Clinical trial results:
An open label trial, enrolling subjects aged 6 years to less than 18 years suffering from pain requiring prolonged release opioid treatment, to evaluate the safety and efficacy of tapentadol PR versus morphine PR, followed by an open label extension.

Summary

EudraCT number	2012-004360-22
Trial protocol	GB DE PT ES SK BE IT SI HU BG HR FR
Global end of trial date	15 October 2018

Results information

Result version number	v1
This version publication date	09 March 2019
First version publication date	09 March 2019

Trial information

Trial identification

Sponsor protocol code	KF5503-66

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02151682
WHO universal trial number (UTN)	U1111-1154-4572

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 0049 2415693223, clinical-trials@grunenthal.com
Scientific contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 0049 2415693223, clinical-trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000325-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2017
Global end of trial reached?	Yes
Global end of trial date	15 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial objectives for Part 1 of the trial were:
• To assess the 14-day safety and efficacy of tapentadol prolonged release (PR) in comparison to morphine PR in subjects aged from 6 years to less than 18 years suffering from long-term pain requiring prolonged release opioid treatment.
• To evaluate the pharmacokinetic profile of tapentadol and its major metabolite tapentadol-O-glucuronide after multiple doses of tapentadol PR tablets.

The trial objective for Part 2 of the trial was:
• To describe the long-term safety profile covering up to a 12-month period with treatment of tapentadol PR taken twice daily (Tapentadol Period) in subjects aged 6 years or older suffering from long-term pain requiring prolonged-release opioid treatment, or in subjects without tapentadol treatment (Observation Period) aged 6 years or older who had received at least 1 dose of investigational medicinal product (IMP).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Morphine is a gold standard in the analgesic management of severe pain (De Conno and Kress. Palliative Medicine 2006; 20: S1) including cancer pain (Broomhead et al. J Pain Symptom Manage 1997; 14: 63-73). Morphine is among the top 10 medications given to children in inpatient settings (Lasky et al. Clin Ther 2012; 34 (3): 720-7). It is one of the World Health Organisation Step III pain medications, authorized for use in children.

Actual start date of recruitment	29 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 1

Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Chile: 7
Worldwide total number of subjects	69
EEA total number of subjects	62

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)	19
Adolescents (12-17 years)	50
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial started on 29 Apr 2015 with the enrollment of the first subject in Part 1.
Part 1 was completed on 18 Oct 2017 when the last subject completed the last assessment for the primary endpoint.
The last subject's last assessment in Part 2 was on 15 Oct 2018.

Pre-assignment

Screening details:

73 Subjects signed an informed consent form (assented) for this trial. 1 subject withdrew consent and 2 did not meet in-/exclusion criteria.
70 Subjects were allocated to IMP: 1 of the allocated subjects was not treated, resulting in 69 subjects who were dosed in Part 1.

Pre-assignment period milestones

Number of subjects started	73[1]
Number of subjects completed	69

Pre-assignment subject non-completion reasons

Reason: Number of subjects	not specified: 1
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Inclusion criteria not me/exclusion criteria met: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 73 subjects signed an informed consent form (assented). 1 subject withdrew consent and 2 did not meet in-/exclusion criteria.
70 subjects were allocated to investigational medicinal product (IMP). 1 of the allocated subjects was not treated, resulting in 69 subjects who were dosed in Part 1.

Period 1

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

Blinding implementation details:

Subjects were stratified using interactive response technology: by age group (6 years to less than 12 years and 12 years to less than 18 years, at the second visit [Allocation Visit]) so that at least 25% of subjects were in the younger age group, and by underlying pain condition (cancer/non-cancer-related pain).
Randomization was carried out in blocks and in a 2:1 ratio (tapentadol PR to morphine PR). The block size was not disclosed to sites before the conduct of Part 1 was completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Morphine prolonged release (Part 1)

Arm description:

The treatment group comprised 7 subjects aged 6 years to less than 12 years and 17 subjects aged 12 years to less than 18 years.
Starting doses varied from 10 to 40 milligrams (mg) morphine PR twice daily depending on subject’s weight; if necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 200 mg per day.

Arm type	Active comparator

Investigational medicinal product name	Morphine prolonged release
Investigational medicinal product code	
Other name	Morphine sulfate prolonged-release tablets, MST Mundipharma (Trade Mark)
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg or 30 mg tablets were taken orally twice daily. The dose was based on the subject's weight. The dose had not to exceed a total of 200 mg per day for subjects weighing 55 kg or more.

Arm title	Tapentadol prolonged release (Part 1)

Arm description:

The treatment group comprised 12 subjects aged 6 years to less than 12 years and 33 subjects aged 12 years to less than 18 years.
Subjects starting doses varied from 25 to 100 mg tapentadol PR twice daily depending on subject’s weight. If necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 500 mg per day.

Arm type	Experimental
Investigational medicinal product name	Tapentadol prolonged release
Investigational medicinal product code	
Other name	Tapentadol prolonged-release tablet, Palexia retard, Nucynta, Yantil
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg or 100 mg tablets were taken orally twice daily. The dose was based on the subject's weight. The dose had not to exceed a total of 500 mg per day for subjects weighing 55 kg or more.

Number of subjects in period 1	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)
Started	24	45
Completed	22	40
Not completed	2	5
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2
Technical problems	-	1
No need for opioid	1	1
Reason missing	1	-

Period 2

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

Blinding implementation details:

Subjects who completed Part 1 (on tapentadol PR or morphine PR) could continue or switch to treatment with tapentadol PR for up to 12 months in Part 2.
Subjects who completed Part 1 (on tapentadol PR or morphine PR) or discontinued early from Part 1 could continue directly in the Observation Period in Part 2.
Subjects who completed Part 1 (on tapentadol PR or morphine PR) and discontinued from tapentadol PT treatment in Part 2 could enter the Observation Period in Part 2.

Arms

Are arms mutually exclusive?	No
Arm title	Tapentadol prolonged release in Part 2

Arm description:

36 subjects who completed Part 1 of the trial (26 on tapentadol PR and 10 subjects on morphine PR) continued treatment or switched to treatment with tapentadol PR for up to 12 months in Part 2.

Arm type	Experimental
Investigational medicinal product name	Tapentadol prolonged release
Investigational medicinal product code	
Other name	Tapentadol prolonged-release tablet, Palexia retard; Nucynta, Yantil
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects on tapentadol PR continued on the current dose and if necessary could modify their tapentadol PR dosage. Subjects who were randomized to morphine PR in Part 1 were rotated to tapentadol PR with 70 percent of their current morphine equivalent dose or lower. The dosage could be increased gradually up to approximately 4.5 mg/kg tapentadol PR twice daily.

Arm title	Observation Period After Tapentadol in Part 1

Arm description:

18 Subjects who completed tapentadol PR treatment in Part 1 or discontinued tapentadol treatment early in Part 1 directly entered the Observation Period of Part 2 for up to 12 months.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Arm title	Observation Period After Morphine in Part 1

Arm description:

14 Subjects who completed morphine PR treatment in Part 1 or discontinued morphine treatment early in Part 1 directly entered the Observation Period of Part 2 for up to 12 months.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Arm title	Observation Period After Tapentadol in Part 2

Arm description:

26 Subjects who completed morphine PR or tapentadol PR treatment in Part 1 of the trial entered the Observation Period in Part 2 for up to 12 months after they had discontinued from tapentadol PR treatment in Part 2.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Tapentadol prolonged release in Part 2	Observation Period After Tapentadol in Part 1	Observation Period After Morphine in Part 1
Started	36	18	14
Completed	8	14	14
Not completed	28	4	0
No need for opioid treatment anymore	13	-	-
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	3	-	-
Final post-treatment visit not performed	1	-	-
Missing	-	1	-
Lack of efficacy	3	-	-
Protocol deviation	1	-	-
not specified	6	-	-

Number of subjects in period 2	Observation Period After Tapentadol in Part 2
Started	26
Completed	19
Not completed	7
No need for opioid treatment anymore	-
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Final post-treatment visit not performed	-
Missing	3
Lack of efficacy	-
Protocol deviation	-
not specified	2

Baseline characteristics

Reporting groups	
Reporting group title	Morphine prolonged release (Part 1)
Reporting group description:	
The treatment group comprised 7 subjects aged 6 years to less than 12 years and 17 subjects aged 12 years to less than 18 years. Starting doses varied from 10 to 40 milligrams (mg) morphine PR twice daily depending on subject's weight; if necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 200 mg per day.	
Reporting group title	Tapentadol prolonged release (Part 1)
Reporting group description:	
The treatment group comprised 12 subjects aged 6 years to less than 12 years and 33 subjects aged 12 years to less than 18 years. Subjects starting doses varied from 25 to 100 mg tapentadol PR twice daily depending on subject's weight. If necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 500 mg per day.	

Reporting group values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)	Total
Number of subjects	24	45	69
Age categorical Units: Subjects			
6 years to less than 12 years	7	12	19
12 years to less than 18 years	17	33	50
Age continuous Units: years			
arithmetic mean	13.2	13.2	
standard deviation	± 2.8	± 2.8	-
Gender categorical Units: Subjects			
Female	10	22	32
Male	14	23	37
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	7	11
Not Hispanic or Latino	20	36	56
Unknown or Not Reported	0	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	0	0	0
White	24	44	68
More than one race	0	0	0
Unknown or not reported	0	0	0
Pain cause Units: Subjects			

Cancer-related pain (6 to less than 12 years)	1	0	1
Cancer-related pain (12 to less than 18 years)	4	9	13
Non-cancer-related pain (6 to less than 12 years)	6	12	18
Non-cancer-related pain (12 to less than 18 years)	13	24	37
Type of pain			
Units: Subjects			
Neuropathic	4	9	13
Nociceptive/somatic	13	28	41
Nociceptive/visceral	0	0	0
Neuropathic and nociceptive/somatic	6	6	12
Neuropathic and nociceptive/visceral	0	0	0
Nociceptive/somatic and nociceptive/visceral	1	1	2
All of the pain types	0	1	1
Height			
Units: meter			
arithmetic mean	1.580	1.557	
standard deviation	± 0.170	± 0.166	-
Weight			
Units: kilograms			
arithmetic mean	50.13	49.95	
standard deviation	± 14.97	± 16.98	-
Body mass index			
Units: kilograms per square meter			
arithmetic mean	19.63	20.07	
standard deviation	± 4.12	± 4.68	-
Pain intensity (VAS)			
Subjects were asked to indicate the current level of pain intensity at the time of assessment on a validated vertical visual analog scale (VAS). It was scored such that a score of 0 was equivalent to "no pain" and a score of 100 was equivalent to "pain as bad as it could be". VAS data at baseline were available for 32 subjects on tapentadol PR and for 19 subjects on morphine PR (51 of 69 subjects overall).			
Units: Units on a scale			
arithmetic mean	50.8	47.8	
standard deviation	± 32.5	± 32.4	-
Pain intensity (FPS-R)			
Pain intensity was assessed on a revised Faces Pain Scale (FPS-R). The FPS-R is a validated self-reported 6-point scale with 0 representing "no pain" and 10 representing "very much pain". Facial representations were used to indicate how much the pain hurts. FPS-R data at baseline were available for 32 subject on tapentadol PR and for 19 subjects on morphine PR (51 of 69 subjects overall).			
Units: Units on a scale			
arithmetic mean	4.2	4.6	
standard deviation	± 3.0	± 3.3	-

End points

End points reporting groups

Reporting group title	Morphine prolonged release (Part 1)

Reporting group description:

The treatment group comprised 7 subjects aged 6 years to less than 12 years and 17 subjects aged 12 years to less than 18 years.
Starting doses varied from 10 to 40 milligrams (mg) morphine PR twice daily depending on subject's weight; if necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 200 mg per day.

Reporting group title	Tapentadol prolonged release (Part 1)

Reporting group description:

The treatment group comprised 12 subjects aged 6 years to less than 12 years and 33 subjects aged 12 years to less than 18 years.
Subjects starting doses varied from 25 to 100 mg tapentadol PR twice daily depending on subject's weight. If necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 500 mg per day.

Reporting group title	Tapentadol prolonged release in Part 2

Reporting group description:

36 subjects who completed Part 1 of the trial (26 on tapentadol PR and 10 subjects on morphine PR) continued treatment or switched to treatment with tapentadol PR for up to 12 months in Part 2.

Reporting group title	Observation Period After Tapentadol in Part 1

Reporting group description:

18 Subjects who completed tapentadol PR treatment in Part 1 or discontinued tapentadol treatment early in Part 1 directly entered the Observation Period of Part 2 for up to 12 months.

Reporting group title	Observation Period After Morphine in Part 1

Reporting group description:

14 Subjects who completed morphine PR treatment in Part 1 or discontinued morphine treatment early in Part 1 directly entered the Observation Period of Part 2 for up to 12 months.

Reporting group title	Observation Period After Tapentadol in Part 2

Reporting group description:

26 Subjects who completed morphine PR or tapentadol PR treatment in Part 1 of the trial entered the Observation Period in Part 2 for up to 12 months after they had discontinued from tapentadol PR treatment in Part 2.

Primary: Number of subjects classified as responder (Part 1)

End point title	Number of subjects classified as responder (Part 1)

End point description:

A subject was defined as responder if both of the following criteria were met:
- Completion of the 14-day Treatment Period (Part 1).
- One of the following calculated from the scheduled pain assessments ("pain right now") documented during the last 3 days of the Treatment Period:
• Average pain less than 50 on a visual analog scale (VAS, range 0 [no pain] to 100 [pain as bad as it could be]) for subjects aged 12 years to less than 18 years; or less than 5 on the Faces Pain Scale-revised (FPS-R, range 0 [no pain] and 10 [very much pain]) for subjects aged 6 years to less than 12 years.
• Average reduction from baseline of pain greater than or equal to 20 on a VAS for subjects aged 12 years to less than 18 years; or greater than or equal to 2 on the FPS-R for subjects aged 6 years to less than 12 years.

The proportion of subjects classified as responders was assessed and compared between the treatment groups.

End point type	Primary

End point timeframe:

From Day 1 up to Day 14 (End of Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[1]	45[2]		
Units: Number of subjects				
Number of subjects classified as responder	19	32		

Notes:

[1] - Full Analysis Set; missing pain assessments (last 3 days) were imputed using multiple imputation.

[2] - Full Analysis Set; missing pain assessments (last 3 days) were imputed using multiple imputation.

Statistical analyses

Statistical analysis title	Responder analysis

Statistical analysis description:

A logistic regression model was fitted to the response using baseline pain, age group, treatment and underlying pain condition as explanatory variables, followed by a Farrington-Manning test for non-inferiority, based on Full Analysis Set.

Comparison groups	Morphine prolonged release (Part 1) v Tapentadol prolonged release (Part 1)
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.079 [4]
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	-0.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.19
upper limit	0.06

Notes:

[3] - A confidence interval for the risk difference (RD) completely above the pre-specified non-inferiority margin of -0.2 represents non-inferiority of tapentadol prolonged-release versus morphine prolonged-release.

[4] - The p-value is based on Farrington-Manning variance estimator using a pre-specified non-inferiority margin of -0.2. A 1-sided alpha of <0.1 was used. A p-value <0.1 represents non-inferiority.

Secondary: Extent of constipation (Part 1)

End point title	Extent of constipation (Part 1)

End point description:

Constipation was assessed using the modified constipation assessment scale (mCAS). This is an 8-item questionnaire where the observer has scored constipation on a nominal scale (no Problem [score 0], some problem [score 1] or severe Problem [score 2]). The response to an item could also be scored as "unable to assess".
The Total Score can vary from 0-16; the higher the Total Score the higher the extent of constipation. A positive change from Day 1 to Day 14 indicates a worsening, a negative change an improvement.

End point type	Secondary

End point timeframe:

From Day 1 to Day 14 (End of Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[5]	45[6]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 1 (N = 23/40)	2.7 (± 3.0)	1.5 (± 1.4)		
Day 14 (N = 24/41)	2.7 (± 2.4)	1.8 (± 2.0)		
Change from Day 1 (N = 23/39)	-0.1 (± 1.6)	0.4 (± 2.4)		

Notes:

[5] - Safety Set

[6] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability (number of TEAEs per subjects)

End point title	Tolerability (number of TEAEs per subjects)

End point description:

Tolerability was assessed by the number of subjects with exactly 1 to more than 5 treatment emergent adverse events (TEAE) by treatment group during the different trial periods, on a subject level.

End point type	Secondary

End point timeframe:

Part 1: Day 1 (Start of Part 1) to day 14; Part 2: Day 15 to Day 379 (End of Part 2)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)	Tapentadol prolonged release in Part 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[7]	45[8]	36[9]	
Units: Number of subjects				
Subjects without any TEAEs	12	19	6	
Subjects with at least 1 TEAE	12	26	30	
Subjects with exactly 1 TEAE	1	7	5	
Subjects with exactly 2 TEAEs	2	5	2	
Subjects with exactly 3 TEAEs	2	4	2	
Subjects with exactly 4 TEAEs	2	1	4	
Subjects with exactly 5 TEAEs	1	3	3	
Subjects with more than 5 TEAEs	4	6	14	

Notes:

[7] - Safety Set

[8] - Safety Set

[9] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability (number of subjects with related TEAEs)

End point title	Tolerability (number of subjects with related TEAEs)

End point description:

Tolerability was assessed by the number of subjects with treatment emergent adverse events (TEAEs) which were considered by the investigator to be at least possibly related to the treatment the subject received.

End point type	Secondary

End point timeframe:

Part 1: Day 1 (Start of Part 1) to day 14; Part 2: Day 15 to Day 379 (End of Part 2)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)	Tapentadol prolonged release in Part 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[10]	45[11]	36[12]	
Units: Number of subjects	6	12	13	

Notes:

[10] - Safety Set

[11] - Safety Set

[12] - Safety Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in pain intensity in the open-label, active-controlled Treatment Period (Part 1)

End point title	Change in pain intensity in the open-label, active-controlled Treatment Period (Part 1)

End point description:

Pain intensity was assessed by scoring “pain right now” twice daily up to Day 14 by every subject using the Visual Analog Scale (VAS) as well as the Faces Pain Scale-Revised (FPS-R) in an electronic diary. Pain intensity was first documented using the VAS and directly thereafter the FPS-R. If required, pain intensity diary entry could be assisted by the legal guardian or a health care provider.
The VAS is scored from 0, equivalent to “no pain”, to 100, equivalent to “pain as bad as it could be”.
The FPS-R is a validated self-reported 6-point scale with 0 representing “no pain” and 10 representing “very much pain”. Facial representations were used to indicate how much the pain hurts.
The "pain right now" scores at baseline (last evaluation before starting IMP) and the mean of last 6 assessments collected up to the time point of last IMP intake in Part 1 (i.e., Day 14 or the day of early discontinuation) were used for the calculation of the change in pain intensity from baseline.

End point type	Other pre-specified

End point timeframe:

From baseline up to Day 14 (End of Part 1) or early discontinuation

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[13]	45[14]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Pain intensity change from Baseline (FPS-R)	-2.0 (± 3.5)	-1.9 (± 3.4)		
Pain intensity change from Baseline (VAS)	-23.4 (± 36.9)	-18.8 (± 33.5)		

Notes:

[13] - Full Analysis Set; results based on FPS-R and VAS results for 17 subjects.

[14] - Full Analysis Set; results based on FPS-R and VAS results for 29 subjects.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in pain intensity in the tapentadol open-label Extension Period (Part 2)

End point title	Change in pain intensity in the tapentadol open-label Extension Period (Part 2)

End point description:

Pain intensity was assessed by scoring "Pain right now" using the Visual Analog Scale (VAS) as well as the Faces Pain Scale-Revised (FPS-R) at each visit. The pain intensity was first documented using the VAS and directly thereafter the FPS-R. If required, pain intensity assessments could be assisted by the legal guardian or a health care provider.
The VAS is scored from 0, equivalent to "no pain", to 100, equivalent to "pain as bad as it could be".
The FPS-R is a validated self-reported 6-point scale with 0 representing "no pain" and 10 representing "very much pain". Facial representations were used to indicate how much the pain hurts.
The "pain right now" score at the tapentadol baseline (last evaluation before or at Day 15) and at the last assessment in Part 2 (i.e., 12 months after completion of Part 1 or the day of early discontinuation) were used for the calculation of the change in pain intensity from the tapentadol baseline.

End point type	Other pre-specified

End point timeframe:

From Day 15 to Day 379 (End of Part 2)

End point values	Tapentadol prolonged release in Part 2			
Subject group type	Reporting group			
Number of subjects analysed	36[15]			
Units: Units on scale				
arithmetic mean (standard deviation)				
Pain intensity change (FPR-S) from Day 15	0 (± 2.8)			
Pain intensity change (VAS) from Day 15	-11.7 (± 29.0)			

Notes:

[15] - Full Analysis Set; data from 9 subjects were analyzed, data for 22 subjects were missing.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Use of rescue medication in the open-label, active-controlled Treatment Period (Part 1)

End point title	Use of rescue medication in the open-label, active-controlled Treatment Period (Part 1)

End point description:

Due to an overall low intake of rescue medication it was not appropriate to present the number of doses of oral morphine solution used at different dose levels of investigational medicinal product (IMP) but the average daily dose (milligrams per kilogram body weight) for the treatment period and a modified average daily dose. Average daily dose and modified average daily dose were both calculated based on drug accountability. For the modified average daily doses, unplausible values were excluded from the analysis, i.e. the amount of rescue medication that was lost due to a broken bottle was excluded from the analysis and negative amounts of rescue medication intakes due to measurement inaccuracies for bottle weights were considered as no intake.

End point type	Other pre-specified

End point timeframe:

From Day 1 up to Day 14 (End of Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	45[16]		
Units: milligrams per kilogram per day				
arithmetic mean (standard deviation)				
Average daily dose	0.07 (± 0.154)	0.46 (± 2.426)		
Modified average daily dose	0.08 (± 0.160)	0.11 (± 0.201)		

Notes:

[16] - Full Analysis Set; data from 44 subjects were analyzed.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic concentrations of tapentadol (Part 1)

End point title	Pharmacokinetic concentrations of tapentadol (Part 1)[17]

End point description:

Tapentadol concentrations were measured in subjects in the tapentadol PR treatment arm (Part 1).
All subjects who had quantifiable serum concentrations (i.e., serum concentrations above the lower limit of quantification) during the Treatment Period were included in the descriptive pharmacokinetic analysis. Data from subjects who vomited within 6 hours of administration of IMP during the Treatment Period were carefully assessed to decide if the data should be included in the pharmacokinetic analysis.

End point type	Other pre-specified

End point timeframe:

From Day 1 to Day 14 (End of Part 1)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tapentadol serum concentrations were only determined in subjects receiving tapentadol PR and not in the morphine PR comparator arm. So no statistical analysis between the two arms is possible.

End point values	Tapentadol prolonged release (Part 1)			
Subject group type	Reporting group			
Number of subjects analysed	44[18]			
Units: nanograms per millilter				
arithmetic mean (standard deviation)				
Day 1 (6 to less than 12 years, N = 12)	17.2 (± 7.40)			
Day 1 (12 to less than 18 years, N = 28)	19.9 (± 22.99)			
Day 14 (6 to less than 12 years, N = 12)	35.6 (± 18.14)			
Day 14 (12 to less than 18 years, N = 29)	48.5 (± 38.59)			
Day 1 (all subjects, N = 40)	19.1 (± 19.57)			
Day 14 (all subjects, N = 41)	44.7 (± 34.17)			

Notes:

[18] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic concentrations of tapentadol-O-glucoronide (Part 1)

End point title	Pharmacokinetic concentrations of tapentadol-O-glucoronide (Part 1)[19]

End point description:

Tapentadol-O-glucuronide is a metabolite of tapentadol. The body transforms tapentadol into its metabolites so that it can be more easily/quickly removed from the body. Tapentadol-O-glucoronide concentrations were measured in subjects who received tapentadol PR in Part 1.
All subjects who had quantifiable serum concentrations were included in the descriptive pharmacokinetic analysis. Data from subjects who vomited within 6 hours of administration of IMP during Part 1 were carefully assessed to decide if they should be included in the pharmacokinetic analysis.

End point type	Other pre-specified

End point timeframe:

From Day 1 to Day 14 (End of Part1)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Tapentadol-O-glucuronide serum concentrations were only determined in subjects receiving tapentadol PR and not in the morphine PR comparator arm. So no statistical analysis between the two arms is possible.

End point values	Tapentadol prolonged release (Part 1)			
Subject group type	Reporting group			
Number of subjects analysed	44[20]			
Units: nanograms per milliliter				
arithmetic mean (standard deviation)				
Day 1 (6 to less than 12 years, N = 12)	603.2 (± 312.11)			
Day 1 (12 to less than 18 years, N = 28)	786.7 (± 984.42)			
Day 14 (6 to less than 12 years, N = 12)	1223.8 (± 511.27)			

Day 14 (12 to less than 18 years, N = 28)	1700.3 (± 1363.41)			
Day 1 (all subjects, N = 40)	731.7 (± 840.02)			
Day 14 (all subjects, N = 40)	1557.3 (± 1187.24)			

Notes:

[20] - Pharmacokinetic Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Palatability of trial medication (Part 1, Day 14)

End point title	Palatability of trial medication (Part 1, Day 14)

End point description:

Palatability was determined in Part 1 by asking the subject "How does the medication taste". The subject was requested to give a score on a 5 point hedonic faces rating scale in combination with a verbal rating. The response can range from really bad to really good.

End point type	Other pre-specified

End point timeframe:

Day 14 (Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[21]	45[22]		
Units: Number of subjects				
Really bad	0	0		
Bad	0	1		
A bit bad/ a bit good	9	23		
Good	9	11		
Really good	6	9		
Missing	0	1		

Notes:

[21] - Full Analysis Set

[22] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Palatability of trial medication (Part 1, Day 8)

End point title	Palatability of trial medication (Part 1, Day 8)

End point description:

Palatability was determined in Part 1 by asking the subject "How does the medication taste". The subject was requested to give a score on a 5 point hedonic faces rating scale in combination with a verbal rating. The response can range from really bad to really good.

End point type	Other pre-specified

End point timeframe:

Day 8 (Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[23]	45[24]		
Units: Number of subjects				
Really bad	0	0		
Bad	0	2		
A bit bad/a bit good	13	21		
Good	7	12		
Really good	3	6		
Missing	1	4		

Notes:

[23] - Full Analysis Set

[24] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Acceptability of trial medication (Part 1, Day 8)

End point title	Acceptability of trial medication (Part 1, Day 8)

End point description:

Acceptability of the trial medication was determined in Part 1 by asking the subject "Swallowing the medication is...". The subject was requested to give a score on a 5-point hedonic faces rating scale in combination with a verbal rating. The response can range from really difficult to really easy.

End point type	Other pre-specified

End point timeframe:

Day 8 (Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[25]	45[26]		
Units: Number of subjects				
Really difficult	0	0		
Difficult	0	3		
A bit difficult/a bit easy	3	5		
Easy	8	9		
Really easy	12	24		
Missing	1	4		

Notes:

[25] - Full Analysis Set

[26] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Acceptability of trial medication (Part 1, Day 14)

End point title	Acceptability of trial medication (Part 1, Day 14)

End point description:

Acceptability of the trial medication was determined in Part 1 by asking the subject "Swallowing the medication is...". The subject was requested to give a score on a 5-point hedonic faces rating scale in combination with a verbal rating. The response can range from really difficult to really easy.

End point type	Other pre-specified

End point timeframe:

Day 14 (End of Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[27]	45[28]		
Units: Number of subjects				
Really difficult	1	1		
Difficult	0	1		
A bit difficult/a bit easy	2	7		
Easy	8	16		
Really easy	13	19		
Missing	0	1		

Notes:

[27] - Full Analysis Set

[28] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extent of constipation (Part 2)

End point title	Extent of constipation (Part 2)

End point description:

Constipation was assessed using the modified constipation assessment scale (mCAS). This is an 8-item questionnaire where the observer has scored constipation on a nominal scale (no Problem [score 0], some problem [score 1] or severe Problem [score 2]). The response to an item could also be scored as "unable to assess".
The Total Score can vary from 0-16; the higher the Total Score the higher the extent of constipation. A positive change from baseline to last assessment indicates a worsening, a negative change an improvement.

End point type	Other pre-specified

End point timeframe:

From baseline (Day 15 or switch) to last assessment (up to Day 379 of Part 2)

End point values	Tapentadol prolonged release in Part 2	Observation Period After Tapentadol in Part 1	Observation Period After Morphine in Part 1	Observation Period After Tapentadol in Part 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36[29]	18[30]	14[31]	26[32]
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	2.3 (± 2.4)	1.8 (± 2.3)	2.5 (± 2.5)	1.5 (± 2.5)
Last assessment	1.8 (± 2.7)	0.4 (± 0.8)	0.4 (± 1.2)	0.8 (± 1.7)
Change from baseline	-0.7 (± 3.3)	-1.4 (± 2.1)	-1.6 (± 1.7)	-1.4 (± 2.7)

Notes:

[29] - Safety Set; N =35 subjects at baseline, N=32 at last assessment, and N=32 for change from baseline.
[30] - Safety Set; N=17 subjects at baseline, N=10 at last assessment, and N=9 for change from baseline.
[31] - Safety Set; N=14 subjects at baseline, N=12 at last assessment, and N=12 for change from baseline.
[32] - Safety Set; N=25 subjects at baseline, N=16 at last assessment, and N=15 for change from baseline.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Subjective Opiate Withdrawal Scale (SOWS)

End point title	Change from baseline in Subjective Opiate Withdrawal Scale (SOWS)

End point description:

Opiate withdrawal symptoms were assessed using the Subjective Opiate Withdrawal Scale (SOWS) questionnaire. The SOWS is designed to reflect common motoric, autonomic, musculoskeletal and psychic signs and symptoms of opiate withdrawal.
Each subject was requested to rate the first 15 items of the 16-item questionnaire for 7 days after discontinuation of treatment. Subjects rated the intensity of specific signs and symptoms on a scale of 0 (not at all) to 4 (extremely).
The minimum overall score is 0, the maximum score is 64. SOWS Total Score and changes from baseline are presented.

End point type	Other pre-specified

End point timeframe:

At baseline for Part 1 (i.e., Day 14-17), Part 2 (i.e., Day 352-380), or the day after an early termination visit (Part 1/2), and 2-7 days after last intake of investigational medicinal product (IMP) in Part 1 (up to Day 23) and in Part 2 (up to Day 386).

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)	Tapentadol prolonged release in Part 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24[33]	45[34]	36[35]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total score at baseline	4.0 (± 3.8)	6.9 (± 7.6)	6.1 (± 6.0)	
Change Day 2 after last IMP intake	-0.4 (± 2.0)	-1.7 (± 2.5)	-0.7 (± 2.8)	
Change Day 3 after last IMP intake	-1.6 (± 2.7)	-2.3 (± 4.9)	-0.3 (± 3.1)	
Change Day 4 after last IMP intake	-1.7 (± 4.4)	-3.9 (± 4.7)	-0.1 (± 3.6)	
Change Day 5 after last IMP intake	-1.6 (± 3.6)	-3.8 (± 5.1)	0 (± 5.0)	
Change Day 6 after last IMP intake	-2.3 (± 3.6)	-3.6 (± 4.6)	-0.6 (± 3.1)	
Change Day 7 after last IMP intake	-2.7 (± 3.9)	-5.1 (± 6.3)	-1.4 (± 2.8)	

Notes:

[33] - Safety Set; data for 9 subjects (baseline) and for 10/10/10/10/9/7 subjects 2-7 days after last IMP.

[34] - Safety Set; data for 9 subjects (baseline) and 10/11/12/12/12/12 subjects 2-7 days after last IMP.

[35] - Safety Set; data for 23 subjects (baseline) and 25/25/27/26/25/18 subjects 2-7 days after last IMP.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to discontinuation (lack of efficacy) in Part 1

End point title	Time to discontinuation (lack of efficacy) in Part 1

End point description:

The time to discontinuation from IMP due to lack of efficacy was planned to be analyzed for both treatment arms (tapentadol PR and morphine PR) in Part 1 of the trial. However, no subject was reported with early discontinuation from IMP due to lack of efficacy.

End point type	Other pre-specified

End point timeframe:

From first day in Part 1 (Day 1) to last day in Part 1.

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[36]	45[37]		
Units: Number of subjects				
Early discontinuation due to lack of efficacy	0	0		

Notes:

[36] - Safety Set

[37] - Safety Set

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to first intake of rescue medication in the open-label, active-controlled Treatment Period (Part 1)

End point title	Time to first intake of rescue medication in the open-label, active-controlled Treatment Period (Part 1)

End point description:

Morphine oral solution could be given during Part 1 as rescue medication in both treatment groups. The dose per rescue medication intake was 1/6 of the total daily dose of the scheduled tapentadol PR or morphine PR intakes. Rescue medication administration times and doses were recorded.

18 subjects in the morphine PR group and 27 subjects in the tapentadol PR group had no documented intake of rescue medication between Day 1 and Day 14.
Summary statistics were calculated based on subjects with any intake, i.e., those that took at least 1 dose of rescue medication. The mean (standard deviation) time (hours) to first dose of rescue medication following the first dose of the IMP (on Day 1) is presented.

End point type	Other pre-specified

End point timeframe:

From Day 1 up to Day 14 (End of Part 1)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[38]	45[39]		
Units: hours				
arithmetic mean (standard deviation)	39.7 (± 63.75)	74.6 (± 94.45)		

Notes:

[38] - Full Analysis Set; data for N=6 subjects with any intake analyzed.

[39] - Full Analysis Set; data for N=18 subjects with any intake analyzed.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to discontinuation (treatment emergent adverse events) in Part 1

End point title	Time to discontinuation (treatment emergent adverse events) in Part 1

End point description:

The time to discontinuation from IMP due to treatment emergent adverse events (TEAEs) was analyzed for both treatment arms (tapentadol PR and morphine PR) in Part 1 of the trial.
Note that no subject discontinued due to treatment emergent adverse events in the morphine PR arm.

End point type	Other pre-specified

End point timeframe:

From first day in Part 1 (Day 1) to last day in Part 1 (Day 14)

End point values	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[40]	45[41]		
Units: Days				
median (full range (min-max))	0 (0 to 0)	3.0 (2 to 4)		

Notes:

[40] - Safety Set; no subject discontinued due to treatment emergent adverse events.

[41] - Safety Set; N=2 subjects discontinued due to treatment emergent adverse events

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to discontinuation (lack of efficacy) in Part 2

End point title	Time to discontinuation (lack of efficacy) in Part 2

End point description:

The time to discontinuation from IMP due to lack of efficacy was analyzed for tapentadol PR treatment in Part 2 of the trial.

End point type	Other pre-specified

End point timeframe:

From first day in Part 2 (Day 15) to last day in Part 2 (Day 379)

End point values	Tapentadol prolonged release in Part 2			
Subject group type	Reporting group			
Number of subjects analysed	36[42]			
Units: Weeks				
median (full range (min-max))	30.9 (9 to 36)			

Notes:

[42] - Safety Set; 3 subjects with early discontinuation from IMP due to lack of efficacy.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to discontinuation (treatment emergent adverse events) in Part 2

End point title	Time to discontinuation (treatment emergent adverse events) in Part 2

End point description:

The time to discontinuation from IMP due to treatment emergent adverse events (TEAEs) was analyzed for tapentadol PR treatment in Part 2 of the trial.

End point type	Other pre-specified

End point timeframe:

From first day in Part 2 (Day 15) to last day in Part 2 (Day 379)

End point values	Tapentadol prolonged release in Part 2			
Subject group type	Reporting group			
Number of subjects analysed	36[43]			
Units: Weeks				
median (full range (min-max))	5.3 (3 to 24)			

Notes:

[43] - Safety Set; N=3 subjects discontinued due to treatment emergent adverse events.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were regularly assessed by the investigator using a standard set of questions.
Treatment emergent adverse events (TEAEs) were collected from first dose (on Day 1) to last intake of IMP plus 72 hours (therapeutic reach).

Adverse event reporting additional description:

Part 1: TEAEs from first to last dose in Part 1 if subject continued on tapentadol PR in Part 2; from first to last dose in Part 1 + 72 hours if subject did not continue on tapentadol PR in Part 2.
Part 2: TEAEs from start of Tapentadol Period to the last IMP intake in Part 2 + 72 hours (therapeutic reach).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Overall (Part 1)

Reporting group description:

Overall (Part 1) includes all subjects with a 2-week treatment with tapentadol PR or morphine PR tablets.

One subject who completed the tapentadol PR treatment in Part 1 died in the Observation Period (Part 2; standard-of-care treatment, no IMP) due to progression of Ewing's sarcoma, which started progressing in Part 1. A second subject died in the Observation Period after Tapentadol in Part 1 due to serious progression of osteosarcoma with fatal outcome. The progression started in the Observation Period.

Reporting group title	Morphine prolonged release (Part 1)

Reporting group description:

The treatment group comprised 7 subjects aged 6 years to less than 12 years and 17 subjects aged 12 years to less than 18 years.
Starting doses varied from 10 to 40 milligrams (mg) morphine PR twice daily depending on subject's weight; if necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 200 mg per day.

Reporting group title	Tapentadol prolonged release (Part 1)

Reporting group description:

The treatment group comprised 12 subjects aged 6 years to less than 12 years and 33 subjects aged 12 years to less than 18 years.
Subjects starting doses varied from 25 to 100 mg tapentadol PR twice daily depending on subject's weight. If necessary, doses were gradually increased up to a maximum dose defined per weight group. The highest dose defined for subjects weighing 55 kg and more was 500 mg per day.

Reporting group title	Tapentadol prolonged release in Part 2

Reporting group description:

Tapentadol prolonged release in Part 2 comprises all subjects who completed Part 1 (on tapentadol PR or morphine PR) and continued on or switched to an extended treatment with tapentadol PR for up to 12 months.

No deaths were reported during treatment with tapentadol PR in Part 2.
Following tapentadol PR treatment in Part 2, 1 subject died during the Observation Period (under standard-of-care treatment, no IMP) due to malignant neoplasm progression (sarcoma). The progression started in the Observation Period.

Serious adverse events	Overall (Part 1)	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 69 (5.80%)	1 / 24 (4.17%)	3 / 45 (6.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 69 (1.45%)	0 / 24 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Limb operation			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 69 (1.45%)	1 / 24 (4.17%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breakthrough pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Dissociation			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Movement disorder			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 24 (4.17%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 69 (1.45%)	1 / 24 (4.17%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 69 (1.45%)	0 / 24 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			

subjects affected / exposed	1 / 69 (1.45%)	1 / 24 (4.17%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 24 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Application site infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tapentadol prolonged release in Part 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 36 (36.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Limb operation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breakthrough pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Dissociation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
White blood cell count decreased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Movement disorder			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sickle cell anaemia with crisis			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Application site infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall (Part 1)	Morphine prolonged release (Part 1)	Tapentadol prolonged release (Part 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 69 (53.62%)	11 / 24 (45.83%)	26 / 45 (57.78%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 69 (5.80%)	0 / 24 (0.00%)	4 / 45 (8.89%)
occurrences (all)	4	0	4
Dysarthria			
subjects affected / exposed	2 / 69 (2.90%)	2 / 24 (8.33%)	0 / 45 (0.00%)
occurrences (all)	2	2	0
Headache			
subjects affected / exposed	9 / 69 (13.04%)	3 / 24 (12.50%)	6 / 45 (13.33%)
occurrences (all)	12	3	9
Somnolence			
subjects affected / exposed	2 / 69 (2.90%)	2 / 24 (8.33%)	0 / 45 (0.00%)
occurrences (all)	2	2	0

Paraesthesia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 69 (7.25%)	3 / 24 (12.50%)	2 / 45 (4.44%)
occurrences (all)	5	3	2
Pyrexia			
subjects affected / exposed	4 / 69 (5.80%)	1 / 24 (4.17%)	3 / 45 (6.67%)
occurrences (all)	6	1	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 69 (8.70%)	0 / 24 (0.00%)	6 / 45 (13.33%)
occurrences (all)	7	0	7
Abdominal pain upper			
subjects affected / exposed	2 / 69 (2.90%)	2 / 24 (8.33%)	0 / 45 (0.00%)
occurrences (all)	2	2	0
Constipation			
subjects affected / exposed	11 / 69 (15.94%)	4 / 24 (16.67%)	7 / 45 (15.56%)
occurrences (all)	11	4	7
Diarrhoea			
subjects affected / exposed	3 / 69 (4.35%)	0 / 24 (0.00%)	3 / 45 (6.67%)
occurrences (all)	3	0	3
Nausea			
subjects affected / exposed	14 / 69 (20.29%)	4 / 24 (16.67%)	10 / 45 (22.22%)
occurrences (all)	15	5	10

Vomiting			
subjects affected / exposed	13 / 69 (18.84%)	7 / 24 (29.17%)	6 / 45 (13.33%)
occurrences (all)	15	9	6
Toothache			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 69 (5.80%)	3 / 24 (12.50%)	1 / 45 (2.22%)
occurrences (all)	4	3	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 69 (2.90%)	2 / 24 (8.33%)	0 / 45 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			
Nightmare			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 69 (4.35%)	0 / 24 (0.00%)	3 / 45 (6.67%)
occurrences (all)	3	0	3
Pain in extremity			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Tapentadol prolonged release in Part 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 36 (83.33%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Dysarthria			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	24		
Somnolence			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	4		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 2 / 36 (5.56%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	 0 / 36 (0.00%) 0		
Psychiatric disorders Nightmare subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	 2 / 36 (5.56%) 3 2 / 36 (5.56%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 5 / 36 (13.89%) 5 3 / 36 (8.33%) 9		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 5 / 36 (13.89%) 7		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 2 / 36 (5.56%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2015	The amendment was enacted to: • Explicitly allow a home visit to take place instead of a site visit after a case-by-case approval by the sponsor. • Allow more flexibility in selecting the supplier of the rescue medication by allowing both morphine sulfate and morphine hydrochloride to be used, and by using an interactive response technology system (voice and web based) to assign subjects to rescue medication. • Allow the results of a non-protocol blood sample taken within 14 days of Visit 2 to be used for assessing the exclusion criteria and for baseline values without the need to repeat the sample at the Enrollment Visit. This was done to potentially reduce the volume of blood taken from the subject. • Clarify and correct the definitions of the endpoints, populations, and statistical analyses. • Clarify and correct the days on which the SOWS questionnaire is completed, and the questions to be assessed. • Add the measurement of height for the calculation of the glomerular clearance at 3 monthly intervals in the Tapentadol Period (Part 2). • Specify that if a subject turns 18 years old before Visit VE, an additional subject would be allocated to IMP. • Specify that subjects who vomit after IMP intake must not take additional IMP until the time of their next scheduled IMP dose. • Correct the labeling specification for the pharmacokinetic samples. • Add an additional exclusion criterion to exclude female subjects who are breast-feeding a child. Although there is no information on the excretion of tapentadol in human milk, there are pre-clinical data indicating that tapentadol is excreted in animal milk. Morphine is known to be excreted in breast milk, and may thus cause respiratory depression in the newborn.
25 September 2017	This amendment introduced the following changes: • The alpha for the primary endpoint analysis was updated based on the methodology proposed by Hlavin et al. (2016). As a consequence of the alpha adjustment, the sample size was reduced. • A definition of long-term pain was added. • Specifications of the trial population were modified, requiring the inclusion of fewer subjects in the lower age group. The expectation that at least 15 subjects would be treated with tapentadol PR for a minimum of 12 weeks was added. • The estimated dates of last subject out for Part 1 and Part 2 were updated. • The main analysis was rescheduled such that it will be performed after all subjects complete the first 12 weeks of Part 2. • The interim analysis for the sample size re-assessment was removed due to the reduced sample size. The adaptive 2-stage design of the trial was simplified to a fixed 1-stage design. • Instructions pertaining to ECG-related discontinuation were added. • The timing of the Early Termination Visit was explicitly defined. • History of CRPS and history of a pain indication that is unlikely to respond to opioids was added to the exclusion criteria. • Safety experience from post-marketing data was updated. • Instructions for calculating the starting dose in Part 1 and Part 2 were revised. Hlavin G, Koenig F, Male C, Posch M, Bauer P. Evidence, eminence and extrapolation. Stat Med 2016; 35 (13): 2117-32.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported