Clinical trial results:
Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years.

Summary

EudraCT number	2013-002016-27
Trial protocol	Outside EU/EEA
Global end of trial date	24 February 2014

Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	02 August 2015
Summary attachment (see zip file)	ClinicalTrialsGov summary (KF5503-68 ClinicalTrialsGov.pdf)

Trial information

Trial identification

Sponsor protocol code	KF5503/68

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01729728
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 116020

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr 6, Aachen, Germany, 52078
Public contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, 49 241 569 3223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, 49 241 569 3223, Clinical-Trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	Final
Date of interim/final analysis	28 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2014
Global end of trial reached?	Yes
Global end of trial date	24 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic profile of tapentadol and its major metabolite tapentadol-O-glucuronide after the administration of a single dose of tapentadol oral solution in children and adolescents aged from 2 years to less than 18 years after a surgical procedure that routinely produces acute severe post-surgical pain.

Protection of trial subjects:

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

The communication with the child or adolescent was done by staff who had experience with the informing of minors. The subject was asked for assent.
This trial was designed to protect the interests of the children and adolescent subjects, including minimizing risk to subjects and ensuring compliance with the recommendations made by an EMEA ad hoc working party (2008) regarding the amount of blood to be drawn as well as the monitoring of children in a controlled environment (post-operative setting that provides intensive monitoring).

Background therapy:

The trial enrolled healthy male or female subjects aged from 3 years to less than 18 years who had completed either dental surgery or a tonsillectomy and subjects aged 2 years to less than 3 years who had undergone ear, nose, or throat surgery (including but not limited to tonsillectomy).

During anesthesia, the use of pre-medication, intraoperative medication and opioid analgesics were allowed according to the usual standard of care.
During surgery, very short-acting benzodiazepines (i.e., t1/2 4 hours) and local anesthetics were allowed.
It was expected that local anesthetics, such as those used for dental procedures, may take about 1 hour to 4 hours to dissipate.
After the end of anesthesia, no opioid analgesics were given. Non-opioid analgesics were allowed.
The interval between the last administration of a non-opioid analgesic and the administration of tapentadol oral solution was at least 30 minutes.

After administration of tapentadol oral solution non-opioid analgesics were allowed as supplemental analgesic medication for persistent pain.
Subjects were encouraged, but not required, to wait at least 1 hour after the intake of tapentadol oral solution before receiving further supplemental non-opioid analgesic medication.
Morphine or another opioid were given according to medical judgment and usual standard of care if the subject continued to have persistent intolerable pain (subject perception) 2 hours or more after the administration of tapentadol oral solution despite having received a non-opioid analgesic.

Evidence for comparator:

Not applicable - no comparator was used in this trial.

Actual start date of recruitment	15 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	86
EEA total number of subjects	0

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)	61
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on the 15 Nov 2012 and the last participant completed the trial on the 24 Feb 2014.

Pre-assignment

Screening details:

Consent was obtained for 86 subjects in the trial. 66 subjects were allocated and received study drug (investigational medicinal product). Pharmacokinetic data was obtained for the planned 56 subjects.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adolescents

Arm description:

Single dose of Tapentadol Oral Solution in Adolescents Age 12 to Less than 18 years.

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

Dosage and administration details:

Single dose of 1mg/kg body weight

Arm title	Children aged 6 to less than 12 years

Arm description:

Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years.

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

Dosage and administration details:

Single dose of 1mg/kg body weight

Arm title	Children aged 2 to less than 6 years

Arm description:

Single Dose of Tapentadol Oral Solution in Children Age 2 to less than 6 years.

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

Dosage and administration details:
Single dose of 1mg/kg body weight

Number of subjects in period 1[1]	Adolescents	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years
Started	21	28	17
Completed	20	22	16
Not completed	1	6	1
Adverse event, non-fatal	-	6	-
Protocol deviation	1	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Consent was obtained for 86 subjects.
66 subjects received IMP.
Pharmacokinetic data was obtained for the planned 56 subjects.

Baseline characteristics

Reporting groups	
Reporting group title	Adolescents
Reporting group description:	
Single dose of Tapentadol Oral Solution in Adolescents Age 12 to Less than 18 years.	
Reporting group title	Children aged 6 to less than 12 years
Reporting group description:	
Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years.	
Reporting group title	Children aged 2 to less than 6 years
Reporting group description:	
Single Dose of Tapentadol Oral Solution in Children Age 2 to less than 6 years.	

Reporting group values	Adolescents	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years
Number of subjects	21	28	17
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	28	17
Adolescents (12-17 years)	21	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	15.5	8.3	3.4
standard deviation	± 1.6	± 1.6	± 1.1
Gender categorical Units: Subjects			
Female	9	17	8
Male	12	11	9
American Society of Anesthisiology Physical Status Units: Subjects			
P1	21	26	16
P2	0	2	1
Prior Medication Units: Subjects			
Prior medication	21	28	17
Concomitant medication Units: Subjects			
Concomitant medication	17	21	15
No concomitant medication	4	7	2
Type of surgery			

Units: Subjects			
Dental surgery	16	0	0
Tonsillectomy	5	28	17
Weight			
Units: kilogram(s)			
arithmetic mean	61.3	28.85	16.34
standard deviation	± 9.78	± 5.89	± 2.2
Height			
Units: meter			
arithmetic mean	1.706	1.329	1.017
standard deviation	± 0.107	± 0.111	± 0.081

Reporting group values	Total		
Number of subjects	66		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	45		
Adolescents (12-17 years)	21		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	34		
Male	32		
American Society of Anesthisiology Physical Status			
Units: Subjects			
P1	63		
P2	3		
Prior Medication			
Units: Subjects			
Prior medication	66		
Concomitant medication			
Units: Subjects			
Concomitant medication	53		
No concomitant medication	13		
Type of surgery			
Units: Subjects			
Dental surgery	16		
Tonsillectomy	50		

Weight Units: kilogram(s) arithmetic mean standard deviation	- 		
Height Units: meter arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Adolescents
Reporting group description:	
Single dose of Tapentadol Oral Solution in Adolescents Age 12 to Less than 18 years.	
Reporting group title	Children aged 6 to less than 12 years
Reporting group description:	
Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years.	
Reporting group title	Children aged 2 to less than 6 years
Reporting group description:	
Single Dose of Tapentadol Oral Solution in Children Age 2 to less than 6 years.	

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution in Adolescents

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol after a Single Dose of Tapentadol Oral Solution in Adolescents[1][2]
End point description:	
Mean and Standard Deviation of Serum Concentrations of Tapentadol. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 0.2 ng/mL.	
End point type	Primary
End point timeframe:	
Up to 15 hours after IMP administration	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	19[3]			
Units: nanogram(s) / milliliter				
arithmetic mean (standard deviation)				
15 minutes after administration (N = 19)	23.2 (± 34)			
30 minutes after administration (N=18)	45.6 (± 33)			
1 hour after administration (N=18)	49.4 (± 21.2)			
2 hours after administration (N=18)	43.1 (± 14.2)			
4 hours after administration (N=17)	32.8 (± 10.8)			
6 hours after administration (N=18)	22.3 (± 11.9)			
11 hours after administration (N=18)	8.14 (± 6.35)			
15 hours after administration (N=17)	3.66 (± 3.26)			

Notes:

[3] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose Tapentadol Oral Solution in Adolescents

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose Tapentadol Oral Solution in Adolescents[4][5]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Tapentadol-O-glucuronide is the metabolite of tapentadol. Metabolites are sometimes referred to as "breakdown products". The body alters the administered medication to a metabolite so that it can be more easily or quickly removed from the body. Tapentadol-O-glucuronide concentrations were measured in subjects. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 10 ng/mL.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[6]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
15 minutes after administration (N = 18)	404 (± 581)			
30 minutes after administration (N=17)	855 (± 672)			
1 hour after administration (N=17)	1424 (± 542)			
2 hours after administration (N=18)	1202 (± 366)			
4 hours after administration (N=17)	824 (± 191)			
6 hours after administration (N=18)	497 (± 138)			
11 hours after administration (N=18)	150 (± 69)			
15 hours after administration (N=17)	66.9 (± 35.4)			

Notes:

[6] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol After a Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol After a Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years[7][8]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 0.2 ng/mL.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

End point values	Children aged 6 to less than 12 years			
Subject group type	Reporting group			
Number of subjects analysed	22[9]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
15 minutes to 1 hour after administration (N = 22)	36.5 (± 21.8)			
1 to 4 hours after administration (N=22)	36.5 (± 15.7)			
4 to 11 hours after administration (N=22)	13.5 (± 6.52)			
11 to 15 hours after administration (N=22)	3.71 (± 1.96)			

Notes:

[9] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years[10][11]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Tapentadol-O-

glucuronide is the metabolite of tapentadol. Metabolites are sometimes referred to as "breakdown products". The body alters the administered medication to a metabolite so that it can be more easily or quickly removed from the body. Tapentadol-O-glucuronide concentrations were measured in participants. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 10 ng/mL.

End point type	Primary

End point timeframe:

Up to 15 hours after dosing

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model

End point values	Children aged 6 to less than 12 years			
Subject group type	Reporting group			
Number of subjects analysed	22[12]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
15 minutes to 1 hour after administration (N = 20)	676 (± 343)			
1 to 4 hours after administration (N=22)	900 (± 330)			
4 to 11 hours after administration (N=22)	321 (± 123)			
11 to 15 hours after administration (N=22)	86.3 (± 37.8)			

Notes:

[12] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol After a Single Dose of Tapentadol Oral Solution in Children Age 3 to less than 6 years

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol After a Single Dose of Tapentadol Oral Solution in Children Age 3 to less than 6 years[13][14]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 0.2 ng/mL.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

End point values	Children aged 2 to less than 6 years			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
15 minutes after administration (N=11)	30.1 (± 19.2)			
4 to 11 hours after administration (N=11)	26.4 (± 10.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose of Tapentadol Oral Solution in Children Age 3 to less than 6 years

End point title	Pharmacokinetic Profile of Serum Concentrations of Tapentadol-O-glucuronide After a Single Dose of Tapentadol Oral Solution in Children Age 3 to less than 6 years[15][16]

End point description:

Mean and Standard Deviation of Serum Concentrations of Tapentadol-O-glucuronide. Tapentadol-O-glucuronide is the metabolite of tapentadol. Metabolites are sometimes referred to as "breakdown products". The body alters the administered medication to a metabolite so that it can be more easily or quickly removed from the body. Tapentadol-O-glucuronide concentrations were measured in participants. Serum was analyzed by means of liquid chromatography coupled to tandem mass spectrometry with a lower limit of quantification (LLOQ) at 10 ng/mL.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic profiles for the different arms are reported as separate endpoints, as the pharmacokinetic sampling schemes differ between the different age groups. Sampling schemes were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.

End point values	Children aged 2 to less than 6 years			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)				
15 minutes to 1 hour after administration (N = 10)	494 (± 377)			
4 to 11 hours after administration (N=11)	504 (± 112)			

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter of Tapentadol Area Under the Concentration-Time Curve (AUC0-15) After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter of Tapentadol Area Under the Concentration-Time Curve (AUC0-15) After a Single Dose of Tapentadol in Adolescents[17][18]

End point description:

Serum samples for pharmacokinetic analysis were obtained using frequent sampling techniques in participants 12 years to less than 18 years of age.
The area under the curve from dose to 15 hours (AUC 0-15) is a summary measure of data from each pharmacokinetic blood sample taken over the 15 hour time period. The area is that below the line fitted to the data points. Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[19]			
Units: ng*hr/mL				
arithmetic mean (full range (min-max))	302 (218 to 636)			

Notes:

[19] - Subjects with pharmacokinetic data.

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter: Cmax (Maximum Concentration) of Tapentadol After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter: Cmax (Maximum Concentration) of Tapentadol After a Single Dose of Tapentadol in Adolescents[20][21]

End point description:

Serum samples for pharmacokinetic analysis were obtained using frequent sampling techniques in participants 12 years to less than 18 years of age.
Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours. The concentration of tapentadol (active drug) is assessed during absorption and distribution.
The maximum concentration is derived from the Area Under the Curve, from dose to 15 hours (AUC 0-15). It is the highest amount of active drug observed in the blood sample.

End point type	Primary

End point timeframe:

Up 15 hours after IMP administration

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[22]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard error)	67.5 (± 26.3)			

Notes:

[22] - Subjects with pharmacokinetic data.

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter: Time to Maximum Concentration (Tmax) of Tapentadol After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter: Time to Maximum Concentration (Tmax) of Tapentadol After a Single Dose of Tapentadol in Adolescents[23][24]

End point description:

Serum samples for pharmacokinetic analysis were obtained using frequent sampling techniques in participants 12 years to less than 18 years of age.
The time to maximum concentration is derived from the area under the curve from dose to 15 hours (AUC 0-15). The Tmax is the time after dosing at which the maximum concentration of the tapentadol (active drug) occurs.
Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[25]			
Units: hour(s)				
arithmetic mean (standard deviation)	1.4 (± 1.1)			

Notes:

[25] - Subjects with pharmacokinetic data.

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter of Tapentadol-O-glucuronide Area Under the Concentration-Time Curve (AUC 0-15) After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter of Tapentadol-O-glucuronide Area Under the Concentration-Time Curve (AUC 0-15) After a Single Dose of Tapentadol in Adolescents[26][27]

End point description:

Serum samples for pharmacokinetic analysis were obtained using frequent sampling techniques in subjects 12 years to less than 18 years of age.
Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours. The concentration of tapentadol-O-glucuronide (metabolite) is assessed during absorption and distribution.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng*hr/mL				
arithmetic mean (full range (min-max))	7082 (4946 to 9689)			

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter: Time to Maximum Concentration (Tmax) of Tapentadol-O-glucuronide After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter: Time to Maximum Concentration (Tmax) of Tapentadol-O-glucuronide After a Single Dose of Tapentadol in Adolescents[28][29]

End point description:

Tapentadol-O-glucuronide is the metabolite of tapentadol. Metabolites are sometimes referred to as "breakdown products". The body alters the administered medication to a metabolite so that it can be more easily or quickly removed from the body. Serum samples for pharmacokinetic analysis were obtained using frequent sampling techniques in subjects 12 years to less than 18 years of age. The time to maximum concentration is derived from the area under the curve from dose to 15 hours (AUC 0-15). The Tmax is the time after dosing at which the maximum concentration of the tapentadol-O-glucuronide (metabolite) occurs. Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[30]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard deviation)	1.7 (± 1.19)			

Notes:

[30] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Primary: Non-Compartmental Pharmacokinetic (PK) Parameter: Cmax (Maximum Concentration) of Tapentadol-O-glucuronide After a Single Dose of Tapentadol in Adolescents

End point title	Non-Compartmental Pharmacokinetic (PK) Parameter: Cmax (Maximum Concentration) of Tapentadol-O-glucuronide After a Single Dose of Tapentadol in Adolescents[31][32]

End point description:

Tapentadol-O-glucuronide is the metabolite of tapentadol. Metabolites are sometimes referred to as "breakdown products". The body alters the administered medication to a metabolite so that it can be more easily or quickly removed from the body. Serum samples (frequent sampling) were drawn at 0.25, 0.5, 1, 2, 4, 6, 11, and 15 hours. The concentration of tapentadol-O-glucuronide (metabolite) is assessed to study absorption and distribution.
The maximum concentration is derived from the Area Under the Curve, from dose to 15 hours (AUC 0-15). It is the highest amount of metabolite observed in the blood sample.

End point type	Primary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The sample sizes for the age groups were not chosen based on statistical considerations of clinical endpoints, but were selected to limit the exposure in pediatric subjects whilst providing sufficient data to explore a population pharmacokinetic model.
[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic sampling schemes differ between the different age groups, and only a frequent pharmacokinetic sampling scheme as applicable for this arm allows for determination of non-compartmental pharmacokinetic parameters.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	18[33]			
Units: nanogram(s)/milliliter				
arithmetic mean (standard error)	1487 (± 495)			

Notes:

[33] - Subjects with pharmacokinetic data available.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Assessments Using the Visual Analog Scale (VAS) in Adolescents

End point title	Pain Intensity Assessments Using the Visual Analog Scale (VAS) in Adolescents[34]

End point description:

At predefined times after investigational medicinal product administration participants in the Arms with Adolescents (age 12 to less than 18 years) were asked to rate their pain on 100 mm line (visual analog scale - VAS) by marking a point on the line in response to:
“My pain at this time is”. The mark was scored between “no pain” and ” pain as bad as it could be”. The distance was then measured by a clinician and reported.
A value of 0 indicates "no pain". A value of 100 indicates "pain as bad as it could be".

End point type	Secondary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain intensity was assessed using age appropriate pain scales. Therefore, different pain scales were used for the different arms, and are thus reported separately.

End point values	Adolescents			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: units on a scale				
arithmetic mean (standard deviation)				
Pre-dosing	71.5 (± 13.3)			
15 minutes after dosing	63.6 (± 24.4)			
30 minutes after dosing	53.2 (± 27.3)			
1 hour after dosing	46.3 (± 26.5)			
2 hours after dosing	34 (± 24.6)			
4 hours after dosing	43.5 (± 26.8)			
6 hours after dosing	34.8 (± 24.3)			
11 hours after dosing	32.7 (± 21.1)			
15 hours after dosing	33.4 (± 20.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Assessments Using the McGrath Color Analog Scale in Adolescent Subjects and Children Age 6 years and older

End point title	Pain Intensity Assessments Using the McGrath Color Analog Scale in Adolescent Subjects and Children Age 6 years and older[35]

End point description:

Pain intensity assessments were with a 0 (no pain) to 10 (worst pain) scored McGrath color analog scale (CAS) in participants aged 6 years to less than 18 years, i.e. in Adolescents and Older Children. Subjects were presented with the CAS and instructed to place the sliding bar on the color that best represented their pain intensity level at the time of assessment. The CAS is a pocket size tool used to measure the self-reported pain intensity of the older participants. The CAS consists of a 145 mm long triangular shaped strip of plastic, varying in width and hue from 1 mm wide and light pink hue at the bottom (and text no pain), to 3 mm wide and deep red hue at the top (most pain).
This instrument includes 2 sides. One side shows the color pain intensity scale as described and the other shows a graduated scale, which provides a specific numeric value for the subject-reported level of pain.

End point type	Secondary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain intensity was assessed using age appropriate pain scales. Therefore, different pain scales were used for the different arms, and are thus reported separately.

End point values	Adolescents	Children aged 6 to less than 12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[36]	28[37]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Pre-dose	6.643 (± 1.461)	4.67 (± 1.602)		
15 minutes after dosing	6.131 (± 2.18)	3.071 (± 1.718)		
30 minutes after dosing	5.262 (± 2.311)	2.571 (± 1.824)		
1 hour after dosing	4.393 (± 2.299)	2.407 (± 1.723)		
2 hours after dosing	3.475 (± 2.173)	2.292 (± 1.793)		
4 hours after dosing	4.2 (± 2.113)	2.341 (± 1.899)		
6 hours after dosing	3.438 (± 1.96)	2.636 (± 2.152)		
11 hours after dosing	3.35 (± 1.836)	3.352 (± 1.851)		
15 hours after dosing	3.288 (± 1.578)	3.568 (± 2.549)		

Notes:

[36] - Subjects with data available.

[37] - Subjects with data available.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Assessments Using the Faces Pain Scale (Revised) in Children Age 3 to Less Than 12 Years

End point title	Pain Intensity Assessments Using the Faces Pain Scale (Revised) in Children Age 3 to Less Than 12 Years[38]

End point description:

This assessment tool was used in 3 to less than 12 year old participants.
The Faces Pain Scale (Revised) [FPS-R] score as allocated to a selected face by the subject.
There are 6 faces and the subject is asked to indicate on a face to express how much it hurts.
The numeric value 0 (no pain) to 10 (very much pain) is read off the reverse side of the scale by the clinician.

The protocol pre-specified that the Faces Pain Scale (Revised) would not be administered in the very young subjects (aged 2 to less than 3 years).

End point type	Secondary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain intensity was assessed using age appropriate pain scales. Therefore, different pain scales were used for the different arms, and are thus reported separately.

End point values	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	12[39]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Pre-dose	4.8 (± 1.6)	6.8 (± 3.2)		
15 minutes after dosing	3.5 (± 1.8)	4.5 (± 3.2)		
30 minutes after dosing	2.9 (± 1.8)	2.8 (± 3.2)		
1 hour after dosing	2.4 (± 1.6)	1.8 (± 3.3)		
2 hours after dosing	2.6 (± 1.7)	1.2 (± 2.9)		
4 hours after dosing	2.5 (± 1.6)	3.5 (± 3.2)		
6 hours after dosing	2.7 (± 2.1)	1.8 (± 2.3)		
11 hours after dosing	2.7 (± 1.7)	2.3 (± 2.4)		
15 hours after dosing	3.5 (± 2.2)	2.8 (± 2.9)		

Notes:

[39] - 2 year old subjects were excluded.

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Assessment Using the Face, Legs, Activity, Cry, Consolability Scale Children Age 2 to Less Than 6 Years

End point title	Pain Intensity Assessment Using the Face, Legs, Activity, Cry, Consolability Scale Children Age 2 to Less Than 6 Years[40]

End point description:

The Face Legs Activity Cry Consolability (FLACC) Scale was developed by the Department of Anesthesiology, University of Michigan Medical School and Health Systems. The FLACC Scale is a behavioral scale for scoring postoperative pain in children between the ages of two months and seven years or in persons unable to communicate.
In this trial the scale was used in the young and very young children, i.e. in participants aged 2 to less than 6 years.
This tool includes five categories of pain behaviors, including facial expression, leg movement, activity, cry, and consolability the clinician observes the participant for 5 minutes or more and scores each category with a 0, 1 or 2. The scores are added together for a total score ranging from 0 (no pain) to 10 (worst pain). The higher the total score the higher the pain.

The protocol pre-specified that the young (3 to less than 6 year olds) and very young children (2 to less than 3 year olds) will be reported as one group.

End point type	Secondary

End point timeframe:

Up to 15 hours after IMP administration

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pain intensity was assessed using age appropriate pain scales. Therefore, different pain scales were used for the different arms, and are thus reported separately.

End point values	Children aged 2 to less than 6 years			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Pre-dose	4.2 (± 2.2)			
15 minutes after dosing	1.8 (± 1.6)			
30 minutes after dosing	1.2 (± 1.6)			
1 hour after dosing	1.1 (± 1.4)			
2 hours after dosing	0.8 (± 1.1)			
4 hours after dosing	1.5 (± 1.7)			
6 hours after dosing	0.8 (± 1.6)			
11 hours after dosing	0.9 (± 2.1)			
15 hours after dosing	0.8 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sum of Pain Intensity Differences Over the 4 Hours After Dosing Derived From the Different Pain Scales and for Children Age 2 to less than 18

End point title	Sum of Pain Intensity Differences Over the 4 Hours After Dosing Derived From the Different Pain Scales and for Children Age 2 to less than 18

End point description:

Different pain intensity assessment tools were used in the different age groups. Therefore the sum of pain intensities were calculated and are reported for each age group based on the tool used.
Adolescents - Age 12 to Less than 18 Years - VAS (100 mm Visual Analog Scale) [Theoretical Range: -400 to + 400],
Age 6 to Less Than 12 Years - CAS (McGrath color analog scale) [Theoretical Range: -40 to + 40],
Young and Very young children - Age to less than 6 Years - FLACC (Face, Legs, Activity, Cry, and Consolability score) [Theoretical Range: -40 to + 40].

A mean score of zero indicates that there was no pain intensity change over the 4 hours.
The positive values indicate that in the group as a whole the sum of all pain intensity values over the first 4 hours lead to a reduction in pain in the time period.

End point type	Secondary

End point timeframe:

Up to 4 hours after IMP administration

End point values	Adolescents	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[41]	22[42]	16[43]	
Units: units on a scale				
arithmetic mean (standard deviation)	106.282 (± 75.35)	9.698 (± 7.61)	11.831 (± 8.193)	

Notes:
[41] - SPID based on VAS
[42] - SPID based on CAS
[43] - SPID based on FLACC

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event that started on the intake of tapentadol up to 48 hours thereafter.

Adverse event reporting additional description:

For tapentadol oral solution, the therapeutic reach is defined as 48 hours after intake.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Adolescents

Reporting group description:

Single dose of Tapentadol Oral Solution in Adolescents Age 12 to Less than 18 years.

Reporting group title	Children aged 6 to less than 12 years

Reporting group description:

Single Dose of Tapentadol Oral Solution in Children Age 6 to less than 12 years.

Reporting group title	Children aged 2 to less than 6 years

Reporting group description:

Single Dose of Oral Solution in Children Age 2 to less than 6 years.

Serious adverse events	Adolescents	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 3.6 %

Non-serious adverse events	Adolescents	Children aged 6 to less than 12 years	Children aged 2 to less than 6 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 21 (57.14%)	20 / 28 (71.43%)	6 / 17 (35.29%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	1	0	1
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Cardiac murmur			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 21 (14.29%)	3 / 28 (10.71%)	0 / 17 (0.00%)
occurrences (all)	3	3	0
Headache			
subjects affected / exposed	2 / 21 (9.52%)	0 / 28 (0.00%)	2 / 17 (11.76%)
occurrences (all)	2	0	2
Somnolence			
subjects affected / exposed	1 / 21 (4.76%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Infusion site irritation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	1	1	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal upper pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Enlarged uvula			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	6 / 21 (28.57%)	9 / 28 (32.14%)	1 / 17 (5.88%)
occurrences (all)	6	12	1
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	8 / 28 (28.57%)	0 / 17 (0.00%)
occurrences (all)	3	9	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 28 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0

Rash			
subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 21 (4.76%)	0 / 28 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Otitis media viral			
subjects affected / exposed	0 / 21 (0.00%)	1 / 28 (3.57%)	0 / 17 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2012	This amendment reflected the feedback from regulatory authorities, and implemented correction of inconsistencies in the original protocol including minor editorial changes. This amendment was implemented before the start of subject recruitment.
26 March 2013	This amendment enabled the enrollment of children aged 3 years to less than 6 years. An interim analysis of safety and pharmacokinetic data from this trial was required regarding the need for dose determination and validation via population pharmacokinetic models prior to the start of other trials investigating the efficacy of tapentadol in moderate to severe acute and chronic pain in the pediatric population.
20 August 2013	This amendment enabled the enrollment of children aged 2 years to less than 3 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Another opioid may have been given according to medical judgment/standard of care if the subject had persistent intolerable pain 2 hours or more after administration of tapentadol oral solution even if a non-opioid analgesic had been administered.

Notes: