrences (all)	7	5	
Hypokalaemia			
subjects affected / exposed	4 / 62 (6.45%)	2 / 59 (3.39%)	
occurrences (all)	7	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: