SDR-CTR-SYN-06

Type of report	Full report
Trial code	KF5503/65 R331333PAI3037
Title of trial	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.
Trial design	Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution.
Development phase	Phase III
EudraCT number	2012-004359-35
IND number	108134
ClinicalTrials.gov number	NCT02081391
Paediatric Investigation Plan (PIP)	EMEA-000018-PIP01-07
Investigational medicinal products (IMPs)	Tapentadol oral solution, Placebo
Indication	Post-operative acute pain
International coordinating investigator	Prof Dr [redacted] Division of Clinical Pharmacology, Children's National Health System, 111 Michigan Avenue, N.W. Washington, D.C. 20010, United States of America.
Trial sites	Total: 44 sites: Bulgaria 3, Croatia 2, Czech Republic 3, France 3, Germany 1, Hungary 3, Poland 8, Spain 5, United Kingdom 2, United States 14.
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted], MD, International Clinical Lead. Contact number: +49 (241) 569 0
Trial period	First subject in: 19 Feb 2015 Last subject out (EU PDCO Set): 05 Dec 2016 Last subject out (US FDA Set) 14 Mar 2019
Previous report	23 May 2017 (Version 1.0)

Objectives

This trial was 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]). The objectives and data for the EU part (subjects aged 2 years to <18 years old) were previously presented in Version 1.0 of this report in line with the EU pediatric requirements and plan agreed with the PDCO. At that time, recruitment of subjects aged <2 years required for the completion of the US part was still ongoing. Data obtained from these subjects are now incorporated into this report.

In this report, the objectives and endpoints for the EU and US part are referenced as EU PDCO and US FDA objectives and endpoints respectively.

Primary objectives:

This trial was part of a pediatric development program that fulfills different requirements set out in the Paediatric Investigation Plan (EMEA-000018-PIP01-07) for the EU PDCO and the Pediatric Research Equity Act (PREA) requirement and Written Request for pediatric studies issued by US FDA.

The primary efficacy objective was to evaluate the efficacy of tapentadol oral solution (OS), based on the total amount of supplemental opioid analgesic medication used over 12 hours (US FDA) and 24 hours (EU PDCO) following initiation of IMP, in children and adolescents aged from birth to less than 17 years (US FDA) and in children and adolescents aged 2 years to <18 years (EU PDCO) who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

Another primary objective for both EU PDCO and US FDA was to evaluate the safety of tapentadol OS in children and adolescents aged 2 years to <18 years (EU PDCO) and children and adolescents aged from birth to less than 17 years (US FDA) who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

The primary efficacy objective (either 12 hours or 24 hours) for 1 region was considered as the secondary efficacy objective in the other region, as described above.

Secondary objectives:

To assess the efficacy of tapentadol OS, using multiple subjective and objective measures of the subject's response to treatment.

Investigational medicinal products

The 2 IMPs were:

- Placebo.
- Tapentadol OS (4 mg/mL oral solution and 20 mg/mL oral solution).

Placebo solution matching tapentadol OS: Bulk batch number 12K08/G027 with expiry date10/2017, 14B05/G027 with expiry dates 02/2016 and 01/2019, and 102H with an expiry date 04/2020.

Tapentadol OS 4 mg/mL: Bulk batch number 12K12/F041 with expiry date 10/2017, 14B10/F041 with expiry dates 02/2016 and 01/2019, and G0001 with expiry date 04/2020.

Tapentadol OS 20 mg/mL: Bulk batch number 12K15/F038 with expiry date 10/2017, and 14B13/F038 with expiry dates 02/2016 and 01/2019.

The dosing regimen was as follows:

Age of subject	Dose for the first 24 hours	Dose after the first 24 hours	Body weight	Tapentadol OS or placebo OS
6 months to <18 years old	1.25 mg/kg	1.25 mg/kg or 1.0 mg/kg	<20 kg	4 mg/mL
			≥20 kg	20 mg/mL
30 days to <6 months old	0.5 mg/kg	0.5 mg/kg or 0.3 mg/kg	-	4 mg/mL [a]
Birth to <30 days old	0.1 mg/kg	0.1 mg/kg or 0.075 mg/kg	-	4 mg/mL [a]

a) For subjects aged <6 months, the oral solutions of tapentadol 4 mg/mL or placebo were diluted 4-fold.

The allocation to IMP was stratified by age groups (birth to less than 30 days, 30 days to less than 6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years, and 17 years to <18 years) and by use of morphine or hydromorphone as supplemental opioid analgesia. Subjects were allocated 2:1 to tapentadol OS or placebo.

Trial treatments

The IMP was administered as an oral solution. The dosing interval was 4 hours (range ±15 minutes). If the subject was sleeping at the time of the scheduled dose, they were woken up to take the IMP within a maximum of 6 hours after the previous dose. The administration of IMP was based on the investigator's judgment of the subject's condition and sedation level.

The dose of IMP could be reduced after 24 hours if there was a reduced need for analgesia according to the investigator's judgment.

Trial population

The trial population for this report comprised male and female subjects from birth (≥37 weeks gestational age) to <18 years old who 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). Subjects should have received post-operative morphine or hydromorphone by NCA/PCA, with or without a background infusion of the same opioid, according to standard of care prior to allocation to IMP. The subjects were expected to require morphine or hydromorphone by NCA/PCA after starting IMP. The subjects had to be able to tolerate liquids at the time of allocation to IMP. 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 was not allowed.

Subjects were excluded with a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection, febrile seizure, paralytic ileus) that in the opinion of the investigator could affect or compromise subject safety during the trial participation. Subjects were also excluded if they were obese in the investigator's judgment or if their weight was lower than 2500 g, if they had a history of non-febrile seizure disorder, epilepsy, serotonin syndrome, traumatic or hypoxic brain injury, brain contusion, stroke, transient ischemic attack, intracranial hematoma, post-traumatic amnesia, brain neoplasm, or episodes of unconsciousness of more than 24 hours, moderate to severe renal or hepatic impairment, abnormal pulmonary function or clinically relevant respiratory disease (e.g., acute or severe bronchial asthma, hypercapnia), clinically relevant abnormal electrocardiogram (ECG) findings, post-operative clinically unstable systolic and diastolic blood pressure, heart rate, respiratory depression, or clinically unstable upper or lower airway conditions, or a saturation of peripheral oxygen (SpO_2) <92% at the time of allocation to IMP.

Summary of the trial procedures and assessments

The trial consisted of an Enrollment Period starting up to 28 days before allocation to IMP and lasting up to the time of allocation to IMP, whereby subjects could be enrolled in the trial either pre- or post-operatively; a Treatment and Evaluation Period (up to 96 hours); and a Follow-up Period (10 days to 14 days after the first dose of IMP).

The subjects underwent scheduled surgery. At some time after the surgery, the subject should have been started on NCA/PCA with morphine or hydromorphone, with or without a background opioid infusion, according to the standard of care. The background infusion (if any) had to be with a low dose infusion of the same opioid as that used for the NCA/PCA, i.e., morphine or hydromorphone.

When subjects met all of the inclusion criteria and none of the exclusion criteria, they were allocated/randomized to IMP (tapentadol oral solution or placebo) using an interactive voice/web response system (IVRS/IWRS).

The first dose of IMP was given when the investigator determined that it was medically appropriate for the subject to receive the IMP.

After the first dose of IMP, NCA/PCA was continued with the same opioid as used previously (i.e., morphine or hydromorphone, defined as supplemental opioid analgesia), according to investigator judgment and standard of care.

At the time of the first IMP administration, the background opioid infusion (if any) was discontinued.

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, oxygen saturation, and pain scores (using an age appropriate scale) were measured before each dose of IMP was given.

Dosing with IMP was stopped if:

- A switch to exclusively oral opioid analgesic medication was indicated according to the local standard of care.
- Opioid analgesic medication was no longer needed.

- IMP had been administered for 72 hours.

Trial performance

Protocol amendments

There were 7 protocol amendments implemented.

Clinical hold or early termination of the trial

Recruitment was paused in 2017 to amend the protocol for the inclusion of children <2 years of age and to identify sites able to manage this specific population. The trial was set on voluntary hold from 29 Jun 2018 to 14 Sep 2018 to investigate a potential quality issue with the medication which was not confirmed. There was no early termination of the trial.

Summary of the statistical methods

The sample size determination was based on the primary efficacy endpoint variable for the respective Full Analysis Sets (FASs) for the EU PDCO and US FDA. A linear relationship was assumed between the 12 hour and 24 hour supplemental opioid analgesic use for the purposes of the sample size calculation and the final analyses.

The sample size calculation was based on results from previously conducted trials in post-surgical pediatric subjects where supplemental opioid was measured. A value of 0.20 mg/kg in 24 hours (0.10 mg/kg in 12 hours) for the between-treatment group difference and a more conservative value of 0.42 mg/kg in 24 hours (0.21 mg/kg in 12 hours) for the standard deviation (SD) were considered adequate assumptions. Assuming $\alpha = 0.05$ (two-sided), 80% power ($\beta = 0.2$), and a randomization ratio of 2:1 (tapentadol to placebo) resulted in a sample size of 106 tapentadol-treated subjects and 53 placebo-treated subjects, i.e., 159 subjects in the EU PDCO Set and 159 subjects in the US FDA Set. Due to the overlapping age groups as per regulatory requirements, it was expected that approximately 168 subjects would be treated with IMP overall.

Subjects were assigned to the subject populations during the final statistical review before unblinding.

It was agreed with US FDA to report all analyses using the EU PDCO populations complemented by the respective population of subjects <2 years of age.

Enrolled Set

The Enrolled Set (denoted by *Enrolled-All)* includes all enrolled subjects (as defined in the protocol) of the trial.

For the EU PDCO, the Enrolled Set includes all enrolled subjects (as defined in the protocol) from 2 years to <18 years of age and is denoted by *Enrolled-EU*. For the US FDA, the set of subjects <2 years old is referred to as *Enrolled-All <2*.

Allocated Set

The overall Allocated Set includes all enrolled subjects that are allocated (randomized) to IMP. This set is denoted by *Allocated-All*.

For the EU PDCO, the Allocated Set includes allocated subjects from 2 years to <18 years of age and is denoted by *Allocated-EU.* For the US FDA, the set of subjects <2 years old is referred to as *Allocated -All <2*.

Safety Set

The Safety Set (SAF) comprises all treated subjects in the required age ranges for the EU PDCO and US FDA. The overall SAF includes all treated subjects of the trial. This set is denoted by *SAF-All*. The EU PDCO SAF includes subjects 2 years to <18 years of age and is denoted by *SAF-EU*. For the US FDA, the set of subjects <2 years old is referred to as *SAF-US <2*.

A subject is considered as treated if administered any amount of IMP.

If by error a subject did not receive the allocated medication, the subject was evaluated according to the received IMP.

Full Analysis Set

The overall Full Analysis Set (FAS) includes all subjects that are allocated and treated. This set is denoted by *FAS-All*.

The EU PDCO FAS includes allocated and treated subjects aged 2 years to <18 years old and is denoted by *FAS-EU*. For the US FDA, the set of subjects <2 years old is referred to as *FAS-US <2*.

If by error a subject did not receive the allocated medication, the subject was evaluated as allocated within the FAS following the intention-to-treat principle.

Per Protocol Set

One Per Protocol Set (PPS) defining a subset of the subjects in the FAS-EU without any major protocol deviations affecting the primary efficacy endpoint was used for both primary endpoint analyses. This set is denoted as PPS-EU. The major protocol deviations which led to the exclusion of a subject from the PPS were decided during blinded data review meetings held before locking and unblinding the data.

The primary and all efficacy analyses were based on the FAS-EU. Some of the efficacy analyses were repeated for the FAS-US<2. The safety analyses were conducted on the SAF-EU complemented with a descriptive analysis of SAF-US<2.

The primary null hypothesis to be tested was that the tapentadol group was not different from the placebo group for the primary efficacy endpoints. The alternative hypothesis was that the tapentadol group was different from the placebo group for the primary efficacy endpoints. For the primary efficacy endpoints, descriptive statistics were presented by treatment group and the endpoints were analyzed using an analysis of variance (ANOVA) model (FAS-EU), which included treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Treatment effects were estimated based on least-squares means of the difference. The 95% confidence interval and p-value for tapentadol compared with placebo were presented. The test for the primary efficacy analysis was 2-sided at a 0.05 level of significance. Summary statistics for the 24 hour (EU PDCO) primary efficacy endpoint for this report were provided by age group for subjects aged 2 years and older (2 years to <6 years, 6 years to <12 years, 12 years to <17 years, and 17 years to <18 years) and by method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses. For subjects aged <2 years, both primary endpoints were analyzed descriptively.

Each secondary endpoint was analyzed using appropriate statistical methods. There were no multiplicity adjustments for any of the secondary endpoints.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 19.1). For each adverse event, the percentage of subjects who experienced at least 1 occurrence of the given event was summarized by treatment group. The incidence, type, intensity, onset, relationship, treatment, and outcome of treatment emergent adverse events (TEAEs) was listed and presented descriptively according to treatment group. Serious adverse events were listed.

Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings were provided for summarizing safety laboratory parameters (only for blood samples analyzed at the central laboratory), 12-lead ECG, vital signs, and oxygen saturation across treatment group. Descriptive statistics were provided for the sedation scores.

Changes in physical examination findings compared to Visit 1 were summarized by body system and the results were listed. The Columbia-Suicide Severity Rating Scale (C-SSRS) results were listed.

Summary of results

Subject disposition

A total of 216 subjects were enrolled, 180 of these subjects were allocated to IMP and 175 subjects received IMP (56 subjects on placebo and 119 subjects on tapentadol OS). Of the 175 subjects receiving IMP, 150 subjects (50 subjects on placebo and 100 subjects on tapentadol OS) completed 12 hours of treatment with IMP and 148 of these subjects (49 subjects on placebo and 99 subjects on tapentadol OS) attended the follow up visit thereby completing the trial. In total, 104 subjects (32 subjects on placebo and 72 subjects on tapentadol OS) completed 24 hours of treatment with IMP. All of these subjects attended the follow up visit and completed the trial.

Subject disposition - Enrolled subjects

Parameter	Placebo n (%)	Tapentadol OS n (%)	Overall n (%)
Subjects enrolled			216 (100)
Subjects enrolled but not allocated (randomized)			36 (16.7)
Inclusion Criteria Not Met / Exclusion Criteria Met			28 (13.0)
Adverse Event			1 (0.5)
Withdrawal By Subject			4 (1.9)
Other			3 (1.4)
Allocated subjects	59 (100)	121 (100)	180 (100)
Safety Set (SAF)	56 (94.9)	119 (98.3)	175 (97.2)
Full Analysis Set (FAS)	56 (94.9)	119 (98.3)	175 (97.2)
Per Protocol Set (PPS)	49 (83.1)	105 (86.8)	154 (85.6)
Full Analysis Set	56 (100)	119 (100)	175 (100)
12 hours treatment period completers [a]	50 (89.3)	100 (84.0)	150 (85.7)
Treatment discontinuation before 12 hours	6 (10.7)	19 (16.0)	25 (14.3)
24 hours treatment period completers [a]	32 (57.1)	72 (60.5)	104 (59.4)
Treatment discontinuation before 24 hours	24 (42.9)	47 (39.5)	71 (40.6)

Parameter	Placebo n (%)	Tapentadol OS n (%)	Overall n (%)
12 hours trial completers [a]	49 (87.5)	99 (83.2)	148 (84.6)
12 hours trial non-completers [b]	7 (12.5)	20 (16.8)	27 (15.4)
24 hours trial completers [a]	32 (57.1)	72 (60.5)	104 (59.4)
24 hours trial non-completers [b]	24 (42.9)	47 (39.5)	71 (40.6)
12 hours treatment period completers	50 (100)	100 (100)	150 (100)
24 hours treatment period completers [a]	32 (64.0)	72 (72.0)	104 (69.3)
24 hours treatment period discontinuations between 12 and 24 hours of treatment	18 (36.0)	28 (28.0)	46 (30.7)
12 hours trial completers	49 (100)	99 (100)	148 (100)
24 hours trial completers [a]	32 (65.3)	72 (72.7)	104 (70.3)
24 hours trial discontinuations between 12 and 24 hours of treatment	17 (34.7)	27 (27.3)	44 (29.7)

a) 12/24 hours treatment period completers are subjects for whom is was decided to discontinue treatment later than 12/24 hours after first IMP intake, respectively. 12/24 hours trial completers are 12/24 hours treatment period completer that completed the Follow-up Visit, respectively.

b) Treatment discontinued before 24 hours or follow-up visit not performed.

n = number of subjects; % = Percentage is given as a percentage of number of subjects enrolled, allocated, in the FAS, respectively; OS = oral solution.

Source: Table 15.1.1.1.1, Table 15.1.1.3.1

Demographics

Amongst subjects from 2 years to <18 years (160 subjects), the distribution of males (52.5%) and females (47.5%) was almost equal. Almost all subjects (81.9%) were White and there was a good representation of subjects in all age groups (21.9% of subjects were in the age group 2 to <6 years, 29.4% of subjects in the age group 6 to <12 years, and 48.8% of subjects in the age group 12 to <18 years).

Also for subjects <2 years of age (15 subjects), the distribution of males (53.3%) and females (46.7%) was almost equal. Almost all subjects (93.3%) were White. There were 20% of subjects each in the age groups from birth to <30 days and from 30 days to <6 months, and 60% in the age group from 6 months to <2 years.

The distribution of demographic characteristics was similar between the placebo and tapentadol OS treatment groups, and also within the age groups.

Efficacy

Efficacy results in subjects aged from 2 years to <18 years

Primary efficacy endpoint

Tapentadol OS was shown to be efficacious in children and adolescents compared to placebo based on the use of supplemental opioid analgesic medication during the first 12 hours and the first 24 hours after the first dose of IMP.

Statistically significantly more supplemental opioid analgesic medication was used by subjects in the placebo group than in the tapentadol OS group during the first 12 hours and 24 hours after the first administration of IMP; therefore, this trial meets the primary endpoint defined for US FDA and the EU PDCO.

Sensitivity analyses using the PPS, and a placebo mean imputation and treatment mean imputation to impute missing values for the FAS supported the significant difference observed between placebo and tapentadol OS treatment in the 24 hours (EU PDCO) primary endpoint, i.e., the placebo group used significantly more supplemental opioid analgesic medication than the tapentadol OS group.

In addition, the use of supplemental opioid analgesic medication during the first 24 hours of treatment after first administration of IMP (EU PDCO primary endpoint) was analyzed independently for each pain intensity scale using an analysis of co-variance (ANCOVA) with age at baseline and the baseline pain value as covariates. An analysis of the primary endpoint was also performed using the amount of opioid analgesia taken prior to IMP intake as a covariate in an ANCOVA model with same factors as the primary ANOVA model. Further subgroup analyses for the amount of supplemental opioid analgesic medication used were performed by age group, sex, race, geographical region, type of administration (NCA/PCA) and type of supplemental opioid analgesic medication used. All these analyses are descriptive in nature given the small number of subjects by subgroup category. With the exception of the analyses by age group, by type of administration and the ANCOVA for the FLACC pain scale the results of these analyses were consistent with the results of the primary analysis.

All sensitivity analyses performed for the 12-hour (US FDA) primary endpoint showed a between treatment difference in favor of tapentadol OS. The results were consistent with the results of the primary analysis. The treatment difference estimate obtained from the primary endpoint analysis was equal to -0.05, while for the sensitivity analyses, it varies between -0.04 and -0.05.

An overview of the results of the primary endpoint analyses and the different sensitivity analyses is provided in the following table.

Overview on primary efficacy analyses and sensitivity analyses

Analysis	Time window	LSmean difference tapentadol - placebo (SE)	95% CI of difference	p-value [a]
Primary analysis				
EU PDCO	24 h	-0.1 (0.04)	-0.18 to -0.02	0.0154
Sensitivity EU PDCO				
Per Protocol Set	24 h	-0.10 (0.04)	-0.18 to -0.01	0.0209
Placebo Mean	24 h	-0.08 (0.04)	-0.15 to -0.01	0.0253
Treatment Mean	24 h	-0.09 (0.03)	-0.16 to -0.02	0.0108
ANCOVA/ Baseline Pain - FLACC	24 h	-0.02 (0.03)	-0.04 to 0.08	0.4822
ANCOVA/ Baseline Pain – FPS-R	24 h	-0.10 (0.05)	-0.21 to 0.01	0.0665
ANCOVA/ Baseline Pain - VAS	24 h	-0.16 (0.07)	-0.31 to -0.02	0.0292
ANCOVA/ Baseline SOAM use	24 h	-0.10 (0.04)	-0.18 to -0.02	0.0117
Primary analysis				
US FDA	12 h	-0.05 (0.02)	-0.09 to -0.00	0.0404
Sensitivity US FDA [b]				
Per Protocol Set	12 h	-0.05 (0.02)	-0.09 to 0.00	0.0492
Placebo Mean	12 h	-0.04 (0.02)	-0.08 to 0.00	0.0613
Treatment Mean	12 h	-0.04 (0.02)	-0.08 to -0.00	0.0424
Additional sensitivity analyses agreed with US FDA [c]				
Primary Analysis	12 h	-0.04 (0.03)	-0.09 to 0.01	0.1215
Per Protocol Set	12 h	-0.05 (0.02)	-0.10 to 0.00	0.0508
Placebo Mean	12 h	-0.04 (0.02)	-0.08 to 0.00	0.0743
Treatment Mean	12 h	-0.04 (0.02)	-0.08 to 0.00	0.0458

Least square (LS) mean differences are presented for supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight).

a) p-value for testing superiority of tapentadol compared to placebo based on analysis of covariance.

b) As per protocol.

c) As per amendment 02 of the statistical analysis plan.

ANCOVA = analysis of co-variance; CI = confidence interval; FLACC = Face, Legs, Activity, Cry, Consolability (scale); FPS-R = Faces Pain Scale-Revised; VAS = visual analog scale; SE = standard error of the mean; SOAM = supplemental opioid analgesic medication.

Secondary efficacy endpoints

In the 12-hour segments from 24 hours to 96 hours, the amount of supplemental opioid analgesic medication used decreased. As a result, the separation of the 2 treatment groups disappeared over time. This was expected given the reduced need for analgesia as wound healing progresses after surgery.

The taste (palatability) of tapentadol OS was judged neutral or better by over 60% of the subjects. More than 80% of the subjects rated swallowing (acceptability) of tapentadol OS as neutral (a bit difficult/a bit easy) or better. Therefore, it is concluded that palatability and acceptability in children and adolescents are considered sufficient to ensure intake compliance in all age groups.

Overall, pain scores decreased with time, irrespective of the pain scale used (FLACC, FPS-R, or VAS). The area under the pain curve (AUPC) showed an improvement of pain values in both treatment groups up to 12 hours and 24 hours for all 3 pain scales. For the FPS-R and the VAS, the improvement of pain values was bigger in the tapentadol OS group than in the placebo group.

The Clinical Global Impression of Change (CGIC) and Patient Global [overall] Impression of Change (PGIC) responder rates were not different between placebo and tapentadol OS in a descriptive comparison.

The time to first and time to second NCA/PCA administration after first dose of IMP was numerically longer in the tapentadol OS group ($p = 0.1216$ and $p = 0.2740$, respectively [Log-rank test]).

Only a few subjects discontinued treatment due to lack of efficacy. An analysis of the of time to treatment discontinuation due to lack of efficacy after first dose of IMP showed that the risk of discontinuing was higher for the placebo treated subjects than for the tapentadol OS treated subjects (hazard ratio [SE] of 2.15 (1.52); $p = 0.2681$ [Log-rank test]).

Efficacy results for subjects <2 years of age

Given the small sample size in the age groups <2 years, conclusions are limited and based on descriptive statistics.

The overall use of supplemental opioid analgesic medication was low as was expected in subjects aged <2 years compared to older children.

The supplemental opioid analgesic medication mean use was numerically higher for subjects treated with tapentadol OS compared to placebo during both 12 hours (0.03 mg/kg compared to 0.01 mg/kg, respectively) and 24 hours (0.05 mg/kg compared to 0.02 mg/kg, respectively) after first dose of IMP whereas the median use was lower with tapentadol OS compared to placebo for the 12-hour endpoint (0.02 mg/kg compared to 0.01 mg/kg). The higher mean amount of supplemental opioid analgesic medication with tapentadol was mainly accounted for by a high amount of supplemental opioid analgesic use in 2 subjects in this group.

Overall, pain scores decreased with time (FLACC). The AUPC showed an improvement of pain values in both treatment groups up to 12 hours and up to 24 hours, in line with results reported for the older subjects in this trial.

The CGIC and PGIC responder rates were not different between placebo and tapentadol OS in a descriptive comparison.

Overall efficacy conclusion

Based on the 2 primary efficacy endpoint analyses, tapentadol was shown to be efficacious in pediatric subjects aged 2 years and older compared to placebo. The amount of supplemental opioid analgesic medication used during 12 hours and 24 hours after the first IMP administration was higher in the placebo group than in the tapentadol OS group (p-value 0.0404 for 12 hours and 0.0154 for 24 hours).

A low mean amount of supplemental opioid analgesic medication use was administered to subjects <2 years of age. Numerically, the mean supplemental opioid analgesic medication use was higher

with tapentadol than with placebo; the difference was primarily driven by 2 subjects who received a considerably high amount of supplemental opioid analgesic medication.

Palatability and acceptability in children and adolescents are considered sufficient to ensure intake compliance in all age groups.

Based on the trial design, which allowed NCA/PCA, a difference in PGIC and CGIG was not expected and not observed.

Safety and tolerability

Subjects aged from 2 years to <18 years

There were 26 of 52 subjects (50.0%) in the placebo group and 62 of 108 subjects (57.4%) in the tapentadol OS group with at least 1 TEAE.

There were 11 of 52 subjects (21.2%) in the placebo group and 29 of 108 subjects (26.9%) in the tapentadol OS group with at least 1 TEAE that was considered to be related to the administration of IMP by the investigator.

The most common TEAEs (at least 5% of subjects in at least 1 treatment group) were vomiting (11.5% of subjects), constipation (11.5%), nausea (7.7%), pruritus (5.8%), somnolence (3.8%), and pyrexia (1.9%) in the placebo group, and vomiting (23.1%), nausea (14.8%), constipation (10.2%), pyrexia (9.3%), somnolence (5.6%), and pruritus (3.7%) in the tapentadol OS group. With the exception of pyrexia, the TEAEs are known adverse drug reactions to tapentadol OS and known opioid class effects. Several confounding factors have been identified as potential causes for pyrexia. Therefore, a causal relationship between the intake of tapentadol OS and pyrexia is unlikely.

Only minor, clinically not relevant observations were made in subgroup analyses by age, geographical region, sex, and race.

The TEAEs started in most cases within the first 24 hours of treatment irrespective of the treatment group. Most TEAEs were classified to have mild intensity (76.1% in the placebo group and 72.0% in the tapentadol OS group) and as not being related to IMP treatment (71.7% on placebo and 60.9% on tapentadol OS).

Approximately half of the TEAEs reported in the placebo group (54.3%) and the tapentadol OS group (47.8%) required countermeasures.

With the exception of 3 TEAEs in the placebo group, all other TEAEs were either recovered or resolving at the last trial visit. There were no relevant differences between the placebo group and the tapentadol OS group.

There were no deaths in the age group from 2 years to <18 years.

Two serious adverse events (an abdominal abscess and a seizure) were reported, both in the tapentadol OS group, 1 in the age group 6 years to <12 years and 1 in the age group 12 years to <18 years of age. These serious adverse events were not considered to be related to the administration of tapentadol OS by the investigator.

There were 2 subjects on placebo and 10 subjects on tapentadol OS discontinued from treatment due to a TEAE reflecting an overall low rate of TEAEs leading to treatment discontinuation.

The Baseline Visit and End of Treatment Visit values for hematology and clinical chemistry were generally similar, both in the placebo and in the tapentadol OS treatment group.

A numerical increase in the eosinophil count was observed between the 2 visits in both treatment groups, consistent with the post-operative status of the trial subjects. The increase was assessed as not clinically relevant by the investigators. Some differences were also observed for a numerical increase in the mean alanine aminotransferase and creatine kinase values in the tapentadol OS treatment group, and mean lactate dehydrogenase values in both treatment groups at the End of Treatment Visit compared to the Baseline Visit, which may be explained by the prior surgery, known to cause similar changes in clinical chemistry.

There were small and clinically not relevant changes in the time course of pulse rate, blood pressure and oxygen saturation measured at the Enrollment Visit, at Baseline, before each administration of IMP, and at the End of Treatment. There was a slightly higher incidence of low respiratory rates in the tapentadol OS group.

Oxygen saturation decrease or hypoxia was reported as a TEAE in 1 subject on placebo and 7 subjects on tapentadol OS. Most of these events were mild and resolved quickly.

Overall, there were no clinically relevant changes in 12-lead ECG parameters.

No subject showed signs of suicidal ideation or behavior after treatment with IMP.

Slightly more subjects were moderately or deeply sedated in the tapentadol OS group than in the placebo group.

Safety results for subjects below 2 years of age

The overall incidence of TEAEs was 60.0% in this age group, was similar to the frequency seen in subjects from 2 years to <18 years old, and was within the expected range considering the known tapentadol safety profile and the present trial population younger than 2 years of age. There were 3 of 4 subjects (75.0%) in the placebo group and 6 of 11 subjects (54.5%) in the tapentadol OS group with at least 1 TEAE. One of 4 subjects (25.0%) in the placebo group and 2 of 11 subjects (18.2%) in the tapentadol OS group experienced at least 1 TEAE that was considered to be related to the administration of IMP by the investigator.

No deaths, serious TEAEs, or an early treatment or trial discontinuation due to treatment emergent adverse event was reported. Constipation, diarrhea, flatulence, aspartate aminotransferase increased, oxygen saturation decreased, and agitation were reported (Preferred Terms) in the tapentadol OS group in 1 subject each (9.1%) and vomiting in 2 subjects (18.2%). Impaired gastric emptying, administration related reaction, and respiratory rate decreased were reported in 1 subject each in the placebo group (25.0%). All events were of mild or moderate intensity.

The observed TEAEs were either common tapentadol adverse drug reactions and known opioid adverse effects, or are typical for a post-surgical recovery course.

As a conclusion, the observed frequencies and types of TEAEs in subjects aged <2 years do not differ from subjects aged 2 years and older.

Conclusion

The overall conclusions are:

- Tapentadol OS is efficacious in the treatment of moderate to severe acute post-operative pain in children and adolescents aged 2 years to <18 years.
  - Statistically significantly more supplemental opioid medication was used by subjects in the placebo group than in the tapentadol OS group during the first 24 hours of treatment after the first administration of IMP ($p = 0.0154$) (EU PDCO primary efficacy endpoint, US FDA secondary efficacy endpoint).
  - Statistically significantly more supplemental opioid analgesic medication was used by subjects in the placebo group compared to the tapentadol OS at 12 hours ($p = 0.0404$) supporting the observations for the primary endpoint (US FDA primary efficacy endpoint, EU PDCO secondary efficacy endpoint).
  - A Bayesian analysis supports the finding of the EU PDCO primary endpoint (posterior probability for the treatment effect <0 is 0.981.
  - There is a meaningful clinical benefit of tapentadol OS in the treatment of moderate to severe acute pain in subjects from 2 years to <18 years.
  - There was a reduction in pain values over time in both treatment groups. For the FPS-R and the VAS subgroups, the improvement of pain values was considerably larger in the tapentadol OS group than in the placebo group.
- Although in subjects <2 years old the conclusions on efficacy are limited, in general the efficacy data are in line with those in older subjects treated with tapentadol oral solution.
- The CGIC and the PGIC results indicate that the treatments in the placebo and the tapentadol OS groups were assessed as equally beneficial. Therefore, the design of the trial, which included a placebo group, can be considered ethical and adequate to investigate efficacy in a pediatric population.
- The palatability and acceptability of tapentadol OS are considered sufficient to ensure intake compliance in all age groups.
- The safety profile of tapentadol OS was consistent with the known safety profile for tapentadol as observed in other pediatric trial subjects and adults. No new adverse drug reaction was identified.
- There were minor, not relevant differences in abnormal vital signs, clinical laboratory values, and 12-lead ECG parameters between subjects treated with placebo and subjects treated with tapentadol OS.
- Overall, a positive benefit-risk evaluation for use of tapentadol oral solution in acute pain conditions in subjects <18 years old in need of treatment with a strong analgesic can be supported with the data from this adequate and well-controlled clinical trial.

Publications based on this trial

Not applicable.