Report date	25 Feb 2019	DMS version	2.0
Type of report	Final		
Trial code	KF5503-66		
Title of trial	An open-label trial, enrolling subjects aged 6 years to less than 18 years suffering from pain requiring prolonged release opioid treatment, to evaluate the safety and efficacy of tapentadol PR versus morphine PR, followed by an open-label extension.		
Trial design	A 2-part trial: Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial. Part 2 is an open-label Extension Period with tapentadol treatment (Tapentadol Period) or an observation period without tapentadol treatment (Observation Period) lasting for up to 12 months.		
Development phase	Phase II/III		
EudraCT number	2012-004360-22		
NCT number	NCT02151682		
Pediatric investigation plan (PIP)	EMEA-000325-PIP01-08		
Investigational medicinal products	Tapentadol PR tablets Morphine PR tablets		
Indication	Pain requiring prolonged release opioid treatment		
International coordinating investigator	Dr [redacted] Respiratory, Critical Care, Pain and Anaesthesia section in Infection, Immunity, Inflammation and Physiological Medicine UCL Institute of Child Health 30 Guilford Street, London, WC1N 1EH, United Kingdom		
Trial sites recruiting subjects	Belgium (1 site), Bulgaria (4 sites), Chile (2 sites), France (7 sites), Germany (1 site), Hungary (1 site), Italy (1 site), Portugal (2 sites), Spain (1 site), United Kingdom (3 sites).		
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany		
Sponsor's signatory	Dr [redacted] Head of Clinical Science Contact number: +49 (0) 241-569-0		
Trial period	First subject in:		29 Apr 2015
	Last subject out:		15 Oct 2018
Interim report	04 Jul 2018	DMS version:	1.0

Objectives

The trial objectives for Part 1 of the trial were:

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

The trial objective for Part 2 of the trial was:

- To describe the long-term safety profile of tapentadol PR for up to 12 months in subjects aged 6 years or older:
  - When taken twice daily (Tapentadol Period) by those suffering from long-term pain requiring prolonged release opioid treatment.
  - When discontinued after at least 1 dose of investigational medicinal product (IMP) had been taken (Observation Period).

Investigational medicinal products

The 2 IMPs were:

- Tapentadol PR tablets given orally containing 25 mg or 100 mg tapentadol (Part 1 and Tapentadol Period (Part 2)).
- Morphine PR tablets given orally containing 10 mg or 30 mg morphine sulfate (Part 1 only).

IMP	Tablet size	Collective batch number	Expiry date
Tapentadol PR	25 mg	140502	30 Sep 15, 30 Sep 16
		140801	30 Sep 16
		150103	30 Apr 19
		E117107-01, E117107-02, E117107-03	31 Aug 20
	100 mg	140503	31 Jul 15, 31 Jul 17
		150104	31 Mar 19
		E117107-05	31 Jul 20
Morphine (sulfate) PR	10 mg	140504	31 Jul 17
		E117107-07, 150101	31 Jul 19
	30 mg	140505	28 Feb 17
		E117107-08, 150102	31 Dec 18

Trial treatments

Dosing of IMP was twice daily with a dosing interval of about 12 hours (but not less than 6 hours).

The IMP was taken for 14 days in Part 1.

Regardless of the treatment received during the Treatment Period (Part 1), subjects who completed Part 1 and who were still in need of a prolonged release opioid were given the possibility to enter the Tapentadol Period (Part 2) for up to 12 months.

The initial dose administered was adjusted to the weight of the subject and then titrated to the therapeutic effect, defined as a balance between self-reported analgesia and side effects based on the judgment of the investigator and within the given limits as defined per weight group.

Doses could be increased after a minimum of 2 days (4 scheduled intakes of IMP). The dose could be reduced at any time.

Rescue medication

Morphine oral solution could be given during Part 1 as rescue medication in both treatment groups. Subjects were provided with 0.5% or 2% morphine oral solution, depending on weight group and country of enrollment. The dose per rescue medication intake was 1/6 of the total daily dose of the scheduled IMP intakes.

Rescue medication	Collective batch number	Expiry date
Morphine Sulphate Oral solution 2.0% 20ml bottle	E117107-06, 150703, 150704, 150705	31 May 18
Morphine Oral solution 0.5%	140506	31 Dec 15
	150501	28 Feb 18
	151101, 151102	30 Jun 18

Trial population

Subjects were male or female, aged at least 6 years at the Enrollment Visit and less than 18 years of age on the predicted day of the end of the 14-day Treatment Period (Part 1), with an underlying long-term pain condition (e.g., cancer, chronic disease, planned or performed surgery) that was, according to the judgment of the investigator, expected to require a twice-daily prolonged release opioid treatment until at least the end of the 14-day Treatment Period (Part 1).

On the day of allocation, subjects had to have a body weight of ≥17.5 kg and, if taking opioids, were not allowed to take a calculated morphine equivalent dose of 3.5 mg/kg or more per day.

Subjects were not allowed to have a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection) that in the opinion of the investigator could affect or compromise subject safety during the trial participation.

At least 25% of the subjects were to be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years. At least 15 subjects had to be treated with tapentadol PR for a minimum of 12 weeks.

Summary of the trial procedures and assessments

Part 1: After an Enrollment Visit, subjects complying with the inclusion/exclusion criteria entered Part 1, which had weekly visits and lasted for up to 2 weeks. Subjects were allocated to open-label IMP; tapentadol PR or morphine PR in a ratio of 2:1. Doses of IMP were titrated to therapeutic effect within the given limits as defined per weight group, defined as a balance between self-reported analgesia and side effects based on the judgment of the investigator. Subjects were supplied with an electronic diary to record pain 2 times a day using both a visual analog scale (VAS) and Faces Pain Scale–revised (FPS-R), and use of IMP and rescue medication. Constipation was assessed using a modified constipation assessment scale (mCAS). The palatability and acceptability of the IMP were assessed using a 5-point hedonic faces scale with a verbal rating score. Safety laboratory tests (hematology, serum chemistry, and urinalysis) were performed.

Blood samples for pharmacokinetic evaluations were drawn from subjects on tapentadol PR. Electrocardiograms (ECGs) were performed. Adverse events, vital signs, and a physical examination were documented.

Part 2 was a 12-month Extension Period either with tapentadol PR (Tapentadol Period) or without treatment (Observation Period).

Tapentadol Period (12 months): Subjects completing the Treatment Period (Part 1) with tapentadol PR or morphine PR and in need of continued opioid treatment could enter the Tapentadol Period. They were treated with tapentadol PR for up to 12 months. Visits were approximately every month. Subjects recorded pain levels on paper during the visits and the use of IMP in the diary. Constipation was assessed at the end of the Tapentadol Period using the mCAS. Safety laboratory tests (hematology, serum chemistry, and urinalysis) were performed routinely every 3 months.

Observation Period (12 months): Subjects not completing the Treatment Period (Part 1), but who had taken at least 1 dose of IMP, and those who completed the Treatment Period (Part 1) but did not want to continue with tapentadol PR or those no longer requiring treatment with tapentadol PR, entered the Observation Period (12 months). Subjects in the Tapentadol Period (Part 2) could switch to the Observation Period. Visits were scheduled at the trial site or via telephone every 3 months. Concomitant medications and adverse events were recorded at each visit, whereas assessment of constipation using the mCAS, physical examination, vital signs measurements, and laboratory assessments were only performed at the end of the period.

Opiate withdrawal symptoms were assessed by the subjective opiate withdrawal scale (SOWS) questionnaire when the subject stopped IMP.

Trial performance

There were 5 protocol amendments.

There was no premature trial termination and in countries where the trial was initiated there was no suspension (clinical hold) of the trial.

Summary of the statistical methods

The sample size was estimated to reject the null hypothesis of the inferiority of tapentadol PR to morphine PR when comparing responders evaluated at the end of the 14-day Treatment Period (Part 1) i.e., the primary endpoint. The percentage of responders in both treatment groups was estimated to be 80% based on data from previous trials and extrapolation to the trial population under investigation. The non-inferiority margin was set to a difference of 20% for the primary endpoint.

Sixty-nine (69) subjects were required in the Full Analysis Set (FAS), assuming a 2:1 randomization of tapentadol PR:morphine PR to show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.1.

Separate analyses were performed for Part 1 and Part 2. The analysis for Part 1 took into consideration the Treatment Period (Part 1). The analysis for Part 2 took into consideration the Tapentadol Period (Part 2) and Observation Period (Part 2).

Part 1

For the Treatment Period (Part 1), baseline measurements were defined as the last evaluation performed before starting IMP.

For pain assessments, the baseline pain was defined as "pain right now" at the allocation visit, and was assessed before any painful or unpleasant procedure, and before the first intake of IMP.

Part 2

For the Tapentadol Period, baseline measurements were defined as the last evaluation performed before or at the end of the Treatment Period (Visit VE).

For the Observation Period, baseline measurements were defined as the last evaluation performed before or at:

- The end of the Treatment Period (Visit VE [End of Treatment Visit]) for subjects entering the Observation Period directly after Part 1.
- The Early Termination Visit for subjects switching from the Tapentadol Period to the Observation Period.

General

For continuous variables, descriptive statistics included the number of observations, arithmetic mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum. For categorical variables, frequency counts and percentages were used to summarize the results. If applicable, changes from the baseline or predefined time points are presented descriptively.

Data was listed and summarized using graphical displays, as appropriate.

Primary efficacy endpoint (Part 1)

The analysis of the primary endpoint was performed on data collected during the Treatment Period (Part 1). The FAS was the primary analysis set and the Per Protocol Set (PPS) was used as a sensitivity analysis set. The primary analysis assessed the null hypothesis of the inferiority of the responder rate of tapentadol PR compared to the responder rate of morphine PR versus the alternative, that the responder rate of tapentadol PR is non–inferior to the responder rate of morphine PR by a non-inferiority margin of a difference of 20%.

As this endpoint is a binomial event rate, it was summarized by descriptive statistics grouped by treatment group. The standard maximum likelihood (ML) estimators for the proportion of subjects classified as responders in each group were the estimated proportions adjusted for the baseline pain intensity, age group, and underlying pain condition. To obtain these estimators, a logistic regression model was fitted to the response using the baseline pain intensity, age group, treatment, and underlying pain condition as explanatory variables. The Farrington-Manning test was applied to the derived ML estimates, and a 2-side 80% Farrington-Manning confidence interval (CI) of the difference in proportion between the 2 treatments was calculated. Non-inferiority of tapentadol compared with morphine was established if the lower limit of this 80% CI was above the negative non-inferiority margin $-\delta$=-0.2.

In addition, a Bayesian logistic regression model was fitted as a sensitivity analysis.

Analysis of safety data (Part 1 and Part 2)

Adverse events were categorized by seriousness, intensity, outcome, countermeasures, and relationship to IMP and were tabulated by system organ class and preferred term. Adverse events were tabulated separately for the treatment periods.

Summary of results

Subject disposition

Part 1:

A total of 73 subjects were enrolled, 70 of these subjects were allocated to IMP; 1 allocated subject did not receive IMP.

In Part 1, 45 subjects received tapentadol PR and 40 of these subjects completed Part 1; 24 subjects received morphine PR and 22 subjects completed Part 1.

In the tapentadol PR group of Part 1, 1 allocated subject was discontinued before receiving IMP. Five (5) subjects were discontinued from IMP: 2 subjects due to TEAEs, and 1 subject each due to withdrawal by the subject, technical problems (difficulty swallowing the tablet), and no further need for opioid treatment.

In the morphine PR group of Part 1, 2 subjects discontinued IMP: 1 subject due to no further need for opioid treatment, and for 1 subject the reason was not given.

Tapentadol Period (Part 2):

Thirty-six (36) subjects entered the Tapentadol Period (Part 2); 26 subjects previously treated with tapentadol PR and 10 subjects previously treated with morphine PR.

Fourteen (14) of 26 subjects previously treated with tapentadol PR and 6 of 10 subjects, previously treated with morphine PR in Part 1 took tapentadol PR for at least 12 weeks in the Tapentadol Period (Part 2). Therefore, 20 subjects were exposed to tapentadol PR for 12 weeks, fulfilling a requirement to have at least 15 subjects exposed for 12 weeks to tapentadol PR.

Of the 26 subjects previously treated with tapentadol PR in Part 1, 20 subjects discontinued IMP in the Tapentadol Period (Part 2), 19 of whom entered the Observation Period (Part 2). Of the 10 subjects previously treated with morphine PR in Part 1, 7 subjects discontinued IMP in the Tapentadol Period (Part 2), all of whom entered the Observational Period. In total, 9 subjects completed IMP in the Tapentadol Period (Part 2), i.e., were exposed to tapentadol PR for 12 months. One subject, previously treated with tapentadol PR in Part 1, completed IMP in the Tapentadol Period (Part 2) but did not attend a final post treatment visit and thereby discontinued the trial.

Observation Period (Part 2):

A total of 58 subjects entered the Observation Period, 47 of whom completed that part of the trial. Eleven (11) subjects discontinued: 3 subjects died (due to deterioration of the underlying cancer), 2 subjects withdrew (both suffering cancer), and 2 subjects discontinued for other reasons (withdrawal of consent, and non-compliance); and for 4 subjects, Visit F12M was completed too early and the subjects were considered as discontinued subjects.

Demographics

There were 69 subjects (32 female and 37 male) in the Safety Set of the trial; 45 subjects (22 female and 23 male) were treated in the tapentadol PR group and 24 subjects (10 female and 14 male) were treated in the morphine PR group. All but 1 subject was White (a native Hawaiian or other in the Tapentadol PR group). Overall, 56 of 69 subjects (81.2%) were of Not Hispanic or Latino ethnicity, 11 subjects (15.9%) were of Hispanic or Latino ethnicity, and data on 2 subjects was missing.

There were 12 subjects (26.7%) in the tapentadol PR group and 7 subjects (29.2%) in the morphine PR group aged 6 years to less than 12 years, thereby fulfilling a requirement that 25% of subjects were less than 12 years.

For the Safety Set, the mean age (SD) in the 6 years to less than 12 years age group was 9.3 (1.8) years in the tapentadol PR group and 9.4 (1.7) years in the morphine PR group. The mean age (SD) in the 12 years to less than 18 years age group was 14.6 (1.5) years in the tapentadol PR group and 14.7 (1.3) years in the morphine PR group.

The baseline pain was mostly of non-cancer origin (approximately 80% of the subjects). There was no apparent difference between the two treatment groups in the described origin of the baseline pain.

Pharmacokinetics

The mean serum concentrations of tapentadol and tapentadol-O-glucuronide appeared to be slightly lower in the younger age group of children (6 - <12 years) than those observed for children in the older age group (12 - <18 years); further analysis is presented in the pharmacometric report of this trial. In the older age group of children, the mean data suggest that steady state concentrations of tapentadol had already been reached by the second visit, i.e., after 1 week of repeated dosing, as expected. Mean serum concentrations of tapentadol observed in both age groups were generally in the range of concentrations observed in adult subjects using a comparable weight adjusted dose.

The final population estimates obtained for CL/f, V/f and K_a, for the pediatric age range from 6 years to less than 18 years, were 170 L/h, 725 L and 0.106 h^{-1}, respectively. The corresponding population estimates obtained in adults were 257 L/h, 1870 L, and 2.01 h^{-1}, respectively.

The data were insufficient to appropriately describe the concentration-time profile of the metabolite tapentadol-O-glucuronide.

The estimate of accumulation in the pediatric population of 1.86 was in line with that obtained in adults.

Efficacy

<u>Primary efficacy endpoint:</u>

The primary endpoint was a binary variable “responder” comprising the elements specified degree of pain relief and completion of a 14-day Treatment Period (Part 1). Treatment with tapentadol PR was shown to be non-inferior to morphine PR as the primary endpoint met the predefined limits for the demonstration of non-inferiority, i.e., the lower bound of the CI was above the negative non-inferiority margin of -0.2.

Responder rates - primary endpoint analysis - Full Analysis Set - Treatment Period (Part 1):

		Tapentadol PR N = 45	**Morphine PR N = 24**
Primary analysis [a]	Observed responders n (%) [b]	32.0 (71.0)	19.0 (79.2)
	ML estimates (80% CI) [c]	0.76 (0.64; 0.85)	0.83 (0.69; 0.91)
	Difference in ML estimates (80% CI) [d]	-0.06 (-0.19; 0.06)	
	p-value [d]	0.0790	

a) Logistic regression model using baseline pain, age group, treatment and underlying pain condition as explanatory variables, followed by a Farrington-Manning test for non-inferiority, based on Full Analysis Set.

b) Mean number (%) of responders throughout multiple imputations to impute missing pain assessments during the last 3 days of the Treatment Period. Without covariate adjustment.

c) Mean estimates obtained by logistic regression model fitted to the response throughout multiple imputations.

d) 80% CI and p-value are based on variance estimator computed by the method of Farrington and Manning using a non-inferiority margin of 0.2. A p-value below the predefined alpha level of 0.1 is considered to be statistically significant.

CI = confidence interval; ML = maximum likelihood; n = number of responders; N = total number of subjects; PR = prolonged release.

Sensitivity analyses:

The results of the sensitivity analyses were consistent with the primary endpoint analysis (a lower bound of the CI above -0.2 indicates success): using the different pain scales FPS-R (80% CI for the difference in ML estimates -0.16; 0.09) and VAS (-0.18; 0.09), a different completer definition (-0.21; 0.03), a different imputation method (-0.19; 0.06), different adjustment factors, i.e., discarded baseline pain intensity (-0.19; 0.05), and included pooled IMP dose level (-0.21; 0.09), analyses on the PPS for the interim report (-0.06; 0.24) and for this report (-0.06; 0.23), the exclusion of subjects with complex regional pain syndrome (CRPS) (-0.15; 0.10), and a Bayesian analysis (80% CrI for the difference in the Bayesian estimate -0.11; 0.02).

Secondary efficacy endpoints:

The secondary endpoints related to constipation and tolerability are covered in the safety section.

Other efficacy endpoints:

Changes in pain from baseline were assessed using the VAS and the FPS-R for Part 1 and the Tapentadol Period (Part 2). The change from baseline was similar for both tapentadol PR and morphine PR treated subjects in Part 1, irrespective of the pain scale used or the age group of the subjects.

Pain levels continued to decrease during Part 2.

Rescue medication intake was assessed as an efficacy parameter in Part 1. The mean time (SD) to the first intake of rescue medication was longer in the tapentadol PR group than in the morphine PR group (74.6 [94.45] hours versus 39.7 [63.75] hours). However, there was no overall clinically relevant difference between the tapentadol PR and morphine PR groups with respect to the use of rescue medication.

Palatability and acceptability of the IMP was assessed by a 5-point hedonic faces scale with the verbal rating score at Visit V3 and Visit VE.

At Visit VE, the taste was rated as good or really good by 44.4% of subjects and ease of swallowing was rated to be easy or really easy by 77.8% of subjects taking tapentadol PR.

There were insufficient subjects discontinuing the trial during Part 1 for a meaningful comparative survival analysis assessment of time to discontinuation of IMP.

Safety results

Part 1:

In Part 1, there were 26 of 45 subjects (57.8%) in the tapentadol PR group (112 TEAEs) and 12 of 24 subjects (50.0%) in the morphine PR group (53 TEAEs) with at least 1 TEAE.

The most frequently reported (>10% subjects) TEAEs were nausea (22.2%), constipation (15.6%), abdominal pain (13.3%), vomiting (13.3%), and headache (13.3%) in the tapentadol PR group, and vomiting (33.3%), constipation (16.7%), nausea (16.7%), fatigue (12.5%), headache (12.5%), and pruritus (12.5%) in the morphine PR group.

Most adverse events were of mild intensity (60.7%) in the tapentadol PR group and moderate intensity (52.8%) in the morphine PR group.

There were no deaths during the Treatment Period (Part 1).

No pregnancies were reported.

There were 3 subjects with a single serious TEAE each (cystitis, malignant neoplasm progression, acute kidney injury) in the tapentadol PR group and 1 subject with 4 serious TEAEs (diarrhoea, vomiting, mucosal inflammation, and clostridium difficile infection) in the morphine PR group. Three (3) subjects had TEAEs leading to discontinuation from IMP in the tapentadol PR group.

As expected for the population in the trial, there were small fluctuations in hematological and clinical chemistry parameters in Part 1, without a particular trend in the time course of any parameter.

There were small but clinically not relevant fluctuations in mean pulse rates both in the tapentadol PR and morphine PR groups in Part 1.

Commensurate with the medical history of the subjects, abnormalities were present in 36.2% of the 12-lead ECG recordings at the Enrollment Visit, and in 42.0% at Visit VE. However, no finding was considered to be clinically relevant.

The degree of constipation assessed by the mCAS remained unchanged during the Treatment Period (Part 1) in both subjects treated with tapentadol PR and subjects treated with morphine PR. There was no indication of clinically relevant withdrawal symptoms (SOWS questionnaire) after stopping tapentadol PR or morphine PR.

Tapentadol Period (Part 2):

In the Tapentadol Period (Part 2), 30 of 36 subjects (83.3%) reported 226 TEAEs. In 13 subjects (36.1%), 35 TEAEs were considered by the investigator to be related to the IMP. No deaths or pregnancies were reported. Thirteen (13) subjects (36.1%) had 23 serious TEAEs and 4 subjects (11.1%) had a TEAE leading to discontinuation of tapentadol PR. The most frequently reported (>10% subjects) TEAEs were nausea (30.6%), headache (27.8%), constipation (13.9%), vomiting (13.9%), nasopharyngitis (13.9%), back pain (13.9%), and oropharyngeal pain (11.1%). Most TEAEs (54.4%) were of mild intensity.

Of the 226 TEAEs, 211 (93.4%) were reported to have recovered or resolved. One (1) TEAE (malignant neoplasm progression) was recovered/resolved with sequelae, 9 TEAEs (dry mouth, fatigue [2 TEAEs], fungal infection, pain in extremity, scoliosis, depressed mood, dissociation, photosensitivity reaction) were not recovered/not resolved and 4 TEAEs (photophobia, ligament sprain, paraesthesia, acne) were recovering/resolving. One TEAE (malignant neoplasm progression) had an unknown outcome.

The most frequent non-IMP related countermeasure was newly started medication, used against 101 of 226 TEAEs (44.7%). The most frequent action taken with IMP was dose reduced, used in response to 11 of 226 TEAEs (4.9%).

There were 13 subjects with 23 serious adverse events (lymphopenia, sickle cell anaemia with crisis, breakthrough pain, malaise, pain, pyrexia, appendicitis, application site infection, herpes zoster, infection, fall, white blood cell count decreased [3 serious adverse events], malignant neoplasm progression, movement disorder, neuralgia, somnolence, dissociation, cutaneous lupus erythematosus [2 serious adverse events], limb operation, and superficial thrombophlebitis).

As expected for the population in the trial, there were small fluctuations in hematological and clinical chemistry parameters without a particular trend in the time course of any parameter.

There were small but clinically not relevant fluctuations in both systolic and diastolic blood pressure and in mean and median pulse rates.

Observation Period (Part 2):

There were 3 deaths during the Observation Period (Part 2), caused by the underlying diseases of the subjects. Post-treatment non-TEAEs, occurring in 27 of 58 subjects, were not considered to be long-term effects of opioid treatment. Physical examination findings, laboratory values, and vital signs were either unchanged at the end of the period, or as expected for the underlying disease.

Conclusions

Efficacy:

- The efficacy of tapentadol PR compared to morphine PR has been established in a non-inferiority trial based on responder rates in children and adolescents aged 6 years to less than 18 years suffering from cancer and non-cancer related pain.

Safety:

- Tapentadol PR was well tolerated and safe in subjects aged 6 years to less than 18 years with long-term pain requiring prolonged release opioid treatment, both in the 14-day Treatment Period (Part 1) and in the Tapentadol Period (Part 2), during which the average exposure was 5.8 months, with 9 subjects being exposed for 12 months.
- TEAEs seen with tapentadol were mostly expected and also reflected underlying condition(s).
- The safety profile of tapentadol PR observed in subjects aged 6 years to less than 18 years was comparable to the established safety profile of tapentadol PR in subjects aged 18 years or over.
- No new safety issues or adverse drug reactions specific to the pediatric population were identified.

- No long-term opioid effects were identified up to 12 months after the end of treatment with tapentadol PR.