Clinical trial results:
Evaluation of the effectiveness, safety, and tolerability of tapentadol PR versus oxycodone/naloxone PR in non-opioid pre-treated subjects with uncontrolled severe chronic low back pain with a neuropathic pain component.

Summary

EudraCT number	2012-002943-11
Trial protocol	DE IT AT ES
Global end of trial date	28 January 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	KF5503/60

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01838616
WHO universal trial number (UTN)	-
Other trial identifiers	Grünenthal GmbH: 822818

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
Public contact	GRT Trial Information Desk, Grünenthal GmbH, +49 2415693223, Clinical-Trials@grunenthal.com
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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	19 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2014
Global end of trial reached?	Yes
Global end of trial date	28 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effectiveness, safety, and tolerability of tapentadol PR versus oxycodone/naloxone PR in non-opioid pre-treated subjects with uncontrolled severe chronic low back pain with a neuropathic pain component.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory and competent authorities were notified of the trial as required by national regulations, and, where necessary, relevant authorization was obtained.

This effectiveness trial tried to stay in in close link to clinical practice and has an exploratory character related to highly important scientific questions. Therefore, an open-label setting, which may be questionned with regards to bias for typical regulatory trials, is justified. Relevant parameters related to tolerability (bowel function), safety (hormone blood levels) and neuropathic symptoms were not expected to be impacted by non-blinding in this respect. The pitfalls of a double-dummy regimen imposing further burden on the subjects and their compliance can be avoided.

Upon discontinuation access to suitable alternative analgesia outside of the trial were at the discretion of the investigator.

Background therapy:

Alllowed:
Subjects taking NSAIDs (including cyclooxygenase-II inhibitors) and paracetamol continued their pre-treatment regimen without further adjustment of the dose (i.e., on a stable level).
Selective serotonin reuptake inhibitors were only allowed for the treatment of uncomplicated depression if taken at a stable dose for at least 30 days before the Randomization Visit and if it was planned that they were to be continued on a stable dose for the duration of the trial.
Compounds used to treat subjects with a diagnosis of psychiatric or neurological disorders requiring treatment (other than those listed as prohibited) were allowed provided they had been taken at a controlled, stable dose for at least 3 months prior to the Randomization Visit and if it was planned that they were to be continued on a stable dose for the duration of the trial.
Physiotherapy packs and massages could be used during the trial period if their use was at the same frequency as before the trial, and if they were started at least 14 days prior to the Randomization Visit.

Prohibited:
Monoamine oxidase inhibitors were prohibited within 14 days before the Randomization Visit and during the trial.
The use of laxatives and antiemetic medications were prohibited within 14 days before the Enrollment Visit as a prophylaxis prior to starting IMP and, unless medically indicated, during the course of the trial.
Any intake of WHO Step II and Step III analgesics (including use of opioids as rescue medication) was prohibited within 30 days prior to enrollment and, except for the IMP, during the trial.
The starting of medication with any centrally acting co-analgesics (e.g., anticonvulsants, antidepressants) and starting or changing WHO Step I analgesics (e.g., NSAIDs, paracetamol) was prohibited throughout the entire trial.
Interventional adjunctive therapies, acupuncture or transcutaneous electrical nerve stimulation were not allowed during the course of the trial.

Evidence for comparator:

The prolonged release formulation of oxycodone/naloxone is indicated for severe pain, which can be adequately managed only with opioid analgesics (based on the Summary of Product Characteristics). Oxycodone/naloxone prolonged release is reported to have a better constipation profile compared to oxycodone (Simpson et al. 2008). Further, the incidence of nausea, vomiting, abdominal pain, and dyspepsia was lower in the oxycodone/naloxone prolonged release group versus the oxycodone prolonged release group.

Actual start date of recruitment	25 February 2013
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	Austria: 17
Country: Number of subjects enrolled	Germany: 202
Country: Number of subjects enrolled	Spain: 39
Worldwide total number of subjects	258
EEA total number of subjects	258

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)	171
From 65 to 84 years	83
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The trial started on 22 Mar 2013 with the enrollment of the first subject and was completed on 28 Jan 2014 when the last subject completed the last follow-up examination according to the protocol.
367 subjects signed informed consent: 89 did not met in/exclusion criteria, 16 withdrew and 4 subjects were not dosed due to other reasons.

Pre-assignment

Screening details:

The duration of the washout period depended on previous coanalgesics, the doses & on the subject's need (3 to 14 days). Analgesics and co-analgesics apart from NSAIDs (including COX-II inhibitors) & paracetamol were washed out prior to the Randomization Visit. Subjects not requiring a washout were randomized after lab results permitted this.

Period 1

Period 1 title	Titration period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tapentadol Prolonged Release

Arm description:

All participants started with 50 mg tapentadol prolonged release (twice daily). The dose of tapentadol prolonged release was adjusted in increments of 50 mg to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 250 mg twice a day (500 mg total daily dose).

Arm type	Experimental
Investigational medicinal product name	Tapentadol Prolonged Release
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Upward titration occurred at a minimum of 3-day intervals in increments of 50 mg tapentadol prolonged release BID (morning and evening).
The minimum target of titration at the end of the titration period was:
• NRS-3 ≤4 with acceptable tolerability as reported by the subject or
• Subjects with an NRS-3 score of 5, if pain relief and tolerability were reported as satisfactory to continue in the trial by the subject and investigator and subjects were on maximum daily tapentadol PR 250 mg BID, or the maximum daily tapentadol PR dose could not be achieved because of side effects.
Up-titration occurred at least until the minimum target of titration was achieved and could be continued to optimize the effectiveness/tolerability ratio for the individual subject.
Dose adjustments required by NRS-3 scores was postponed in case of limited tolerability.

Arm title	Oxycodone/Naloxone Prolonged Release

Arm description:

All participants started with 10 mg/5 mg oxycodone/naloxone prolonged release (twice daily). The dose of oxycodone/naloxone prolonged release could be adjusted in increments of 10 mg/5 mg oxycodone/naloxone to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 50 mg/20 mg oxycodone/naloxone twice daily (100 mg/40 mg total daily dose).

Arm type	Active comparator

Investigational medicinal product name	Oxycodone/Naloxone Prolonged Release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Upward titration occurred at a minimum of 3-day intervals in increments of 10mg/5mg oxycodone/naloxone prolonged release BID (morning and evening).
The minimum target of titration at the end of the titration period was:
• NRS-3 ≤4 with acceptable tolerability as reported by the subject or
• Subjects with an NRS-3 score of 5, if pain relief and tolerability were reported as satisfactory to continue in the trial by the subject and investigator and subjects were on maximum daily dose of oxycodone/naloxone prolonged release 40mg/20mg BID plus oxycodone prolonged release 10 mg BID, or the maximum daily oxycodone/naloxone dose could not be achieved because of side effects.
Up-titration occurred at least until the minimum target of titration was achieved and could be continued to optimize the effectiveness/tolerability ratio for the individual subject.
Dose adjustments required by NRS-3 scores were postponed in case of limited tolerability.

Number of subjects in period 1[1]	Tapentadol Prolonged Release	Oxycodone/Naloxone Prolonged Release
Started	130	128
Completed	100	62
Not completed	30	66
Consent withdrawn by subject	5	5
Adverse event, non-fatal	18	16
Not specified	2	-
Transferred to other arm/group	-	43
Lack of efficacy	5	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Subjects in the oxycodone/naloxone PR treatment arm that did not reach the minimum target of titration or experiencing intolerable side effects at the end of the Titration Period were switched to the Pick-up Arm. They could also enter the Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment Pick-up Arm at any time during the Titration Period or Continuation Period, via an unscheduled visit, due to lack of tolerability or lack of efficacy under treatment with oxycodone/naloxone PR.

Period 2

Period 2 title	Continuation Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Tapentadol prolonged release

Arm description:

In the continuation period, subjects continued their end of titration period tapentadol PR dose (stablized dose); however, it was permitted to make a single titration step (up or down; except for subjects already on the maximum dose of tapentadol PR for whom up-titration was not permitted) using the same titration step as used in the titration period.
The continuation period lasted 9 weeks.

Arm type	Experimental
Investigational medicinal product name	Tapentadol Prolonged Release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were suitable to enter the continuation period if the minimum target of titration was reached. In the continuation period, subjects continued their treatment with the tapentadol prolonged release dose achieved at the end of the titration period; however, it was permitted to make a single titration step (up or down; except for subjects already on the maximum dose of tapentadol PR for whom up-titration was not permitted) using the same titration step as used in the titration period. Subjects were permitted a maximum dose of 250 mg tapentadol prolonged release twice a day (500 mg total daily dose).

Arm title	Oxycodone/Naloxone Prolonged Release

Arm description:

In the continuation period, subjects continued their end of titration period tapentadol PR dose (stablized dose); however, it was permitted to make a single titration step (up or down; except for subjects already on the maximum dose of tapentadol PR for whom up-titration was not permitted) using the same titration step as used in the titration period.
The continuation period lasted 9 weeks.

Arm type	Active comparator
Investigational medicinal product name	Oxycodone/Naloxone Prolonged Release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were suitable to enter the continuation period if the minimum target of titration was reached. Subjects titrated to oxycodone/naloxone PR 40 mg/20 mg BID requiring higher oxycodone doses were supplemented with oxycodone PR 10 mg BID. One titration step with oxycodone PR 10 mg BID was allowed, to be performed at the regular titration dates. Subjects were permitted a maximum dose of 50 mg/20 mg oxycodone/naloxone twice daily (100 mg/40 mg total daily dose).

Arm title	Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment

Arm description:

Subjects in the oxycodone/naloxone PR treatment arm that did not reach the minimum target of titration or experiencing intolerable side effects at the end of the Titration Period were switched to the Pick-up Arm. They could also enter the Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment Pick-up Arm at any time during the Titration Period, via an unscheduled visit, due to lack of tolerability or lack of efficacy under treatment with oxycodone/naloxone PR.

Arm type	Experimental
Investigational medicinal product name	Tapentadol Prolonged Release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

All subjects were directly switched from oxycodone/naloxone PR to tapentadol PR using an equianalgesic ratio of 1:5 (oxycodone : tapentadol), together with a down-titration step under tapentadol PR (except for participants on oxycodone/naloxone PR 10 mg/5 mg twice daily).

Number of subjects in period 2[2]	Tapentadol prolonged release	Oxycodone/Naloxone Prolonged Release	Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment
Started	100	62	50
Completed	86	48	35
Not completed	14	14	15
Consent withdrawn by subject	-	4	1
Adverse event, non-fatal	8	1	9
Not specified	-	1	1
Transferred to other arm/group	-	7	-
Lost to follow-up	1	-	-
Lack of efficacy	3	1	4
Protocol deviation	2	-	-

Notes:

[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: Subjects in the oxycodone/naloxone PR treatment arm that did not reach the minimum target of titration or experiencing intolerable side effects at the end of the Titration Period were switched to the Pick-up Arm. They could also enter the Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment Pick-up Arm at any time during the Titration Period or Continuation Period, via an unscheduled visit, due to lack of tolerability or lack of efficacy under treatment with oxycodone/naloxone PR.

Baseline characteristics

Reporting groups	
Reporting group title	Tapentadol Prolonged Release
Reporting group description:	
All participants started with 50 mg tapentadol prolonged release (twice daily). The dose of tapentadol prolonged release was adjusted in increments of 50 mg to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 250 mg twice a day (500 mg total daily dose).	
Reporting group title	Oxycodone/Naloxone Prolonged Release
Reporting group description:	
All participants started with 10 mg/5 mg oxycodone/naloxone prolonged release (twice daily). The dose of oxycodone/naloxone prolonged release could be adjusted in increments of 10 mg/5 mg oxycodone/naloxone to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 50 mg/20 mg oxycodone/naloxone twice daily (100 mg/40 mg total daily dose).	

Reporting group values	Tapentadol Prolonged Release	Oxycodone/Naloxone Prolonged Release	Total
Number of subjects	130	128	258
Age categorical Units: Subjects			
Adults (18-64 years)	88	83	171
From 65-84 years	40	43	83
85 years and over	2	2	4
Age continuous Units: years			
arithmetic mean	58.1	58.4	
standard deviation	± 11.48	± 12.23	-
Gender categorical Units: Subjects			
Female	77	84	161
Male	53	44	97
Dermatol pain present			
Typical dermatol pain radiating beyond the knee towards the foot.			
Units: Subjects			
Yes	113	103	216
No	17	23	40
Missing	0	2	2
Evoked typical dermatol pain			
Typical dermatol pain evoked by stretching of the sciatic nerve.			
Units: Subjects			
Yes	99	92	191
No	31	36	67
Missing	0	0	0
Lumbar radiculopathy			
Lumbar radiculopathy is defined as lumbarspinal nerve or sacralspinal nerve impingement caused by (for example) a herniated disc, resulting in pain and possibly numbness and tingling and/or weakness sensation into one or both legs. A diagnosis of lumbar radiculopathy was assessed according to the following specification: • Typical dermatomal pain: – Radiating beyond the knee towards the foot (sciatica). – Evoked by stretching of the sciatic nerve.			

and • Signs of root dysfunction.			
Units: Subjects			
Yes	76	75	151
No	54	53	107
painDetect			
The painDETECT was a participant completed questionnaire. The questionnaire consists of 14 questions in four domains. Based on these questions a final assessment score was calculated. The minimum score ranged from zero to a maximum of 38. Participants with a score between 0 and 12 were scored as being "negative" (had no neuropathic pain component). A value between 19 and 38 was rated as being "positive" (neuropathic component present). Values from 13 to 18 were scored as being "unclear".			
Units: Subjects			
painDetect positive	96	97	193
painDetect unclear	33	27	60
missing	1	4	5
Sleep Evaluation: Overall Quality of Sleep Last Night			
The sleep evaluation questionnaire was completed by the subject. One of the main concepts is the overall quality of sleep. This was rated as being one of the following: excellent, good, fair or poor.			
Units: Subjects			
excellent	2	4	6
good	37	27	64
fair	49	67	116
poor	42	27	69
missing	0	3	3
History of low back pain - duration of pain			
Units: months			
arithmetic mean	115.8	102.4	
standard deviation	± 121.26	± 101.44	-
Height			
Units: centimeters			
arithmetic mean	168.9	167.1	
standard deviation	± 11	± 9.71	-
Weight			
Units: kilograms			
arithmetic mean	85.3	81.6	
standard deviation	± 18.23	± 18.43	-
Recalled Average Pain Intensity			
The recalled average pain intensity score on the NRS-3 was assessed using the 11-point NRS. This scale recalled the average pain intensity during the last 3 days.			
Units: units on a scale			
arithmetic mean	7.7	7.6	
standard deviation	± 1.04	± 0.95	-
Average Pain Intensity Over Three Days for Pain Radiating Towards or Into the Leg			
Typical dermatomal pain was defined as being pain that radiates beyond the knee towards the foot (sciatica) or pain evoked by stretching of the sciatic nerve. The participant was asked to rate their pain intensity over the past 3 days with regards to this particular pain characteristic. The recalled average pain intensity over the past 3 days for the pain radiating towards or into the leg was assessed by using an 11-point Numeric Rating Scale (NRS), where 0 = no pain and 10 = pain as bad as you can imagine.			
Units: units on a scale			
arithmetic mean	7.5	7.6	

standard deviation	± 1.25	± 1.025	-
Worst Pain Intensity Over the Past 24 Hours			
The recalled worst pain intensity during the last 24 hours was assessed using an 11-point Numeric Rating Scale, where 0 = no pain and 10 = pain as bad as you can imagine. The participant was asked: "Please rate your pain intensity by assessing the one number that best describes your worst pain during the last 24 hours prior to the visit"			
Units: units on a scale			
arithmetic mean	8.1	8	
standard deviation	± 1.03	± 1.06	-
painDETECT Assessment			
The painDETECT was a participant completed questionnaire. The questionnaire consists of 14 questions in four domains. Based on these questions a final assessment score was calculated. The minimum score ranged from zero to a maximum of 38. Participants with a score between 0 and 12 were scored as being "negative" (had no neuropathic pain component). A value between 19 and 38 was rated as being "positive" (neuropathic component present). Values from 13 to 18 were scored as being "unclear".			
Units: units on a scale			
arithmetic mean	22.3	22.5	
standard deviation	± 5.25	± 4.79	-
Neuropathic Pain Symptom Inventory (NPSI) Overall Score Assessment			
In the NPSI the subject rated their symptoms of neuropathic pain. Ten pain questions were answered on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity, e.g. worst burning imaginable). The overall NPSI score was calculated by the summation of all ten responses and ranges between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale			
arithmetic mean	0.598	0.612	
standard deviation	± 0.1769	± 0.1445	-
Neuropathic Pain Symptom Inventory (NPSI) Sub-Score Burning Pain			
The subject rated their symptom of burning pain on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity). The overall sub-score for burning pain was calculated by the summation of all subjects that responded and the response range reported between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale			
arithmetic mean	0.612	0.634	
standard deviation	± 0.2652	± 0.2279	-
Neuropathic Pain Symptom Inventory (NPSI) Sub-Score Pressing Pain			
The subject rated their symptom of pressing pain on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity). The overall sub-score for pressing pain was calculated by the summation of all subjects that responded and the response range reported between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale			
arithmetic mean	0.595	0.608	
standard deviation	± 0.2523	± 0.1848	-
Neuropathic Pain Symptom Inventory (NPSI) Sub-Score Paroxysmal Pain			
The subject rated their symptom of paroxysmal (pain like electric shocks or stabbing) pain on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity).The overall sub-score for paroxysmal pain was calculated by the summation of all subjects that responded and the response range reported between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale			
arithmetic mean	0.638	0.67	
standard deviation	± 0.2312	± 0.172	-
Neuropathic Pain Symptom Inventory (NPSI) Sub-Score Evoked Pain			
The subject rated their symptom of evoked (due to touch) pain on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity). The overall sub-score for evoked pain was calculated by the summation of all subjects that responded and the response range reported			

between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale arithmetic mean standard deviation	 0.555 ± 0.2536	 0.548 ± 0.23	 -
Neuropathic Pain Symptom Inventory (NPSI) Sub-Score Paresthesia/Dysesthesia			
The subject rated their symptom of paresthesia (sensation that is not unpleasant) or dysesthesia (unpleasant) on an 11-point scale; from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity). The overall sub-score for paresthesia/dysesthesia was calculated by the summation of all subjects that responded and the response range reported between 0 (absent) and 1 (worst possible intensity).			
Units: units on a scale arithmetic mean standard deviation	 0.621 ± 0.2292	 0.642 ± 0.1809	 -
Short Form Health Survey (SF-12) Physical Component Summary			
The Short Form Health Survey (SF-12) has several brief broad questions on 8 aspects of health that a subjectked to score over the last week. The physical summary scores were calculated from the individual responses to physical functioning, role physical, bodily pain, general health. A higher score indicates a better perceived state of health. All domains were scored on a scale from 0 (lowest level of health) to 100 (highest level of health), with 100 representing the best possible health state.			
Units: units on a scale arithmetic mean standard deviation	 30.319 ± 7.2739	 31.684 ± 6.8313	 -
Short Form Health Survey (SF-12) Mental Component Summary			
The Short Form Health Survey (SF-12) has several brief broad questions on 8 aspects of health that a subjectked to score over the last week. The mental summary scores were calculated from the individual responses to vitality, social functioning, role-emotional and mental health. A higher score indicates a better perceived state of health. All domains were scored on a scale from 0 (lowest level of health) to 100 (highest level of health), with 100 representing the best possible health state.			
Units: units on a scale arithmetic mean standard deviation	 48.736 ± 11.5697	 45.216 ± 11.7462	 -
EuroQol-5 (EQ-5D) Health Status Index Outcome			
The subject scored the EuroQol-5 questionnaire. The EuroQol-5 questionnaire uses a health state classification with 5 dimensions. Each dimension was assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1 (with 1 indicating "full health" and 0 representing "dead"). The higher the values (the closer the value is to 1) the better the health status in a treatment group.			
Units: units on a scale arithmetic mean standard deviation	 0.3186 ± 0.29464	 0.3392 ± 0.31134	 -
Hospital Anxiety and Depression Scale: Anxiety			
The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale for the symptom severity of anxiety disorders and depression. It comprises 14 items. Seven statements describe anxiety. Each answer is scored on a four-point scale (0-3). All seven answers are summed to a total score with a maximum score of 21 points. A score below 7 is not considered to indicate anxiety. A score of 11 or above is considered to be a case of anxiety.			
Units: units on a scale arithmetic mean standard deviation	 7.3 ± 4.06	 8.2 ± 4.28	 -
Hospital Anxiety and Depression Scale: Depression			

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale for the symptom severity of anxiety disorders and depression. It comprises 14 items. Seven statements describe depression. Each answer is scored on a four-point scale (0-3). All seven answers are summed to a total score with a maximum score of 21 points. A score below 7 is not considered to indicate depression. A score of 11 or above is considered to be a case of depression. A decrease in values over time indicates that there has been an improvement.			
Units: units on a scale			
arithmetic mean	7.4	8	
standard deviation	± 4.08	± 4.08	-
Sleep Evaluation: Number of Awakenings			
The participants were requested to answer the following question: How many times did you wake up during the night? The values were calculated from the data that subjects self-reported for the night prior to their Randomization Visit (Baseline).			
Units: Number of Awakenings			
arithmetic mean	3	2.6	
standard deviation	± 2.8	± 1.67	-
Sleep Evaluation: Number of Hours Slept			
The sleep evaluation questionnaire was completed by the subject. The answer was in response to the question: How long did you sleep last night [hours]?			
Units: hours			
arithmetic mean	5.781	5.675	
standard deviation	± 1.5908	± 1.7118	-
Sleep Evaluation: Latency (Time Taken to Fall Asleep)			
The sleep evaluation questionnaire was completed by the subject. The subject was asked: How long after bedtime/lights out did you fall asleep last night [hours]? The values are for the night prior to the randomization visit.			
Units: hours			
arithmetic mean	1.047	1.203	
standard deviation	± 1.1746	± 1.3029	-

End points

End points reporting groups

Reporting group title	Tapentadol Prolonged Release

Reporting group description:

All participants started with 50 mg tapentadol prolonged release (twice daily). The dose of tapentadol prolonged release was adjusted in increments of 50 mg to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 250 mg twice a day (500 mg total daily dose).

Reporting group title	Oxycodone/Naloxone Prolonged Release

Reporting group description:

All participants started with 10 mg/5 mg oxycodone/naloxone prolonged release (twice daily). The dose of oxycodone/naloxone prolonged release could be adjusted in increments of 10 mg/5 mg oxycodone/naloxone to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 50 mg/20 mg oxycodone/naloxone twice daily (100 mg/40 mg total daily dose).

Reporting group title	Tapentadol prolonged release

Reporting group description:

In the continuation period, subjects continued their end of titration period tapentadol PR dose (stablized dose); however, it was permitted to make a single titration step (up or down; except for subjects already on the maximum dose of tapentadol PR for whom up-titration was not permitted) using the same titration step as used in the titration period.
The continuation period lasted 9 weeks.

Reporting group title	Oxycodone/Naloxone Prolonged Release

Reporting group description:

In the continuation period, subjects continued their end of titration period tapentadol PR dose (stablized dose); however, it was permitted to make a single titration step (up or down; except for subjects already on the maximum dose of tapentadol PR for whom up-titration was not permitted) using the same titration step as used in the titration period.
The continuation period lasted 9 weeks.

Reporting group title	Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment

Reporting group description:

Subjects in the oxycodone/naloxone PR treatment arm that did not reach the minimum target of titration or experiencing intolerable side effects at the end of the Titration Period were switched to the Pick-up Arm. They could also enter the Tapentadol (PR) After Oxycodone/Naloxone (PR) Treatment Pick-up Arm at any time during the Titration Period, via an unscheduled visit, due to lack of tolerability or lack of efficacy under treatment with oxycodone/naloxone PR.

Subject analysis set title	Tapentadol Prolonged Release PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set includes all subjects who are included in the Full Analysis Set and had no major protocol deviations which could impact the primary outcome of this trial. Protocol deviations include the following:
• Violation of inclusion/exclusion criteria
• Time schedule deviations
• Non-compliance regarding intake of IMP
• Inappropriate intake of concomitant medication
• Missing essential data
• Subject not discontinued as per protocol
• Other non-compliance

The Per Protocol Set is independent of the period of the trial.

Subject analysis set title	Oxycodone/Naloxone Prolonged Release PPS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Per Protocol Set includes all subjects who are included in the Full Analysis Set and had no major protocol deviations which could impact the primary outcome of this trial. Protocol deviations include the following:
• Violation of inclusion/exclusion criteria
• Time schedule deviations

• Non-compliance regarding intake of IMP
• Inappropriate intake of concomitant medication
• Missing essential data
• Subject not discontinued as per protocol
• Other non-compliance

The Per Protocol Set is independent of the period of the trial.

Subject analysis set title	Tapentadol Prolonged Release FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set includes all randomized subjects who took at least 1 dose of the IMP and had at least one pain intensity assessment (NRS-3) post baseline.
The Full Analysis Set is independent of the period of the trial.

Subject analysis set title	Oxycodone/Naloxone Prolonged Release FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set includes all randomized subjects who took at least 1 dose of the IMP and had at least one pain intensity assessment (NRS-3) post baseline.
The Full Analysis Set is independent of the period of the trial.

Subject analysis set title	Tapentadol Prolonged Release SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set includes all randomized subjects who took at least 1 dose of Tapentadol Prolonged Release.

Subject analysis set title	Oxycodone/Naloxone Prolonged Release SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set includes all randomized subjects who took at least 1 dose of Tapentadol Prolonged Release.

Primary: Change in the Average Pain Intensity Score on an 11-point Numeric Rating Scale (NRS-3)

End point title	Change in the Average Pain Intensity Score on an 11-point Numeric Rating Scale (NRS-3)

End point description:

For this pain assessment, the subject indicated the level of average pain experienced over the previous 3 days on an 11-point Numeric Rating Scale (NRS-3) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The value reported represents the change from the randomization visit (i.e., the last 3 days in the washout period prior to Investigational Medicinal Product initiation and titration) to the end of the continuation period (i.e., up to 9 weeks on the stable dose). The theoretical values range from -10 to 10. A negative sign indicates a decrease in pain from the start of treatment. The higher the absolute values, the greater the change since the start of treatment (Baseline Visit).

End point type	Primary

End point timeframe:

Baseline (Randomization Visit) to the end of the Continuation Period (Week 12).

End point values	Tapentadol Prolonged Release PPS	Oxycodone/Naloxone Prolonged Release PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	112		
Units: units on a scale				
least squares mean (standard error)	-3.7 (± 0.25)	-2.7 (± 0.26)		

Statistical analyses

Statistical analysis title	Change in mean pain intensity (NRS-3, LOCF) - PPS
Comparison groups	Tapentadol Prolonged Release PPS v Oxycodone/Naloxone Prolonged Release PPS
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 [1]
Method	Inverse normal method
Parameter estimate	Repeat Confidence Interval
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.82
upper limit	-0.184

Notes:

[1] - p-value for testing the non-inferiority (non-inferiority margin = 1.3) based on the inverse normal method, adjusting for multiplicity caused by the group sequential design.

Primary: Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) Total Score

End point title	Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) Total Score

End point description:

The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assessed the severity of symptoms of constipation. Subjects were asked "How severe have each of these symptoms been in the last two weeks?" e.g. "Pain in your stomach". There are 3 subscales: 4 questions on abdominal symptoms, 3 on rectal symptoms and 5 on stool symptoms. Responses were rated on a 5-point Likert scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). If the changes in the overall or subscale scores are positive then there is a worsening in symptoms associated with constipation. The change in the assessment of constipation symptoms (PAC-SYM) total score from the Randomization Visit to the Final Evaluation Visit. The PAC-SYM overall score is the sum of scores of all non-missing items divided by the number of non-missing items (if at least 6 items were non-missing).

End point type	Primary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12).

End point values	Tapentadol Prolonged Release PPS	Oxycodone/Naloxone Prolonged Release PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	117	112		
Units: units on a scale				
least squares mean (standard error)	0.07 (± 0.06)	0.14 (± 0.062)		

Statistical analyses

Statistical analysis title	Change in PAC-SYM total score
Comparison groups	Tapentadol Prolonged Release PPS v Oxycodone/Naloxone Prolonged Release PPS
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001
Method	Inverse normal method
Parameter estimate	Repeat Confidence Interval
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.259
upper limit	0.121

Notes:

[2] - p-value for testing the non-inferiority (non-inferiority margin = 0.7) based on the inverse normal method, adjusting for multiplicity caused by the group sequential design.

Secondary: Change in Recalled Average Pain Intensity at the End of Treatment

End point title	Change in Recalled Average Pain Intensity at the End of Treatment

End point description:

The recalled average pain intensity score on the NRS-3 was assessed using an 11-point Numeric Rating Scale (NRS), on this scale 0 indicated "no pain" and 10 indicated "pain as bad as you can imagine". This scale recorded the average pain intensity recalled by the participant during the previous 3 days. The subject was asked: “Please rate your pain intensity by assessing the one number that best describes your pain on average during the last 3 days (the last 72 hours prior to the visit)”. A negative sign indicates a decrease in pain from the start of treatment. The higher the absolute values, the greater the change since the start of treatment (baseline visit).

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12).

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	126		
Units: units on a scale				
least squares mean (standard error)	-3.7 (± 0.24)	-2.8 (± 0.24)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA

Secondary: Change of Average Pain Intensity Over Three Days for Pain Radiating Towards or Into the Leg

End point title	Change of Average Pain Intensity Over Three Days for Pain Radiating Towards or Into the Leg

End point description:

Typical dermatomal pain was defined as being pain that radiates beyond the knee towards the foot (sciatica) or pain evoked by stretching of the sciatic nerve.
Therefore, the subject was asked to rate their pain intensity over the past 3 days with regards to this particular pain characteristic.
The recalled average pain intensity during the last 24 hours was assessed using an 11-point Numeric rating scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine".
A negative sign indicates that there was a decrease in the average pain radiating towards or into the leg.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: units on a scale				
least squares mean (standard error)	-3.9 (± 0.25)	-2.8 (± 0.25)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone

	Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA

Secondary: Change in Worst Pain Intensity Over the Past 24 Hours at the End of Treatment

End point title	Change in Worst Pain Intensity Over the Past 24 Hours at the End of Treatment

End point description:

The recalled worst pain intensity during the last 24 hours was assessed using an 11-point Numeric rating scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine".
The subject was asked: "Please rate your pain intensity by assessing the one number that best describes your worst pain during the last 24 hours prior to the visit".
A negative change indicates that the pain intensity decreased from the start of the trial.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12).

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: units on a scale				
least squares mean (standard error)	-3.7 (± 0.25)	-2.8 (± 0.25)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA

Secondary: Change in painDETECT Final Assessment at the End of Treatment

End point title	Change in painDETECT Final Assessment at the End of Treatment

End point description:

The painDETECT was a subject completed questionnaire. The questionnaire consists of 14 questions in four domains. Based on these questions a final assessment score was calculated. The minimum score ranged from zero to a maximum of 38. Subjects with a score between 0 and 12 were scored as being "negative" (had no neuropathic pain component). A value between 19 and 38 was rated as being "positive" (neuropathic component present). Values from 13 to 18 were scored as being "unclear". The theoretical range of change in this trial ranged from -38 to 15. A negative change indicated a decrease in their neuropathic component of pain.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12).

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	126		
Units: units on a scale				
least squares mean (standard error)	-10.8 (± 0.67)	-7.9 (± 0.69)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA

Secondary: Change in Neuropathic Pain Symptom Inventory (NPSI) Overall Score Assessment at the End of Treatment

End point title	Change in Neuropathic Pain Symptom Inventory (NPSI) Overall Score Assessment at the End of Treatment

End point description:

In the Neuropathic Pain Symptom Inventory (NPSI) the subject rated their symptoms of neuropathic pain. Ten pain questions were answered on an 11-point scale, from 0 (symptom not present) to 10 (symptom at its worst imaginable intensity, e.g. worst burning imaginable). The overall NPSI score was calculated by the summation of all ten responses and ranges between 0 and 1. For pain descriptions burning, pressing, paroxysmal (pain like electric shocks or stabbing), evoked (due to touch) and paresthesia (sensation that is not unpleasant) or dysesthesia (unpleasant) sub-scores are reported. The overall values reported for all subjects that completed the questionnaire are shown. A symptom was absent if the value is 0, the symptom was present in all subjects and all participants rated it at its worst possible intensity if a value is 1. A negative change indicates that the intensity of the symptom has decreased since the start of treatment.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: units on a scale				
least squares mean (standard error)				
Overall Score	-0.353 (± 0.0208)	-0.248 (± 0.0211)		
Sub-Score Burning Pain	-0.375 (± 0.0249)	-0.278 (± 0.0252)		
Sub-Score Pressing Pain	-0.331 (± 0.0235)	-0.226 (± 0.0238)		
Sub-Score Paroxysmal Pain	-0.385 (± 0.0246)	-0.283 (± 0.025)		
Sub-score Evoked Pain	-0.334 (± 0.0222)	-0.225 (± 0.0225)		
Sub-score Paresthesia/Dysesthsia	-0.363 (± 0.0229)	-0.252 (± 0.0231)		

Statistical analyses

Statistical analysis title	Least Square Means - Overall NPSI Score
Comparison groups	Oxycodone/Naloxone Prolonged Release FAS v Tapentadol Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Least Square Means - Burning Pain
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA

Statistical analysis title	Least Square Means - Pressing Pain
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA

Statistical analysis title	Least Square Means - Paroxysmal Pain
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANCOVA

Statistical analysis title	Least Square Means - Evoked Pain
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Least Square Means - Paresthesia/Dysesthesia
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Changes in the Short Form Health Survey (SF-12) at the End of Treatment

End point title	Changes in the Short Form Health Survey (SF-12) at the End of Treatment

End point description:

The Short Form Health Survey (SF-12) has several brief broad questions on 8 aspects of health (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that a subject was asked to score over the last week. The physical and mental summary scores were calculated from the individual responses. A higher score indicates a better perceived state of health. All domains were scored on a scale from 0 (lowest level of health) to 100 (highest level of health), with 100 representing the best possible health state. The change in the SF-12

score shows an improvement in health from baseline if the values are positive. The higher the value the greater the improvement since starting the trial.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: units on a scale				
least squares mean (standard error)				
Physical Functioning	8.358 (± 0.8262)	5.073 (± 0.8361)		
Role-Physical	7.26 (± 0.7115)	4.668 (± 0.7224)		
Bodily Pain	10.99 (± 0.9462)	7.458 (± 0.957)		
General Health	8.447 (± 0.8702)	4.309 (± 0.8818)		
Vitality	4.943 (± 0.8062)	1.468 (± 0.8179)		
Social Functioning	5.246 (± 0.887)	2.286 (± 0.8997)		
Role-Emotional	4.764 (± 0.9472)	2.587 (± 0.9807)		
Mental Health	5.158 (± 0.8386)	2.973 (± 0.8575)		
Physical Component Summary	9.735 (± 0.7948)	6.202 (± 0.8058)		
Mental Component Summary	3.077 (± 0.8457)	1.146 (± 0.8679)		

Statistical analyses

Statistical analysis title	Least Square Means - SF-12 Physical functioning
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Role-physical
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Bodily pain
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 General health
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Vitality
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Social functioning
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Role-emotional
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	ANCOVA

Statistical analysis title	Least Square Means - SF-12 Mental health
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	ANCOVA

Statistical analysis title	Least Square Means - Physical Component Summary
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA

Statistical analysis title	Least Square Means - Mental Component Summary
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	ANCOVA

Secondary: Change in EuroQol-5 (EQ-5D) Health Status Index Outcome at the End of Treatment

End point title	Change in EuroQol-5 (EQ-5D) Health Status Index Outcome at the End of Treatment

End point description:

The subject scored the EuroQol-5 questionnaire. The EuroQol-5 questionnaire uses a health state classification with 5 dimensions. Each dimension was assessed on a 3-point ordinal scale (1=no problems, 2=some problems, 3=extreme problems). The responses to the five EQ-5D dimensions were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1 (with 1 indicating "full health" and 0 representing "dead"). The higher the values (the closer the value is to 1) the better the health status in a treatment group.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: units on a scale				
least squares mean (standard error)	0.3395 (± 0.02785)	0.2398 (± 0.02811)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA

Secondary: Change in Hospital Anxiety and Depression Scale at the End of Treatment: Anxiety

End point title	Change in Hospital Anxiety and Depression Scale at the End of

	Treatment: Anxiety

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale for the symptom severity of anxiety disorders and depression. It comprises 14 items. Seven statements describe anxiety. Each answer is scored on a four-point scale (0-3). All seven answers are summed to a total score with a maximum score of 21 points. A score below 7 is not considered to indicate anxiety. A score of 11 or above is considered to be a case of anxiety. A negative sign indicates that there has been a decrease in anxiety since the start of treatment.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	126		
Units: units on a scale				
least squares mean (standard error)	-2.1 (± 0.34)	-1.1 (± 0.35)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	ANCOVA

Secondary: Change in Hospital Anxiety and Depression Scale at the End of Treatment: Depression

End point title	Change in Hospital Anxiety and Depression Scale at the End of Treatment: Depression

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale for the symptom severity of anxiety disorders and depression. It comprises 14 items. Seven statements describe depression. Each answer is scored on a four-point scale (0-3). All seven answers are summed to a total score with a maximum score of 21 points. A score below 7 is not considered to indicate depression. A score of 11 or above is considered to be a case of depression. A decrease in values over time indicates that there has been an improvement. A negative change value indicates a decrease in the depression score since the start of treatment.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	114		
Units: units on a scale				
least squares mean (standard error)	-2.4 (± 0.34)	-1.1 (± 0.36)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANCOVA

Secondary: Patient Global Impression of Change at the End of Treatment

End point title	Patient Global Impression of Change at the End of Treatment

End point description:

In the Patient Global Impression of Change (PGIC) the subject indicated the perceived change over the treatment period. PGIC is a 7 point scale depicting a patient's rating of overall improvement. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	125		
Units: subjects				
Very Much Improved	27	18		
Much Improved	43	19		
Minimally Improved	32	46		
No Change	21	29		
Minimally Worse	3	6		

Much Worse	2	4		
Very Much Worse	1	3		

Statistical analyses

Statistical analysis title	Fisher’s exact test (α = 0.05, two-sided)
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Fisher exact

Secondary: Clinician Global Impression of Change at the End of Treatment

End point title	Clinician Global Impression of Change at the End of Treatment

End point description:

In the Clinician Global Impression of Change (CGIC) the clinician indicated the perceived change over the treatment period. The clinician was requested to choose one of seven categories for each subject. The Clinician rated the subjcect's change as “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.”

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	128	123		
Units: subjects				
Very Much Improved	32	18		
Much Improved	44	25		
Minimally Improved	22	37		
No Change	21	26		
Minimally Worse	6	7		
Much Worse	3	9		
Very Much Worse	0	1		

Statistical analyses

Statistical analysis title	Fisher’s exact test (α = 0.05, two-sided)
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Fisher exact

Secondary: Sleep Evaluation at the End of Treatment: Change in the Number of Awakenings

End point title	Sleep Evaluation at the End of Treatment: Change in the Number of Awakenings

End point description:

The participants were requested to answer the question: How many times did you wake up during the night? The values were calculated from the data that participants self-reported. The change from baseline in the number of times of waking up during the night in a treatment group is reported. A negative symbol indicates that there was a reduction in the number of awakenings.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	128	123		
Units: number of awakenings				
least squares mean (standard error)	-0.8 (± 0.15)	-0.5 (± 0.16)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	ANCOVA

Secondary: Sleep Evaluation at the End of Treatment: Change in the Number of Hours Slept

End point title	Sleep Evaluation at the End of Treatment: Change in the Number of Hours Slept

End point description:

The sleep evaluation questionnaire was completed by the participant. The answer was in response to the question: Sleep evaluation: How long did you sleep last night [hours]? The value reported is the change in the number of hours of sleep from baseline. The positive value indicates that there was an increase in the number of hours of sleep in a treatment group.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	114		
Units: hours				
least squares mean (standard error)	0.46 (± 0.1714)	0.412 (± 0.1763)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Oxycodone/Naloxone Prolonged Release FAS v Tapentadol Prolonged Release FAS
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	ANCOVA

Secondary: Sleep Evaluation at the End of Treatment: Change in Latency (Change in the Time Taken to Fall Asleep)

End point title	Sleep Evaluation at the End of Treatment: Change in Latency (Change in the Time Taken to Fall Asleep)

End point description:

The sleep evaluation questionnaire was completed by the participant. The participant was asked: How long after bedtime/lights out did you fall asleep last night [hours]? The values are for the night prior to the visits. The negative change from baseline indicates that the time to falling asleep decreased from baseline in a treatment group.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Visit (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	114		
Units: hours				
least squares mean (standard error)	-0.3 (± 0.1)	-0.177 (± 0.1025)		

Statistical analyses

Statistical analysis title	Least Square Means for Treatment Comparison
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378
Method	ANCOVA

Secondary: Comparison of the Number of Participants Affected by Gastrointestinal Treatment Emergent Adverse Events (TEAEs) Typical for Opioids

End point title	Comparison of the Number of Participants Affected by Gastrointestinal Treatment Emergent Adverse Events (TEAEs) Typical for Opioids

End point description:

In this outcome measure the number of participants affected by early gastrointestinal-related treatment emergent adverse events (TEAEs). As the trial population was opioid-naïve this was considered of interest. The composition score from participant who reported: Mild, moderate to severe nausea and/or Mild, moderate to severe vomiting and/or Mild, moderate to severe constipation was evaluated.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit) to End of Titration Period (End of Week 3)

End point values	Tapentadol Prolonged Release	Oxycodone/Naloxone Prolonged Release		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: subjects	42	59		

Statistical analyses

Statistical analysis title	Fisher’s exact test (α = 0.05, two-sided)
Comparison groups	Tapentadol Prolonged Release v Oxycodone/Naloxone Prolonged Release
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fisher exact

Secondary: Composite Event Based Comparison of Gastrointestinal Treatment Emergent Adverse Events (TEAEs) Typical for Opioids

End point title	Composite Event Based Comparison of Gastrointestinal Treatment Emergent Adverse Events (TEAEs) Typical for Opioids

End point description:

In this outcome measure the early gastrointestinal-related treatment emergent events (TEAEs) were evaluated. As the trial population was opioid-naïve this was considered of interest.
The composition score of reported events of Mild, moderate to severe nausea and/or Mild, moderate to severe vomiting and/or Mild, moderate to severe constipation was evaluated.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Week 3 (End of Titration Period)

End point values	Tapentadol Prolonged Release	Oxycodone/Naloxone Prolonged Release		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: number of events	56	81		

Statistical analyses

Statistical analysis title	Fisher’s exact test (α = 0.05, two-sided)
Comparison groups	Tapentadol Prolonged Release v Oxycodone/Naloxone Prolonged Release
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Fisher exact

Secondary: Sleep evaluation: Overall quality of sleep last night

End point title	Sleep evaluation: Overall quality of sleep last night

End point description:

The sleep evaluation questionnaire was completed by the subject. The questionnaire measures 4 main concepts: 1 of the 4 main concepts being the overall quality of sleep.
The subject rated this categorically as being one of the following: excellent, good, fair or poor.
The improvement, no change or worsening is reported based on the replies scored by the subject given at their End of Continuation Visit.

End point type	Secondary

End point timeframe:

Baseline (Randomization Visit); End of Continuation Period (Week 12)

End point values	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	114		
Units: subjects				
Improvement	62	43		
No change	46	56		
Worsening	16	15		

Statistical analyses

Statistical analysis title	Fisher’s exact test (α = 0.05, two-sided)
Comparison groups	Tapentadol Prolonged Release FAS v Oxycodone/Naloxone Prolonged Release FAS
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events occurring after first administration of study drug were listed (Treatment emergent adverse events - TEAEs) and within 3 days after the last intake were considered as TEAEs. Pre-treatment adverse events that worsened were considered TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Tapentadol Prolonged Release FAS

Reporting group description:

All participants started with 50 mg tapentadol prolonged release (twice daily). The dose of tapentadol prolonged release was adjusted in increments of 50 mg to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 250 mg twice a day (500 mg total daily dose). After titration participants remained on the stable dose for 9 weeks.

Reporting group title	Oxycodone/Naloxone Prolonged Release FAS

Reporting group description:

All participants started with 10 mg/5 mg oxycodone/naloxone prolonged release (twice daily). The dose of oxycodone/naloxone prolonged release could be adjusted in increments of 10 mg/5 mg oxycodone/naloxone to a level that provided adequate analgesia. The next titration step was after a minimum of 3 days on a dose. Participants were permitted a maximum dose of 50 mg/20 mg oxycodone/naloxone twice daily (100 mg/40 mg total daily dose). After titration participants remained on the stable dose for 9 weeks.

Reporting group title	Tapentadol (PR) after Oxycodone/Naloxone (PR) treatment

Reporting group description:

Subjects in the oxycodone/naloxone PR treatment arm experiencing lack of efficacy, intolerable side effects, or not reaching the minimum target of titration at the end of the Titration Period could be switched to tapentadol PR in the Pick-up Arm.

Serious adverse events	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS	Tapentadol (PR) after Oxycodone/Naloxone (PR) treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 130 (2.31%)	2 / 128 (1.56%)	0 / 50 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (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
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (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
Infections and infestations			
Tracheobronchitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tapentadol Prolonged Release FAS	Oxycodone/Naloxone Prolonged Release FAS	Tapentadol (PR) after Oxycodone/Naloxone (PR) treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 130 (76.92%)	106 / 128 (82.81%)	29 / 50 (58.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 130 (5.38%)	4 / 128 (3.13%)	0 / 50 (0.00%)
occurrences (all)	7	4	0
Hypertension			

subjects affected / exposed	3 / 130 (2.31%)	1 / 128 (0.78%)	2 / 50 (4.00%)
occurrences (all)	3	1	2
Hypertensive crisis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Surgical and medical procedures			
Vocal cord polypectomy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	39 / 130 (30.00%)	31 / 128 (24.22%)	2 / 50 (4.00%)
occurrences (all)	42	32	2
Influenza like illness			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Local swelling			
subjects affected / exposed	0 / 130 (0.00%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Thirst			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dry throat			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Respiratory distress			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Claustrophobia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Drug dependence			

subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Euphoric mood			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	4 / 130 (3.08%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	4	2	0
Restlessness			
subjects affected / exposed	2 / 130 (1.54%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Sleep disorder			
subjects affected / exposed	1 / 130 (0.77%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Tic			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Withdrawal syndrome			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Investigations			
Biopsy chest wall			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Blood phosphorus decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Blood testosterone decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0

Hepatic enzyme increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Injury			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 130 (0.00%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Thermal burn			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Tachycardia paroxysmal			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Balance disorder			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	24 / 130 (18.46%)	22 / 128 (17.19%)	6 / 50 (12.00%)
occurrences (all)	26	22	6
Headache			
subjects affected / exposed	10 / 130 (7.69%)	5 / 128 (3.91%)	1 / 50 (2.00%)
occurrences (all)	10	5	1
Hypoaesthesia			
subjects affected / exposed	3 / 130 (2.31%)	5 / 128 (3.91%)	1 / 50 (2.00%)
occurrences (all)	3	6	1
Neuromuscular blockade			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Orthostatic intolerance			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Sciatica			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	3 / 130 (2.31%)	3 / 128 (2.34%)	0 / 50 (0.00%)
occurrences (all)	4	3	0
Speech disorder			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1

Tremor			
subjects affected / exposed	1 / 130 (0.77%)	2 / 128 (1.56%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Vertigo CNS origin			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Cervicobrachial syndrome			
subjects affected / exposed	2 / 130 (1.54%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 130 (0.00%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	2 / 130 (1.54%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			

subjects affected / exposed	5 / 130 (3.85%)	5 / 128 (3.91%)	1 / 50 (2.00%)
occurrences (all)	5	6	1
Bowel movement irregularity			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	20 / 130 (15.38%)	33 / 128 (25.78%)	1 / 50 (2.00%)
occurrences (all)	20	34	1
Diarrhoea			
subjects affected / exposed	6 / 130 (4.62%)	0 / 128 (0.00%)	3 / 50 (6.00%)
occurrences (all)	6	0	3
Dry mouth			
subjects affected / exposed	9 / 130 (6.92%)	7 / 128 (5.47%)	0 / 50 (0.00%)
occurrences (all)	9	8	0
Dyspepsia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Eructation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 130 (0.77%)	3 / 128 (2.34%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Gastritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	29 / 130 (22.31%)	23 / 128 (17.97%)	7 / 50 (14.00%)
occurrences (all)	31	23	7
Paraesthesia oral			

subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Saliva altered			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	10 / 130 (7.69%)	21 / 128 (16.41%)	4 / 50 (8.00%)
occurrences (all)	11	24	4
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Erythema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Haematidrosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	8 / 130 (6.15%)	13 / 128 (10.16%)	4 / 50 (8.00%)
occurrences (all)	8	13	4
Pruritus			
subjects affected / exposed	8 / 130 (6.15%)	11 / 128 (8.59%)	0 / 50 (0.00%)
occurrences (all)	9	12	0
Rash			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Rash pruritic			

subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Renal pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Myosclerosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 130 (0.77%)	2 / 128 (1.56%)	0 / 50 (0.00%)
occurrences (all)	1	2	0
Plantar fasciitis			

subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Tendon pain			
subjects affected / exposed	2 / 130 (1.54%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 128 (0.78%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Cystitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	3 / 130 (2.31%)	3 / 128 (2.34%)	0 / 50 (0.00%)
occurrences (all)	3	3	0
Gastrointestinal infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 130 (6.15%)	5 / 128 (3.91%)	2 / 50 (4.00%)
occurrences (all)	8	5	2
Oral herpes			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	2 / 130 (1.54%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0

Pulpitis dental			
subjects affected / exposed	2 / 130 (1.54%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Tooth abscess			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 130 (3.08%)	5 / 128 (3.91%)	0 / 50 (0.00%)
occurrences (all)	5	5	0
Fluid retention			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Exostosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 130 (0.00%)	0 / 128 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26095455