Clinical trial results:
An evaluation of the efficacy and safety of tapentadol oral solution in the treatment of post-operative acute pain requiring opioid treatment in pediatric subjects aged from birth to less than 18 years old.

Summary

EudraCT number	2012-004359-35
Trial protocol	SE DE GB ES AT FR PL HR HU BG CZ
Global end of trial date	

Results information

Result version number	v1
This version publication date	20 November 2018
First version publication date	15 June 2017

Trial information

Trial identification

Sponsor protocol code	R331333PAI3037

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02081391
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 108134, Grünenthal: KF5503/65, Depomed: R331333PAI3037

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000018-PIP01-07
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	Interim
Date of interim/final analysis	26 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This trial is performed to meet the requirements for pediatric development plans agreed with authorities in 2 regions (Paediatric Committee of the European Medicines Agency [EU PDCO] and United States Food and Drug Administration [US FDA]). Only the objectives and data for the EU part (subjects aged 2 years to less than 18 years old) are presented in this posting. The recruitment of the remaining subjects aged less than 2 years old for the completion of the US part (subjects from birth to less than 17 years old) is ongoing.
Main objectives of the trial for the EU PDCO population:
Efficacy and safety of tapentadol oral solution in children and adolescents aged 2 years to less than 18 years who had undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment. Efficacy was analysed based on the total amount of supplemental opioid analgesic medication used over 24 hours following initiation of IMP.

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
The competent authorities approved the trial as required by national regulations.
Regulatory authorities were notified of the trial and amendments as required by national regulations.
An independent data monitoring committee was established to oversee subject's safety in ongoing tapentadol trials in the pediatric population.
Subjects were carefully observed, especially during the first hour after the initiation of IMP.
Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate), sedation score, and oxygen saturation were measured before each dose of IMP was given.
Respiratory rate and heart rate had to be constantly monitored for 24 hours after first does of IMP and afterwards according local standard of care. Oxygen saturation had to be monitored constantly using pulse oximetry from before first dose of IMP until 4 hours after the last dose of IMP.

Background therapy:

At some time after the surgery, the subject had started on NCA/PCA with morphine or hydromorphone according to the standard of care.
Medications for the treatment of adverse events were allowed according to the investigator's judgment and post-operative standard of care e.g. clinically relevant respiratory depression treated with naloxone, and nausea/vomiting treated with antiemetics, which may have been given prophylactically according to the standard of care.
In exceptional cases, if a subject has unbearable pain despite using NCA/PCA (Nurse controlled analgesia/Patient controlled analgesia), an additional bolus of morphine or hydromorphone were allowed using either the NCA/PCA pump system or by an intravenous bolus injection.

Evidence for comparator:

N/A

Actual start date of recruitment	19 February 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	Poland: 30

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	193
EEA total number of subjects	105

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)	95
Adolescents (12-17 years)	98
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 19 Feb 2015 with the enrollment of the first subject. Recruitment for the EU PDCO set (subjects aged 2 years to less than 18 years old) was completed on 05 Dec 2016 with the last subject out. The recruitment of the remaining subjects aged less than 2 years old for the US FDA population is ongoing.

Pre-assignment

Screening details:

A total of 193 subjects gave informed consent to participate in the trial, 165 of these subjects were allocated to study drug (investigational medicinal product = IMP) and 160 subjects received IMP (52 subjects on placebo and 108 subjects on tapentadol).

Pre-assignment period milestones

Number of subjects started	193
Number of subjects completed	160

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by the parent(s) or subjects: 4
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Other: 4
Reason: Number of subjects	Inclusion criteria not met /exclusion criteria met: 24

Period 1

Period 1 title	12 hours treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The trial was double-blinded to prevent bias.
The blind was broken for the EU PDCO set before recruitment of the less than 2 year olds in the US FDA set was completed.
Subjects less than 2 years old in the US FDA set remain blinded, as independent randomization lists are used for subjects aged less than 2 years old.

Arms

Are arms mutually exclusive?	No
Arm title	12 hours treatment period - Overall Trial

Arm description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of IMP are considered for this arm.
Subject had undergone surgery that, in the investigator’s opinion, would reliably produce moderate to severe pain requiring opioid treatment via nurse controlled analgesia (NCA) or patient controlled analgesia (PCA) .

Arm type	Overall

No investigational medicinal product assigned in this arm

Arm title	12 hours treatment period - Tapentadol

Arm description:

This arm includes all subjects who received at least one dose of Tapentadol oral solution.
12 hours treatment period completers were defined as subjects who did not discontinue the treatment

period before 12 hours.

Arm type	Experimental
Investigational medicinal product name	Tapentadol oral solution
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The dose administered depended on the subject's body weight.
The dose to be administered was 1.25 mg/kg during the first 24 hours (the maximum individual dose of tapentadol was 100 mg).
The dosing interval was 4 hours (range ±15 minutes). If the subject was sleeping at the time of the scheduled dose, they were woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP was given as soon as possible after the subject was awake. The administration of IMP was based on the investigator’s judgment of the subject’s condition and sedation level.

Arm title	12 hours treatment period - Placebo

Arm description:

This arm includes all subjects who received at least one dose of placebo.
12 hours treatment period completers were defined as subjects who did not discontinue the treatment period before 12 hours.

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

Dosage and administration details:

The dose administered depended on the subject's body weight.
The dose to be administered was 1.25 mg/kg during the first 24 hours (equivalent to tapentadol).
The dosing interval was 4 hours (range ±15 minutes). If the subject was sleeping at the time of the scheduled dose, they were woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP was given as soon as possible after the subject was awake. The administration of IMP was based on the investigator’s judgment of the subject’s condition and sedation level.

Number of subjects in period 1	12 hours treatment period - Overall Trial	12 hours treatment period - Tapentadol	12 hours treatment period - Placebo
Started	160	108	52
Completed	136	90	46
Not completed	24	18	6
Physician decision	5	4	1
Recovery (opioid analgesic no longer needed)	2	2	-
Adverse event, non-fatal	6	4	2
Other	3	2	1
Consent withdrawn by the parent(s) or subjects	5	3	2
Lack of efficacy	3	3	-

Period 2

Period 2 title	24 hours treatment and trial completion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The trial was double-blinded to prevent bias.
The blind was broken for the EU PDCO set before recruitment of the less than 2 year olds in the US FDA set was completed.
Subjects less than 2 years old in the US FDA set remain blinded, as independent randomization lists are used for subjects aged less than 2 years old.

Arms

Are arms mutually exclusive?	No
Arm title	24 hours treatment and trial completion - Overall Trial

Arm description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of IMP and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow up visit (24 hours trial completers).

Arm type	Overall

No investigational medicinal product assigned in this arm

Arm title	24 hours treatment and trial completion - Tapentadol

Arm description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of tapentadol and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow up visit (24 hours trial completers).

Arm type	Experimental
Investigational medicinal product name	Tapentadol oral solution
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The dose administered depended on the subject's body weight.
The dose to be administered was 1.25 mg/kg during the first 24 hours (the maximum individual dose of tapentadol was 100 mg).
The dosing interval was 4 hours (range ±15 minutes). If the subject was sleeping at the time of the scheduled dose, they were woken to take the IMP within a maximum of 6 hours after the previous dose.
The dose of IMP was given as soon as possible after the subject was awake. The administration of IMP was based on the investigator’s judgment of the subject’s condition and sedation level.

Arm title	24 hours treatment and trial completion - Placebo

Arm description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of Placebo and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow

up visit (24 hours trial completers).

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

Dosage and administration details:

The dose administered depended on the subject's body weight.
The dose to be administered was 1.25 mg/kg during the first 24 hours (equivalent to tapentadol).
The dosing interval was 4 hours (range ±15 minutes). If the subject was sleeping at the time of the scheduled dose, they were woken to take the IMP within a maximum of 6 hours after the previous dose.
The dose of IMP was given as soon as possible after the subject was awake. The administration of IMP was based on the investigator’s judgment of the subject’s condition and sedation level.

Number of subjects in period 2	24 hours treatment and trial completion - Overall Trial	24 hours treatment and trial completion - Tapentadol	24 hours treatment and trial completion - Placebo
Started	136	90	46
Completed	91	63	28
Not completed	45	27	18
Physician decision	15	10	5
Recovery (opioid analgesic no longer needed)	16	11	5
Adverse event, non-fatal	1	1	-
Other	7	3	4
Technical Problems	2	1	1
Lack of efficacy	4	1	3

Baseline characteristics

Reporting groups[1]	
Reporting group title	12 hours treatment period - Overall Trial
Reporting group description:	
All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of IMP are considered for this arm. Subject had undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment via nurse controlled analgesia (NCA) or patient controlled analgesia (PCA) .	
Reporting group title	12 hours treatment period - Tapentadol
Reporting group description:	
This arm includes all subjects who received at least one dose of Tapentadol oral solution. 12 hours treatment period completers were defined as subjects who did not discontinue the treatment period before 12 hours.	
Reporting group title	12 hours treatment period - Placebo
Reporting group description:	
This arm includes all subjects who received at least one dose of placebo. 12 hours treatment period completers were defined as subjects who did not discontinue the treatment period before 12 hours.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period are based on the number of subjects allocated and treated.

Reporting group values	12 hours treatment period - Overall Trial	12 hours treatment period - Tapentadol	12 hours treatment period - Placebo
Number of subjects	160	108	52
Age categorical Units: Subjects			
Children (2-11 years)	82	55	27
Adolescents (12-17 years)	78	53	25
Age continuous Units: years			
arithmetic mean	10.7	10.8	10.4
standard deviation	± 4.7	± 4.7	± 4.8
Gender categorical Units: Subjects			
Female	76	53	23
Male	84	55	29
Type of opioid analgesia used Units: Subjects			
Hydromorphone	51	33	18
Morphine	109	75	34
Height Units: meter			
arithmetic mean	144.4	145	143.3
standard deviation	± 28.2	± 27.7	± 29.5
Weight Units: kilogram(s)			
arithmetic mean	42.8	43.09	42.22
standard deviation	± 21.08	± 21.72	± 19.88
Body Mass index			

Units: kilogram(s)/square meter			
arithmetic mean	18.92	18.83	19.12
standard deviation	± 4.03	± 4.13	± 3.84
Amount of morphine or hydromorphone taken prior to IMP			
Amount of morphine or hydromorphone taken prior to IMP documented within 24 hours prior to first IMP administration.			
Units: milligram(s)/kilogram			
arithmetic mean	0.55	0.59	0.45
standard deviation	± 1.07	± 1.2	± 0.71

Reporting group values	Total		
Number of subjects	160		
Age categorical			
Units: Subjects			
Children (2-11 years)	82		
Adolescents (12-17 years)	78		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	76		
Male	84		
Type of opioid analgesia used			
Units: Subjects			
Hydromorphone	51		
Morphine	109		
Height			
Units: meter			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilogram(s)			
arithmetic mean			
standard deviation	-		
Body Mass index			
Units: kilogram(s)/square meter			
arithmetic mean			
standard deviation	-		
Amount of morphine or hydromorphone taken prior to IMP			
Amount of morphine or hydromorphone taken prior to IMP documented within 24 hours prior to first IMP administration.			
Units: milligram(s)/kilogram			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	12 hours treatment period - Overall Trial

Reporting group description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of IMP are considered for this arm.
Subject had undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment via nurse controlled analgesia (NCA) or patient controlled analgesia (PCA) .

Reporting group title	12 hours treatment period - Tapentadol

Reporting group description:

This arm includes all subjects who received at least one dose of Tapentadol oral solution.
12 hours treatment period completers were defined as subjects who did not discontinue the treatment period before 12 hours.

Reporting group title	12 hours treatment period - Placebo

Reporting group description:

This arm includes all subjects who received at least one dose of placebo.
12 hours treatment period completers were defined as subjects who did not discontinue the treatment period before 12 hours.

Reporting group title	24 hours treatment and trial completion - Overall Trial

Reporting group description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of IMP and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow up visit (24 hours trial completers).

Reporting group title	24 hours treatment and trial completion - Tapentadol

Reporting group description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of tapentadol and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow up visit (24 hours trial completers).

Reporting group title	24 hours treatment and trial completion - Placebo

Reporting group description:

All EU PDCO male and female subjects aged 2 years to less than 18 years and received at least one dose of Placebo and did not discontinue treatment before or at 12 hours of treatment are considered for this arm.
Subjects completing this period were defined as those subjects who did not discontinue treatment before 24 hours (24 hours treatment period completers) and completed the trial by attending the follow up visit (24 hours trial completers).

Subject analysis set title	FAS - Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set included allocated and treated EU PDCO subjects aged 2 years to less than 18 years old.
If by error a subject did not receive the allocated medication, the subject was evaluated as allocated following the intention-to-treat principle.

Subject analysis set title	FAS - Tapentadol
Subject analysis set type	Full analysis

Subject analysis set description:

This subject analysis set included all EU PDCO subjects aged 2 years to less than 18 years old who were allocated to Tapentadol and received at least one dose of IMP.
If by error a subject did not receive the allocated medication, the subject was evaluated as allocated following the intention-to-treat principle.

Subject analysis set title	FAS - Placebo

Subject analysis set type	Full analysis

Subject analysis set description:

This subject analysis set included all EU PDCO subjects aged 2 years to less than 18 years old who were allocated to placebo and received at least one dose of IMP.
If by error a subject did not receive the allocated medication, the subject was evaluated as allocated following the intention-to-treat principle.

Subject analysis set title	SAF - Tapentadol
Subject analysis set type	Safety analysis

Subject analysis set description:

This subject analysis set included all EU PDCO subjects aged 2 years to less than 18 years old who were allocated to Tapentadol and received at least one dose of IMP.

Subject analysis set title	SAF - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

This subject analysis set included subjects aged 2 years to less than 18 years old who were allocated to placebo and received at least one dose of IMP.

Primary: Total amount of supplemental opioid analgesic medication used within 24 hours after first IMP

End point title	Total amount of supplemental opioid analgesic medication used within 24 hours after first IMP

End point description:

The primary efficacy endpoint was the amount of supplemental opioid analgesic medication used within the first 24 hours after first IMP intake.
Supplemental opioid analgesia was expressed in mg/kg of morphine IV equivalents.

End point type	Primary

End point timeframe:

up to 24 hours

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: milligram(s)/kilogram				
least squares mean (standard error)	0.14 (± 0.03)	0.24 (± 0.03)		

Statistical analyses

Statistical analysis title	Difference Tapentadol –Placebo

Statistical analysis description:

The endpoint was analyzed using an analysis of variance model. This included treatment, baseline age group and the used supplemental opioid analgesic as factors. For subjects discontinuing treatment before 24 hours for any other reason than no further need of opioid analgesics or switch to exclusively oral opioid analgesics, cumulative supplemental opioid analgesia over the respective time period was based on the observed supplemental opioid use up to the time of the subject’s discontinuation.

Comparison groups	FAS - Tapentadol v FAS - Placebo

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0154
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Total amount of supplemental opioid analgesic medication used within 12 hours after first IMP

End point title	Total amount of supplemental opioid analgesic medication used within 12 hours after first IMP

End point description:

Total amount of supplemental opioid analgesic medication used within 12 hours after first IMP.
Supplemental opioid analgesia was expressed in mg/kg of morphine IV equivalents.

End point type	Secondary

End point timeframe:

up to 12 hours

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: milligram(s)/kilogram				
arithmetic mean (standard deviation)	0.09 (± 0.11)	0.14 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP

End point title	Total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP

End point description:

Total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP.
Supplemental opioid analgesia was expressed in mg/kg of morphine IV equivalents

End point type	Secondary

End point timeframe:

24 to 96 hours after IMP

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	108		
Units: milligram(s)/kilogram				
arithmetic mean (standard deviation)				
24h - 36h (N=38/19)	0.08 (± 0.09)	0.14 (± 0.21)		
36h - 48h (N=30/12)	0.06 (± 0.09)	0.06 (± 0.12)		
48h - 60h (N=20/8)	0.05 (± 0.1)	0.06 (± 0.14)		
60h - 72h (N=10/6)	0.06 (± 0.08)	0.03 (± 0.07)		
72h - 84h (N=3/2)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in pain intensity using the Face, Legs, Activity, Cry, Consolability Scale in children from birth to less than 6 years

End point title	Changes from baseline in pain intensity using the Face, Legs, Activity, Cry, Consolability Scale in children from birth to less than 6 years

End point description:

The FLACC scale was used for children from 2 years to less than 6 years, or in older children who were not able to report their pain using the other scales.
It was developed by the Department of Anesthesiology, University of Michigan Medical School and Health Systems. It is a behavioral scale for scoring postoperative pain in young children. This tool includes five categories of pain behaviors, including facial expression, leg movement, activity, cry, and consolability. Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolabilityis scored from 0-2, which results in a total score between zero and ten.
The Pain intensity scores have been obtained before and after first dose of IMP, and before each subsequent dose of IM, whenever possible.
Pain intensity scores and change from baseline values have been summarized descriptively for each time point.

End point type	Secondary

End point timeframe:

Change from baseline to first dose of IMP until the 8th dose of IMP and End of Treatment

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	13		
Units: units on a scale				
arithmetic mean (standard deviation)				
30-60 mins after 1st IMP (N=22/13)	1.1 (± 1.93)	1.9 (± 1.75)		
Before 2nd dose of IMP (N=23/13)	1.4 (± 1.92)	1.3 (± 1.75)		
Before 3rd dose of IMP (N=23/13)	1.7 (± 2.08)	1.6 (± 1.89)		
Before 4th dose of IMP (N=21/12)	1.4 (± 1.99)	1.3 (± 2.06)		
Before 5th dose of IMP (N=20/11)	1.8 (± 1.82)	1.9 (± 2.02)		
Before 6th dose of IMP (N=19/8)	1.6 (± 1.89)	2.3 (± 2.55)		
Before 7th dose of IMP (N=19/8)	1.6 (± 2.24)	2.1 (± 2.59)		
Before 8th dose of IMP (N=13/5)	1.2 (± 1.59)	2.2 (± 3.35)		
End of Treatment (N=23/13)	2.4 (± 2.52)	2 (± 2.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in pain intensity using the Faces Pain Scale in children aged 6 years to less than 12 years

End point title	Changes from baseline in pain intensity using the Faces Pain Scale in children aged 6 years to less than 12 years

End point description:

For children aged 6 years (if possible) to less than 12 years, the pain intensity has been assessed by the use of the Faces Pain Scale-Revised (FPS-R).
The FPS-R is a validated self-report measure of pain intensity developed for children. 6 facial representations were used to indicate how much the pain hurts.
It was adapted from the Faces Pain Scale to make it possible to score the sensation of pain on the widely accepted 0-to-10 metric.
The Pain intensity scores have been obtained before and after first dose of IMP, and before each subsequent dose of IM, whenever possible
Pain intensity scores and change from baseline values have been summarized descriptively for each time point

End point type	Secondary

End point timeframe:

Change from baseline to first dose of IMP until the 8th dose of IMP and End of Treatment

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	14		
Units: units on a scale				
arithmetic mean (standard deviation)				
30-60 mins after 1st IMP (N=30/14)	1 (± 1.72)	0.7 (± 1.86)		
Before 2nd dose of IMP (N=27/12)	1 (± 2.5)	0.5 (± 2.84)		
Before 3rd dose of IMP (N=26/12)	1 (± 2.35)	-0.2 (± 2.17)		
Before 4th dose of IMP (N=24/12)	1.3 (± 2.33)	-0.3 (± 3.7)		

Before 5th dose of IMP (N=24/11)	0.8 (± 2.75)	0 (± 2.19)		
Before 6th dose of IMP (N=23/10)	0.5 (± 2.43)	0.2 (± 2.2)		
Before 7th dose of IMP (N=21/9)	2 (± 2.37)	0.7 (± 2.24)		
Before 8th dose of IMP (N=14/9)	1.3 (± 2.55)	0.2 (± 2.73)		
End of Treatment (N=32/14)	2.8 (± 2.93)	3.4 (± 3.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in pain intensity using the Visual Analog Scale in children aged 12 years to less than 18 years

End point title	Changes from baseline in pain intensity using the Visual Analog Scale in children aged 12 years to less than 18 years

End point description:

For children aged 12 years to less than 18 years, the pain intensity has been assessed by the use of a Visual analog scale (VAS).
The subject were asked to draw a single line to indicate the current level of pain intensity on a 100 mm line (visual analog scale - VAS) by marking a point on the line in response to: "My pain right now is"". The mark was scored between "no pain" and "pain as bad as it could be". A value of 0 indicates "no pain". A value of 100 indicates "pain as bad as it could be".
The Pain intensity scores have been obtained before and after first dose of IMP, and before each subsequent dose of IM, whenever possible.
Pain intensity scores and change from baseline values have been summarized descriptively for each time point.

End point type	Secondary

End point timeframe:

Change from baseline to first dose of IMP until the 8th dose of IMP and End of Treatment

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	25		
Units: units on a scale				
arithmetic mean (standard deviation)				
30-60 mins after 1st IMP (N=50/25)	8 (± 18.67)	6.4 (± 19.58)		
Before 2nd dose of IMP (N=48/24)	6.5 (± 23.61)	6 (± 19.36)		
Before 3rd dose of IMP (N=44/22)	13.1 (± 25.09)	5.9 (± 22.11)		
Before 4th dose of IMP (N=44/22)	8.8 (± 29.01)	5.1 (± 21.7)		
Before 5th dose of IMP (N=42/20)	13 (± 22.92)	-2.7 (± 34.4)		
Before 6th dose of IMP (N=38/17	13 (± 24.74)	6.6 (± 28.4)		
Before 7th dose of IMP (N=28/13)	10.7 (± 25.77)	15 (± 20.27)		
Before 8th dose of IMP (N=19/7)	12.2 (± 28.91)	11.9 (± 14.6)		
End of Treatment (N=51/25)	11 (± 27.87)	11.4 (± 28.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGIC by investigator/clinician after completion of the double-blind IMP treatment

End point title	CGIC by investigator/clinician after completion of the double-blind IMP treatment

End point description:

The Clinical Global Impression of Change has been assessed at the End of Treatment Visit.
The investigator rated the subject's global improvement and satisfaction with the treatment on a 7-point scale that ranges from "very much improved" to "very much worse" with "no change" as the mid-point.
Results have been summarized descriptively.

End point type	Secondary

End point timeframe:

End of Treatment Visit

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Very much improved	15	12		
Much improved	58	22		
Minimally improved	18	8		
No change	11	4		
Minimally worse	3	2		
Much worse	1	1		
Very much worse	0	0		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: PGIC by subject/parent/legal guardian after completion of the double-blind IMP treatment

End point title	PGIC by subject/parent/legal guardian after completion of the double-blind IMP treatment

End point description:

The Patient Global Impression of Change has been assessed at the End of Treatment Visit. Subjects verbally rated their impression of overall status with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse). If the subjects were not capable of completing the questionnaire the parent/legal guardian may have completed the questionnaire on behalf of the subject.
Results have been summarized descriptively.

End point type	Secondary

End point timeframe:

End of Treatment Visit

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Very much improved	16	11		
Much improved	53	23		
Minimally improved	21	12		
No change	13	3		
Minimally worse	1	0		
Much worse	1	0		
Very much worse	0	0		
Missing	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first and time to second NCA/PCA after the first dose of IMP

End point title	Time to first and time to second NCA/PCA after the first dose of IMP

End point description:

The time to first and time to second NCA/PCA after the first dose of IMP were summarized descriptively using time-to-event methods and displayed overall and by relevant treatment groups.
Subjects who completed the End of Treatment Visit before their first/second use of NCA/PCA or subjects who terminate treatment before their first/second use of NCA/PCA were censored at the End of Treatment Visit.

End point type	Secondary

End point timeframe:

Time to first and second NCA/PCA administration

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: minute				
median (confidence interval 95%)				
Time to first NCA/PCA administration	183 (90 to 446)	131.5 (74 to 216)		
Time to second NCA/PCA administration	572 (321 to 1993)	338 (194 to 820)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from first dose of IMP until IMP treatment discontinuation due to lack of efficacy

End point title	Time from first dose of IMP until IMP treatment discontinuation due to lack of efficacy

End point description:

The distributions of the time from the first dose of IMP to treatment discontinuation due to lack of efficacy were summarized descriptively using time-to-event methods.
Subjects who reach the maximum duration of treatment (72 hours) were censored at 72 hours after first IMP intake. Subjects who discontinued during the Treatment Period for reasons other than lack of efficacy were censored at the time of the decision to discontinue treatment.
Due to the low number of subjects with events, the median and the corresponding confidence interval could not be calculated.

End point type	Secondary

End point timeframe:

up to 72 hours

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: Subjects				
Number of censored subjects	104	48		
Number of subjects with event	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of the IMP after the first dose

End point title	Palatability of the IMP after the first dose

End point description:

Palatability of the study medication (IMP) after dosing in subjects aged 2 years to less than 18 years old was assessed using a 5-point rating verbal rating scale.
Palatability has been assessed by asking the following question “How does the medication taste?”. The categorical verbal rating ranged from really good, good, a bit good/a bit bad, bad, and really bad.
Responses were summarized. Missing values were not imputed.

End point type	Secondary

End point timeframe:

After first dose of IMP

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Really bad	13	2		
Bad	28	2		
A bit bad / a bit good	36	10		
Good	24	24		
Really good	6	11		
Missing	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of the IMP after the last dose

End point title	Palatability of the IMP after the last dose

End point description:

Palatability of the study medication (IMP) after dosing in subjects aged 2 years to less than 18 years old was assessed using a 5-point rating verbal rating scale.
Palatability has been assessed by asking the following question “How does the medication taste?”. The categorical verbal rating ranged from really good, good, a bit good/a bit bad, bad, and really bad.
Responses were summarized. Missing values were not imputed.

End point type	Secondary

End point timeframe:

End of Treatment Visit

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Really bad	14	1		
Bad	15	3		
A bit bad / a bit good	38	14		
Good	28	16		
Really good	5	12		
Missing	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability of the IMP after the first dose

End point title	Acceptability of the IMP after the first dose

End point description:

The Acceptability of the study medication (IMP) after dosing in subjects aged 2 years to less than 18 years old was assessed using a 5-point rating verbal rating scale.
Acceptability has been assessed by asking the following question "Swallowing the medication is ...". The categorical verbal rating ranged from was really easy, easy, a bit easy/a bit difficult, difficult, and really difficult.
Responses were summarized. Missing values were not imputed.

End point type	Secondary

End point timeframe:

After first dose of IMP

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Really Difficult	1	0		
Difficult	7	3		
A Bit Difficult / A Bit Easy	17	7		
Easy	46	20		
Really Easy	35	19		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability of the IMP after the last dose

End point title	Acceptability of the IMP after the last dose

End point description:

The Acceptability of the study medication (IMP) after dosing in subjects aged 2 years to less than 18 years old was assessed using a 5-point rating verbal rating scale.
Acceptability has been assessed by asking the following question "Swallowing the medication is ...". The categorical verbal rating ranged from was really easy, easy, a bit easy/a bit difficult, difficult, and really difficult.
Responses were summarized. Missing values were not imputed.

End point type	Secondary

End point timeframe:

End of Treatment Visit

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Really Difficult	3	0		
Difficult	6	2		
A Bit Difficult / A Bit Easy	9	6		
Easy	43	18		
Really Easy	39	20		
Missing	8	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Suicidal ideation/behavior in subjects aged 6 years or older using the Columbia Suicide Severity Rating Scale (C-SSRS) scores before IMP and at the end of the trial

End point title	Suicidal ideation/behavior in subjects aged 6 years or older using the Columbia Suicide Severity Rating Scale (C-SSRS) scores before IMP and at the end of the trial

End point description:

The assessment of suicidal ideation and behavior was a voluntary assessment to determine development of such behaviors after treatment of subjects with IMP. Suicidal ideation and behavior was assessed at baseline using the Columbia-Suicide Severity Rating scale; children´s baseline. Suicidal ideation and behavior was assessed at end of treatment using the Columbia-Suicide Severity Rating scale; children´s Since last visit. Results were presented in a subject data listing.

End point type	Other pre-specified

End point timeframe:

Baseline and End of Treatment Visit

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	24		
Units: Subjects				
Suicidal ideation (N=47/24)	0	0		
Suicidal behaviour (N=45/22)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sedation scores using the University of Michigan Sedation Scale before first dose of IMP

End point title	Sedation scores using the University of Michigan Sedation Scale

	before first dose of IMP

End point description:

Sedation scores were obtained before each dose of IMP and summarized descriptively as a categorical variable.

End point type	Other pre-specified

End point timeframe:

before first dose of IMP

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: category				
Awake and alert	63	37		
Minimally sedated	35	13		
Moderately sedated	8	2		
Deeply sedated	1	0		
Unarousable	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sedation scores using the University of Michigan Sedation Scale before 8th administration of IMP

End point title	Sedation scores using the University of Michigan Sedation Scale before 8th administration of IMP

End point description:

Sedation scores were obtained before each dose of IMP and summarized descriptively as a categorical variable.

End point type	Other pre-specified

End point timeframe:

before 8th administration of IMP

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: Subjects				
number (not applicable)				
Awake and alert	30	14		
Minimally sedated	9	5		
Moderately sedated	4	1		
Deeply sedated	2	1		
Unarousable	0	0		

Missing	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects discontinuing the trial due to TEAEs and drug-related adverse events

End point title	Percentage of subjects discontinuing the trial due to TEAEs and drug-related adverse events

End point description:

The number of subjects with at least one TEAE leading to discontinuation from the trial (i.e. TEAE with "countermeasures": "trial discontinuation") were summarized in one table and respective percentage was calculated.

End point type	Other pre-specified

End point timeframe:

From first administration of IMP until the time of the subject-related end of trial.

End point values	FAS - Tapentadol	FAS - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	52		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal vital signs – Diastolic Blood Pressure

End point title	Percentage of subjects who develop abnormal vital signs – Diastolic Blood Pressure

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: percent				
number (not applicable)				
Non-alert	75.7	73.1		
Alert (low/high)	24.3	26.9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal vital signs – Systolic Blood Pressure

End point title	Percentage of subjects who develop abnormal vital signs – Systolic Blood Pressure

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: percent				
number (not applicable)				
Non-alert	70.1	67.3		
Alert (low/high)	29.9	32.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal vital signs – Heart Rate

End point title	Percentage of subjects who develop abnormal vital signs – Heart Rate

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: percent				
number (not applicable)				
Non-alert	34.6	26.9		
Alert (low/high)	65.4	73.1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal vital signs – Respiratory Rate

End point title	Percentage of subjects who develop abnormal vital signs – Respiratory Rate

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	52		
Units: percent				
number (not applicable)				
Non-alert	42.1	48.1		
Alert (low/high)	57.9	51.9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Hemoglobin

End point title	Percentage of subjects who develop abnormal laboratory

	parameter - Hemoglobin

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	40		
Units: percent				
number (not applicable)				
Non-alert	69.1	60		
Alert (low/high)	30.9	40		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Volume

End point title	Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Volume

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	39		
Units: percent				
number (not applicable)				
Non-alert	85.7	74.4		
Alert (low/high)	14.3	25.6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Hematocrit

End point title	Percentage of subjects who develop abnormal laboratory parameter - Hematocrit

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	39		
Units: percent				
number (not applicable)				
Non-alert	82.4	74.4		
Alert (low/high)	17.6	25.6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Hemoglobin

End point title	Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Hemoglobin

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	40		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - red blood cell count

End point title	Percentage of subjects who develop abnormal laboratory parameter - red blood cell count

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	40		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Hemoglobin Concentration

End point title	Percentage of subjects who develop abnormal laboratory parameter - Mean Corpuscular Hemoglobin Concentration

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	39		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Platelet count

End point title	Percentage of subjects who develop abnormal laboratory parameter - Platelet count

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	39		
Units: percent				
number (not applicable)				
Non-alert	96.7	94.9		
Alert (low/high)	3.3	5.1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - White blood cell count

End point title	Percentage of subjects who develop abnormal laboratory parameter - White blood cell count

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	40		
Units: percent				
number (not applicable)				
Non-alert	86.2	97.5		
Alert (low/high)	13.8	2.5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Sodium

End point title	Percentage of subjects who develop abnormal laboratory parameter - Sodium

End point description:
The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	100	97.6		
Alert (low/high)	0	2.4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Lipase

End point title	Percentage of subjects who develop abnormal laboratory

	parameter - Lipase

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	95.9	100		
Alert (low/high)	4.1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Potassium

End point title	Percentage of subjects who develop abnormal laboratory parameter - Potassium

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	37		
Units: percent				
number (not applicable)				
Non-alert	95.6	100		
Alert (low/high)	4.4	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Triglycerides

End point title	Percentage of subjects who develop abnormal laboratory parameter - Triglycerides

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Chloride

End point title	Percentage of subjects who develop abnormal laboratory parameter - Chloride

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Total Bilirubin

End point title	Percentage of subjects who develop abnormal laboratory parameter - Total Bilirubin

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	41		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Bicarbonate

End point title	Percentage of subjects who develop abnormal laboratory parameter - Bicarbonate

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	41		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Alkaline Phosphatase

End point title	Percentage of subjects who develop abnormal laboratory parameter - Alkaline Phosphatase

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	41		
Units: percent				
number (not applicable)				
Non-alert	97.9	100		
Alert (low/high)	2.1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Blood Urea Nitrogen

End point title	Percentage of subjects who develop abnormal laboratory parameter - Blood Urea Nitrogen

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	41		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Creatine kinase

End point title	Percentage of subjects who develop abnormal laboratory parameter - Creatine kinase

End point description:
The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	40		
Units: percent				
number (not applicable)				
Non-alert	80.9	77.5		
Alert (low/high)	19.1	22.5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Creatinine

End point title	Percentage of subjects who develop abnormal laboratory

	parameter - Creatinine

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	41		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Lactic Acid Dehydrogenase

End point title	Percentage of subjects who develop abnormal laboratory parameter - Lactic Acid Dehydrogenase

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	27		
Units: percent				
number (not applicable)				
Non-alert	97.3	100		
Alert (low/high)	2.7	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Uric acid

End point title	Percentage of subjects who develop abnormal laboratory parameter - Uric acid

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	99	97.6		
Alert (low/high)	1	2.4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Alanine transaminase

End point title	Percentage of subjects who develop abnormal laboratory parameter - Alanine transaminase

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	40		
Units: percent				
number (not applicable)				
Non-alert	96.9	100		
Alert (low/high)	3.1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Calcium

End point title	Percentage of subjects who develop abnormal laboratory parameter - Calcium

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	97.9	95.2		
Alert (low/high)	2.1	4.8		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Aspartate transaminase

End point title	Percentage of subjects who develop abnormal laboratory parameter - Aspartate transaminase

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	36		
Units: percent				
number (not applicable)				
Non-alert	97.8	100		
Alert (low/high)	2.2	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Phosphorus

End point title	Percentage of subjects who develop abnormal laboratory parameter - Phosphorus

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	37		
Units: percent				
number (not applicable)				
Non-alert	98.9	97.3		
Alert (low/high)	1.1	2.7		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Glucose

End point title	Percentage of subjects who develop abnormal laboratory parameter - Glucose

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	37		
Units: percent				
number (not applicable)				
Non-alert	98.9	100		
Alert (low/high)	1.1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Total Protein

End point title	Percentage of subjects who develop abnormal laboratory parameter - Total Protein

End point description:
The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:
until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	42		
Units: percent				
number (not applicable)				
Non-alert	100	100		
Alert (low/high)	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal laboratory parameter - Glomerular filtration rate

End point title	Percentage of subjects who develop abnormal laboratory

	parameter - Glomerular filtration rate

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	40		
Units: percent				
number (not applicable)				
Non-alert	97.9	100		
Alert (low/high)	2.1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - RR Duration

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - RR Duration

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	48		
Units: percent				
number (not applicable)				
Non-alert	58.4	45.8		
Alert (low/high)	41.6	54.2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - PR Duration

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - PR Duration

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	48		
Units: percent				
number (not applicable)				
Non-alert	97	100		
Alert (low/high)	3	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QRS Duration

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QRS Duration

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	48		
Units: percent				
number (not applicable)				
Non-alert	75.2	79.2		
Alert (low/high)	24.8	20.8		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QT Duration

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QT Duration

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	48		
Units: percent				
number (not applicable)				
Non-alert	69.3	66.7		
Alert (low/high)	30.7	33.3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QTcF

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - QTcF

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	48		
Units: percent				
number (not applicable)				
Non-alert	95	100		
Alert (low/high)	5	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - Heart Rate

End point title	Percentage of subjects who develop abnormal 12-lead electrocardiogram (ECG) parameters - Heart Rate

End point description:

The percentage of subjects who develop an abnormal value during the treatment period was calculated based on sponsor defined alert ranges.

End point type	Other pre-specified

End point timeframe:

until end of treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	48		
Units: percent				
number (not applicable)				
Non-alert	96	97.9		
Alert (low/high)	4	2.1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in vital signs parameters – Diastolic Blood Pressure

End point title	Changes from baseline in vital signs parameters – Diastolic Blood Pressure

End point description:

Descriptive statistics for the change of value from baseline to subsequent IMP administrations. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to before the 8th dose of IMP

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	21		
Units: mm/Hg				
arithmetic mean (standard deviation)	1 (± 11.74)	4.7 (± 11.66)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in vital signs parameters – Systolic Blood Pressure

End point title	Changes from baseline in vital signs parameters – Systolic Blood Pressure

End point description:

Descriptive statistics for the change of value from baseline to subsequent IMP administrations. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to before the 8th dose of IMP

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	21		
Units: mm/Hg				
arithmetic mean (standard deviation)	-3.7 (± 11.72)	0 (± 9.84)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in vital signs parameters – Heart Rate

End point title	Changes from baseline in vital signs parameters – Heart Rate

End point description:

Descriptive statistics for the change of value from baseline to subsequent IMP administrations. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to before the 8th dose of IMP

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	21		
Units: beats per minute				
arithmetic mean (standard deviation)	-3.5 (± 18.83)	-3.4 (± 17.41)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in vital signs parameters – Respiratory Rate

End point title	Changes from baseline in vital signs parameters – Respiratory Rate

End point description:

Descriptive statistics for the change of value from baseline to subsequent IMP administrations. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to before the 8th dose of IMP

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	21		
Units: breaths per minute				
arithmetic mean (standard deviation)	-0.3 (± 6.33)	2.8 (± 4.55)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Hemoglobin

End point title	Changes from baseline in safety laboratory parameters - Hemoglobin

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified
End point timeframe: baseline to end to treatment	

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	37		
Units: g/L				
arithmetic mean (standard deviation)	-4.7 (± 12.3)	-2.6 (± 14.5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Mean Corpuscular Volume

End point title	Changes from baseline in safety laboratory parameters - Mean Corpuscular Volume
End point description: Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.	
End point type	Other pre-specified
End point timeframe: baseline to end to treatment	

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	36		
Units: fL				
arithmetic mean (standard deviation)	-0.16 (± 3.23)	0.17 (± 3.78)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Hematocrit

End point title	Changes from baseline in safety laboratory parameters - Hematocrit
End point description: Descriptive statistics for the change of value from baseline to end of treatment. The mean difference	

and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	36		
Units: fraction of blood volume				
arithmetic mean (standard deviation)	-0.014 (± 0.04)	-0.009 (± 0.047)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Mean Corpuscular Hemoglobin

End point title	Changes from baseline in safety laboratory parameters - Mean Corpuscular Hemoglobin

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	37		
Units: pg				
arithmetic mean (standard deviation)	-0.02 (± 0.85)	0.22 (± 0.79)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Red blood cell count

End point title	Changes from baseline in safety laboratory parameters - Red blood cell count

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	37		
Units: TI/L				
arithmetic mean (standard deviation)	-0.153 (± 0.431)	-0.108 (± 0.498)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Mean Corpuscular Hemoglobin Concentration

End point title	Changes from baseline in safety laboratory parameters - Mean Corpuscular Hemoglobin Concentration

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	36		
Units: g/L				
arithmetic mean (standard deviation)	0.9 (± 13.6)	1.3 (± 18.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Platelet count

End point title	Changes from baseline in safety laboratory parameters - Platelet count

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	36		
Units: GI/L				
arithmetic mean (standard deviation)	-8.1 (± 66.3)	-15.4 (± 57.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - White blood cell count

End point title	Changes from baseline in safety laboratory parameters - White blood cell count

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	37		
Units: GI/L				
arithmetic mean (standard deviation)	-3.705 (± 5.366)	-3.656 (± 4.431)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Sodium

End point title	Changes from baseline in safety laboratory parameters - Sodium

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.8 (± 4.6)	-1.7 (± 4.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Lipase

End point title	Changes from baseline in safety laboratory parameters - Lipase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: U/L				
arithmetic mean (standard deviation)	4.6 (± 63.3)	5.5 (± 22.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Potassium

End point title	Changes from baseline in safety laboratory parameters - Potassium

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	33		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.09 (± 0.71)	-0.13 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Triglycerides

End point title	Changes from baseline in safety laboratory parameters - Triglycerides

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: mmol/L				
arithmetic mean (standard deviation)	0.202 (± 0.442)	0.086 (± 0.75)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Chloride

End point title	Changes from baseline in safety laboratory parameters - Chloride

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: mmol/L				
arithmetic mean (standard deviation)	-3.6 (± 4.3)	-2.1 (± 4.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Total Bilirubin

End point title	Changes from baseline in safety laboratory parameters - Total Bilirubin

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	40		
Units: umol/L				
arithmetic mean (standard deviation)	-1.154 (± 5.046)	-1.775 (± 5.526)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Bicarbonate

End point title	Changes from baseline in safety laboratory parameters - Bicarbonate

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	40		
Units: mmol/L				
arithmetic mean (standard deviation)	2.24 (± 3.11)	1.21 (± 3.56)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Alkaline Phosphatase

End point title	Changes from baseline in safety laboratory parameters - Alkaline Phosphatase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	40		
Units: U/L				
arithmetic mean (standard deviation)	-11.1 (± 28.2)	-16.8 (± 31.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Blood Urea Nitrogen

End point title	Changes from baseline in safety laboratory parameters - Blood Urea Nitrogen

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	39		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.561 (± 1.45)	-0.672 (± 1.514)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Creatine kinase

End point title	Changes from baseline in safety laboratory parameters - Creatine kinase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	35		
Units: U/L				
arithmetic mean (standard deviation)	121.2 (± 709.4)	168.8 (± 576.5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Creatinine

End point title	Changes from baseline in safety laboratory parameters - Creatinine

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	39		
Units: umol/L				
arithmetic mean (standard deviation)	-5.473 (± 12.207)	-9.564 (± 11.208)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Lactic Acid Dehydrogenase

End point title	Changes from baseline in safety laboratory parameters - Lactic Acid Dehydrogenase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	16		
Units: U/L				
arithmetic mean (standard deviation)	-3.2 (± 80.2)	9.6 (± 41.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Uric acid

End point title	Changes from baseline in safety laboratory parameters - Uric acid

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: umol/L				
arithmetic mean (standard deviation)	-28.086 (± 52.747)	-44.244 (± 70.778)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Alanine transaminase

End point title	Changes from baseline in safety laboratory parameters - Alanine transaminase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	38		
Units: U/L				
arithmetic mean (standard deviation)	4.644 (± 20.952)	1.316 (± 7.256)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Calcium

End point title	Changes from baseline in safety laboratory parameters - Calcium

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.021 (± 0.266)	-0.012 (± 0.207)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Aspartate transaminase

End point title	Changes from baseline in safety laboratory parameters - Aspartate transaminase

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference

and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	28		
Units: U/L				
arithmetic mean (standard deviation)	2.532 (± 44.521)	2.929 (± 15.309)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Phosphorus

End point title	Changes from baseline in safety laboratory parameters - Phosphorus

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	36		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.118 (± 0.34)	-0.117 (± 0.419)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Glucose

End point title	Changes from baseline in safety laboratory parameters - Glucose

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	36		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.927 (± 2.569)	-0.314 (± 1.472)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Total Protein

End point title	Changes from baseline in safety laboratory parameters - Total Protein

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	41		
Units: g/L				
arithmetic mean (standard deviation)	1.1 (± 6)	1 (± 6.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in safety laboratory parameters - Glomerular filtration rate

End point title	Changes from baseline in safety laboratory parameters - Glomerular filtration rate

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	38		
Units: mL/min/1.73m2				
arithmetic mean (standard deviation)	21.264 (± 45.339)	32.868 (± 43.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in 12-lead ECG parameters

End point title	Changes from baseline in 12-lead ECG parameters

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	46		
Units: milliseconds				
arithmetic mean (standard deviation)				
PR Duration (N=97/45)	2.1 (± 16.8)	5.3 (± 14.2)		
QRS Duration (N=99/46)	-1.2 (± 8.4)	-0.1 (± 6.1)		
QT Duration (N=99/46)	-4.2 (± 36.2)	-14.9 (± 36.9)		
QTcF (N=99/46)	-7.6 (± 25.6)	-17.7 (± 23.2)		
RR Duration (N=99/46)	8.5 (± 136.6)	1.8 (± 147.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes from baseline in 12-lead ECG parameters - Heart Rate

End point title	Changes from baseline in 12-lead ECG parameters - Heart Rate

End point description:

Descriptive statistics for the change of value from baseline to end of treatment. The mean difference and standard deviation was calculated.

End point type	Other pre-specified

End point timeframe:

baseline to end to treatment

End point values	SAF - Tapentadol	SAF - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	46		
Units: beats per minute				
arithmetic mean (standard deviation)	-3.9 (± 22.6)	-0.6 (± 19.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any Adverse Events (AE) that started at or after first administration of IMP or starting before the first dose of IMP and worsened in intensity after the first administration of IMP up to the end of the therapeutic reach of last administration of IMP.

Adverse event reporting additional description:

The therapeutic reach is the time after IMP intake that a subject is still considered to be potentially affected by a study drug. For tapentadol oral solution, the therapeutic reach is defined as 48 hours after (last) IMP intake.
Adverse events are listed by treatment and overall.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo - Safety set
Reporting group description:	
All subjects who received at least one dose of placebo.	
Reporting group title	Tapentadol - Safety set
Reporting group description:	
All subjects who received at least one dose of Tapentadol oral solution.	
Reporting group title	Overall – Safety Set
Reporting group description:	
All subjects who received at least one dose of IMP.	

Serious adverse events	Placebo - Safety set	Tapentadol - Safety set	Overall – Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	2 / 108 (1.85%)	2 / 160 (1.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Seizure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Abscess			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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	Placebo - Safety set	Tapentadol - Safety set	Overall – Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 52 (50.00%)	62 / 108 (57.41%)	88 / 160 (55.00%)
General disorders and administration site conditions			
Chest Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Face Oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Infusion Site Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	10 / 108 (9.26%)	11 / 160 (6.88%)
occurrences (all)	1	19	20
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Chylothorax			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Hypoxia			

subjects affected / exposed	0 / 52 (0.00%)	3 / 108 (2.78%)	3 / 160 (1.88%)
occurrences (all)	0	3	3
Nasal Congestion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Painful Respiration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Pleural Effusion			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Psychiatric disorders			
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 52 (3.85%)	0 / 108 (0.00%)	2 / 160 (1.25%)
occurrences (all)	2	0	2
Hallucinations, Mixed			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Initial Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 52 (3.85%)	0 / 108 (0.00%)	2 / 160 (1.25%)
occurrences (all)	2	0	2

Withdrawal syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Investigations			
Alanine Aminotransferase Increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Blood Urea Decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Haematocrit Decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Haemoglobin Decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	1 / 108 (0.93%)	2 / 160 (1.25%)
occurrences (all)	1	1	2
Hepatic Enzyme Increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Oxygen saturation decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	3 / 108 (2.78%)	4 / 160 (2.50%)
occurrences (all)	1	4	5
Po2 Decreased			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	2	2
Red blood cell count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 108 (0.00%)	1 / 160 (0.63%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Anaemia Postoperative			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	1 / 108 (0.93%)	2 / 160 (1.25%)
occurrences (all)	1	1	2
Transfusion Reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Cardiac disorders			
Sinus Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	2 / 108 (1.85%)	3 / 160 (1.88%)
occurrences (all)	1	2	3
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	4 / 108 (3.70%)	5 / 160 (3.13%)
occurrences (all)	1	7	8
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	5 / 108 (4.63%)	6 / 160 (3.75%)
occurrences (all)	1	6	7
Sedation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	2 / 108 (1.85%)	2 / 160 (1.25%)
occurrences (all)	0	2	2
Seizure			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 52 (3.85%)	6 / 108 (5.56%)	8 / 160 (5.00%)
occurrences (all)	2	6	8
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Haemorrhagic Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Eye disorders			
Eye Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal Distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Abdominal Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Constipation			

alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 52 (11.54%)	11 / 108 (10.19%)	17 / 160 (10.63%)
occurrences (all)	6	11	17
Dysphagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 52 (7.69%)	16 / 108 (14.81%)	20 / 160 (12.50%)
occurrences (all)	5	22	27
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 52 (11.54%)	25 / 108 (23.15%)	31 / 160 (19.38%)
occurrences (all)	8	36	44
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	3 / 52 (5.77%)	4 / 108 (3.70%)	7 / 160 (4.38%)
occurrences (all)	3	4	7
Rash			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Rash macular			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	3	3
Urticaria			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 52 (1.92%)	3 / 108 (2.78%)	4 / 160 (2.50%)
occurrences (all)	1	3	4
Infections and infestations			

Abdominal Abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Pneumonia mycoplasmal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Decreased Appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	1 / 108 (0.93%)	2 / 160 (1.25%)
occurrences (all)	1	1	2
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1
Hypomagnesaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 52 (1.92%)	1 / 108 (0.93%)	2 / 160 (1.25%)
occurrences (all)	1	1	2
Lactic Acidosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 52 (0.00%)	1 / 108 (0.93%)	1 / 160 (0.63%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2013	Amendment 01 was implemented to change the site of manufacture of the IMP for logistic reasons.
14 October 2014	Amendment 02 was implemented for clarification and to comply with US FDA requirements: • The definition of completers has been amended. • Subjects who are cognitively impaired in the investigator's judgment such that they cannot comply with the protocol are now excluded from participation in the trial. • The age range of the palatability and taste questionnaire has been extended downwards from 3 years to 2 years. • The dose of tapentadol oral solution for subjects between 2 years and less than 6 years has now been defined. • The list of prohibited medication taken within 14 days of allocation to IMP has been extended to include all serotonergic drugs, including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, triptans, and St. John's Wort (hypericum perforatum) for safety reasons. The time medication for sedation is prohibited has been extended to 6 hours before allocation to IMP. The use of benzodiazepines for muscle cramps and anxiety has been explicitly allowed. • The use of IMP after 24 hours has been modified to reflect medical practice by allowing its use every 4 hours to 6 hours, and by extending use up to 72 hours to comply with a requirement to assess for at least 48 hours. • The use of the University of Michigan Sedation Scale has been added for assessing sedation. • The primary endpoint will also be evaluated using Bayesian statistics as a supportive analysis. The methodology will be described in the statistical analysis plan.
16 April 2015	Amendment 03 was implemented to change the sponsor from Janssen Research & Development, LLC to Grünenthal GmbH. As a consequence, the functions of the sponsor and the operational lead were merged.

23 June 2015	Amendment 04 was implemented to: • Clarify the definition for stopping IMP. • Allow a clinician bolus of morphine or hydromorphone if the subject had unbearable pain in exceptional cases. This has been enacted to ensure that the subjects are not exposed to more pain than would normally be the case. • Add peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia to the prohibited medication from 6 hours prior to time of allocation to IMP until 4 hours after the last administration of IMP. • Exclude continuous positive airway pressure or mechanical ventilation from time of allocation to IMP until 4 hours after the last administration of IMP. • Modify 2 exclusion criteria to: − 8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate body mass index (BMI) charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). − 16. Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia that was terminated less than 6 hours before allocation to IMP. • Add an exclusion criteria of: Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP. • Allow the use of non-sponsor supplied dosing syringes. This has been enacted for logistical reasons and does not affect the outcome parameters. • Specify that the administration of IMP must not be repeated if the subject vomits or regurgitates a complete dose. • Allow the pregnancy test to be done on either a urine sample or a serum sample. • Restrict CGIC and PGIC data to a descriptive analysis in the final report.
27 October 2015	Amendment 05 was implemented to: • Define the dosing for subjects aged 6 months to <2 years old. • Provide restrictions for the medication that can be taken by mothers of a newborn or breastfeeding mother. • Allow the safety laboratory blood sample analysis to be performed at a local laboratory for subjects <2 years old to limit the amount of blood taken.
19 August 2016	Amendment 06 was implemented to: • Enable the EU PDCO data set to be analyzed for regulatory requirements prior to completion of the US FDA data set. • Remove the analysis of non-opioid analgesic medication as a secondary endpoint for logistical reasons. • Clarify an inconsistency with regard to the start of continuous oxygen saturation monitoring. • Update information on post-marketing experience. • Update the collaborator's signatories.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported