2 SYNOPSIS

Type of report	Full report
Trial code	KF5503-75
Title of trial	Open-label investigation of the pharmacokinetic profile, safety, tolerability, and efficacy of multiple administrations of tapentadol oral solution used for treatment of acute pain in children aged 2 years to less than 7 years
Trial design	An interventional, prospective, non-randomized, multi-site, open-label, single-arm, multiple administrations, PK Phase II trial.
Development phase	Phase II
EudraCT number	2019-000205-77
Investigational medicinal product(s)	Tapentadol OS
Indication	Moderate to severe acute pain
International coordinating investigator	[redacted], (MD), [redacted] Center for Hospital Health Care Services Clinic of Pediatric Surgery [redacted] Lwowska Street 60, 35-301 Rzeszow Poland
Trial sites	Poland (3 sites)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted], Medical Lead Contact number: +49 (0) 241-569-[redacted]
Trial period	First subject in: 09 Sep 2019 Last subject out: 06 Aug 2020

Objectives

Primary objective:

- To investigate the PK profile of tapentadol after the administration of multiple doses of tapentadol OS to children aged 2 years to less than 7 years after a painful event that routinely produces acute pain requiring treatment with a strong analgesic medication (e.g., opioids or metamizole).

The primary endpoint was the area under the concentration-time curve for the dosing interval at steady state ($AUC_{\tau,ss}$) for tapentadol.

Secondary objectives:

- To investigate the PK profile of tapentadol-O-glucuronide after the administration of multiple doses of tapentadol OS to children aged 2 years to less than 7 years after a painful event that routinely produces acute pain requiring treatment with a strong analgesic medication (e.g., opioids or metamizole).
- To investigate the PK profile of tapentadol-O-sulfate after the administration of multiple doses of tapentadol OS to children aged 2 years to less than 7 years after a painful event that routinely produces acute pain requiring treatment with a strong analgesic medication (e.g., opioids or metamizole).

The secondary endpoints were $AUC_{\tau,ss}$ for tapentadol-O-glucuronide and tapentadol-O-sulfate.

Investigational medicinal product (IMP)

Tapentadol OS (4 mg/mL OS and 20 mg/mL OS).

Tapentadol OS (4 mg/mL): Bulk batch number G0001, with expiration date Apr 2020

Tapentadol OS (20 mg/mL): Bulk batch number I0023, with expiration date Apr 2022

Trial treatments

Subjects were administered tapentadol OS in 1 of 2 available concentrations, depending on body weight. Subjects weighing ≤16 kg were administered 4 mg/mL tapentadol OS and those >16 kg were administered 20 mg/mL tapentadol OS.

Subjects were administered a target dose of 1.25 mg tapentadol per kilogram bodyweight every 4 hours (±15 minutes). Administration of IMP was stopped if any of the following criteria were met:

- Treatment with a strong analgesic (i.e., IMP) was no longer needed in the judgment of the investigator.
- A discontinuation criterion as specified in the protocol was met.
- 72 hours had elapsed since Dose 1.

Trial population

The trial population comprised male and female subjects for whom informed consent and, if applicable, assent was obtained and who were aged 2 years to less than 7 years from the time of allocation to IMP until Visit 3. Subjects had experienced a painful event (e.g., a painful intervention or surgery) that, in the investigator's opinion, would reliably produce acute pain requiring treatment with a strong analgesic (e.g., opioids or metamizole) for at least 24 hours after Dose 1. Subjects had to be able to tolerate liquids at the time of allocation to IMP and were to have a reliable venous vascular access or the ability to be venipunctured repeatedly for PK blood sampling, depending on which was less burdensome for the individual subject. Subjects were required to remain hospitalized until Visit 3.

Subjects were excluded if they (or their parent or legal representative) were family members or employees of the investigator or trial site, if they had been exposed to tapentadol 28 days or less before enrollment, or if they had received an experimental drug 28 days or less (or <10 half-lives of the drug, if this was shorter) before allocation to IMP. Subjects were excluded if they participated concurrently in another clinical trial with an experimental drug. Further exclusion criteria included

the presence of a disease or disorder (e.g., impaired respiratory function or clinically relevant respiratory disease, endocrine, metabolic, neurological, psychiatric, infection, febrile seizure, clinically relevant abnormal electrocardiogram [ECG]) that, in the opinion of the investigator, may have affected or compromised the subject's safety during participation in the trial. Subjects were also excluded if they were obese, i.e., had a body mass index (BMI) equal to or above the 95th percentile for children based on the World Health Organization (WHO) BMI charts, or if their body weight was below 9.0 kg, if they had (a history of) seizure disorder or epilepsy, renal or hepatic impairment, acute or severe bronchial asthma or hypercapnia, brain tumors, clinically relevant history or a current condition of head injury, or increased intracranial pressure including traumatic and hypoxic brain injuries such as stroke, transient ischemic attack, brain contusion, intracranial hematoma, episode(s) of more than 24 hours duration of unconsciousness, or posttraumatic amnesia. Subjects who had undergone brain surgery or who had undergone an intervention or surgery that would, in the opinion of the investigator, have affected the absorption of tapentadol (e.g., surgery of the gastrointestinal tract) were excluded, as were subjects who displayed signs or symptoms of congestive heart failure (e.g., required more than minimal inotropic support), or hemorrhagic disorder following surgery. Subjects who had biliary tract disease or were suspected of having paralytic ileus were excluded, as were subjects who had, in the judgment of the investigator, clinically unstable systolic and diastolic blood pressure, heart rate, respiratory depression, or clinically unstable upper or lower airway conditions, or a clinically significant decreased/unstable saturation of peripheral oxygen (SpO_2) at the time of allocation to IMP.

Subjects were excluded if they had a clinically relevant history of hypersensitivity, allergy, or contraindication to tapentadol, the excipients, or naloxone, or if they were taking prohibited concomitant medication. Subjects who required continuous positive airway pressure or mechanical ventilation at the time of allocation to IMP were also excluded.

The subjects should not have been mentally retarded, cognitively impaired, or unable to comprehensively understand or follow the trial instructions (as appropriate for the age of the subject, based on medical history and/or in the judgment of the investigator). Furthermore, subjects with aspartate transaminase and/or alanine transaminase above 3 times upper limit of normal (ULN), total bilirubin above 2 times ULN, estimated glomerular filtration rate (GFR) below 60 mL/min (calculated according to Schwartz et al. 1984), lactic acid above 2 times ULN (only if the painful event was cardiac surgery), or alterations in any other parameter which was, in the judgment of the investigator, clinically significant and would have put the subject at undue risk if they were to take part in the trial, were excluded.

Within reason, every effort was made to ensure a balanced distribution of ages across the population of treated subjects. At least 2 treated subjects were to be aged between 2 years and less than 3 years.

Summary of the trial procedures and assessments

The trial consisted of an Enrollment Phase (Visit 1) of up to 28 days, a Treatment and Evaluation Phase (Visit 2 and Visit 3) of up to 4 days, and a Follow-up Phase (Visit 4) of up to 14 days.

Enrollment Phase

After providing written informed consent and, if applicable, assent, subjects entered the Enrollment Phase (Visit 1), within 28 days of allocation of the IMP. Prior/concomitant medication/therapies used within 28 days before allocation to IMP were recorded. Subject demographics, relevant medical and surgical history were recorded, and vital signs and oxygen saturation were assessed.

During this phase, the general suitability of the subject was assessed against the predefined eligibility criteria and a baseline physical examination was performed. According to the protocol, enrollment of the subjects could be started before or after the painful event (e.g., a planned surgery). The painful event was not considered part of the trial; details of the event (e.g., indication for surgery) were recorded on the subject's electronic case report form (eCRF). A local safety laboratory assessment was performed, as per local standard of care. The subject was given a trial card, and any adverse events (AEs) were recorded.

Treatment and Evaluation Phase

During the Treatment and Evaluation Phase subjects remained in hospital. Visit 2 started when the first pre-dose assessment for Dose 1 was performed and ended when the final PK blood sample was collected. Assessments included the recording of oxygen saturation, vital signs and pain intensity, measured using the face, legs, activity, cry, consolability (FLACC) pain scale. Dose 1 was administered within 10 minutes of these assessments being performed. Thereafter, subjects were administered a target dose of 1.25 mg tapentadol per kilogram bodyweight every 4 hours (±15 minutes).

Blood samples for PK analysis (up to a maximum of 6 samples of 0.5 mL volume per sample) were taken at defined time points after Dose 1, Dose 5, Dose 6, Dose 14 (if applicable) and 5.0 hours and 10 hours after the final dose (irrespective of which dose was the final dose).

Visit 3 took place between 12 hours and 24 hours after the final dose. Assessments included the recording of oxygen saturation, vital signs and pain intensity. A physical examination was performed.

Throughout the Treatment and Evaluation Phase, subjects were monitored for safety including assessments of AEs and monitoring of vital signs and oxygen saturation. Concomitant medications/therapies were also recorded throughout the Treatment and Evaluation Phase.

Follow-up Phase

The Follow-up Phase (Visit 4) was scheduled between 10 days and 14 days after Visit 3 and may have been performed by telephone.

At Visit 4, AEs were assessed, and concomitant medication/therapies were recorded.

See Section 9.11 for a summary of the trial, depicted as a flow diagram (Figure 2) and a tabular schedule of events (Table 2).

Trial performance

There were 2 non-substantial protocol amendments throughout the trial period. There was no premature trial termination or suspension (clinical hold) of the trial.

Trial conduct partly overlapped with the coronavirus disease 2019 (COVID-19) pandemic, for which a pandemic status was officially declared by the WHO on 11 Mar 2020. In line with the European Medicines Agency (EMA) "GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC" (EMA 2020), the impact on the clinical trial and trial participants was assessed and the trial risk assessment was updated.

The trial setup was found to be robust and only required minor changes to accommodate the COVID-19 pandemic (e.g., intensified exchange with trial sites to ensure proper subject safety and

trial conduct, recruitment restriction to treat only 1 active subject at a time at each site, minor adaptation to clinical monitoring strategy allowing remote monitoring, however not allowing remote source data verification).

At the time the pandemic status was declared, no active subjects were enrolled into the trial who could have been affected by the pandemic directly. Only the last 2 subjects were enrolled and treated while the pandemic was persisting, after the described minor additional precautionary measures were in place.

Summary of the statistical methods

The sample size of 8 evaluable subjects was determined taking cohort size and experiences from a previous PK trial of a single intravenous (IV) dose of tapentadol solution for injection (KF5503-73) into account. That trial was prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of the primary PK parameters (apparent clearance [CL] and apparent volume of distribution [V]) for each age subgroup (Wang et al. 2012). Based on trial simulations, 8 subjects with 3 PK samples per subject at specific time points were considered sufficient to meet the power criterion of at least 80%. As a result, at least 8 treated subjects who were considered evaluable were required in the trial.

Descriptive and graphical methods were used for exploratory data analyses. Summary statistics of continuous variables included (if not otherwise specified) the number of non-missing observations, arithmetic mean, standard deviation, minimum, first quartile, median, third quartile, and maximum. For categorical variables, absolute and relative (as percentage) frequencies were used to summarize the results. For variables collected at multiple time points, descriptive summaries were provided for each time point.

The serum concentrations of tapentadol and its metabolites were listed for all subjects with available serum concentrations. Descriptive statistics as well as the geometric mean and geometric coefficient of variation (CV) were presented by time point based on the PK Analysis Set (PKS), which included all subjects who had a quantifiable serum concentration of at least tapentadol, tapentadol-O-glucuronide, or tapentadol-O-sulfate. Concentration values below the lower limit of quantification (LLOQ) were not considered for these calculations; the number of such values was to be displayed as a separate measure. Missing data were to be treated as such and were to be shown as a separate category.

Pain intensity scores were summarized descriptively and graphically presented over time based on the Full Analysis Set (FAS), which included all subjects allocated with at least 1 IMP administration. Adverse events, vital signs, oxygen saturation, and changes in physical examination findings were summarized descriptively. All safety data were presented for the Safety Set (SAF), which included all subjects with at least 1 IMP administration.

Summary of the pharmacometric analysis methods

As part of KF5503/75 data exploration, initial simulations were performed using a previously developed population PK (popPK) model (PP0075P report GRT, 2018), to compare predicted tapentadol exposure after multiple dosing of 1.25 mg/kg every 4 hours, with the data observed in this trial. These simulations were intended as *a priori* check for the accuracy of the prediction of tapentadol accumulation from a popPK model that was previously developed based on single-dose PK data only.

Furthermore, the concentration-time data obtained in this trial contributed to the update of the existing tapentadol popPK model and the development of a joint tapentadol-metabolite popPK model to characterize the PK profile of tapentadol and its 2 metabolites, tapentadol-O-glucuronide and tapentadol-O-sulfate in the pediatric population.

The popPK model was developed by means of nonlinear mixed effects modeling using the first-order method with conditional estimation and interaction based on the observed concentration-time data for tapentadol and its metabolites. The model was used to deliver estimates of population and individual PK parameters such as CL, V, the maximum concentration after single dose ($C_{max,sd}$) and at steady state ($C_{max,ss}$), minimum concentration after single dose ($C_{min,sd}$) and at steady state ($C_{min,ss}$), the area under the concentration-time curve for the dosing interval after single dose ($AUC_{\tau,sd}$) and at steady state ($AUC_{\tau,ss}$), and an accumulation factor (AF) of tapentadol, tapentadol-O-glucuronide, and tapentadol-O-sulfate, the $AUC_{\tau,ss}$ estimates being the primary and secondary endpoints of the trial.

Summary of results

A total of 10 subjects were enrolled, all of whom were allocated to and received IMP. All subjects completed the trial and were included in the SAF and FAS. Eight of the 10 subjects were evaluable as per protocol (i.e., the subject received at least Dose 6 before treatment was stopped, and did not vomit within 3 hours of being administered a dose of IMP). Of the 10 treated subjects, all had a quantifiable serum concentration of at least tapentadol, tapentadol-O-glucuronide, or tapentadol-O-sulfate and therefore met the criteria for inclusion in the PKS.

Demographics

A total of 10 (9 male and 1 female) subjects were enrolled in the trial and treated with tapentadol OS. For the SAF, the ages of the subjects spanned the range permitted by the trial inclusion criteria; 4 subjects were aged between 2 years and less than 3 years, 3 were aged between 6 years and less than 7 years, and the age ranges 3 years to less than 4 years, 4 years to less than 5 years, and 5 years to less than 6 years contained 1 subject each. Mean height was 102.8 cm, mean weight was 16.58 kg, and mean BMI was 15.22 kg/m^2.

Pharmacokinetics

Multiple administrations of tapentadol OS as per approved dosing recommendation (i.e., dose of 1.25 mg tapentadol per kilogram bodyweight every 4 hours) to children aged 2 to less than 7 years provided serum concentration-time data for tapentadol and its metabolites, tapentadol-O-glucuronide and tapentadol-O-sulfate, that were further analyzed using popPK modeling and used to update the popPK model.

Pharmacometrics

Prior to any modeling update utilizing KF5503/75 data, initial simulations were performed using an already existing pediatric popPK model that was developed based on combined tapentadol IV and OS data from single-dose trials only (PP0075P report GRT, 2018). These initial ‘pre-trial’ simulations showed a very good agreement between the *a priori* model-based predictions and the observed concentrations in KF5503/75 indicating that tapentadol accumulation after multiple drug dosing every 4 hours was already well captured by the PP0075P model, which was developed based on single-dose PK trials only.

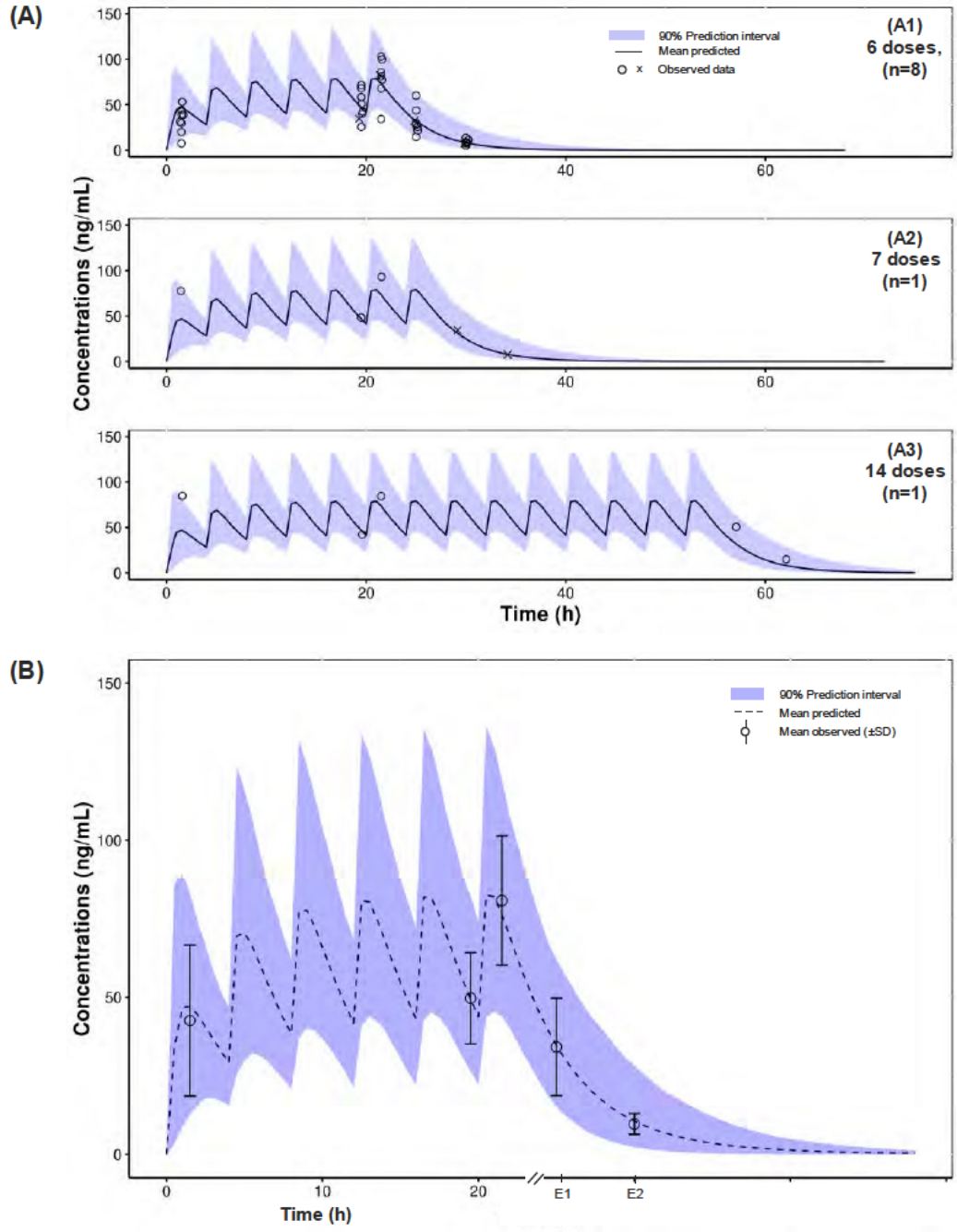

Figure 1: Comparison of tapentadol concentrations observed in the present trial (KF5503-75) with *a priori* simulations using the 'pre-trial' available pediatric popPK model

Comparison of simulation results with (A) individual observed concentration-time data of KF5503/75 subjects, stratified by the number of administered doses, and (B) mean observed data (±SD).

E1 and E2 refer to the samples collected 5 hours and 10 hours after the last given drug dose.

h = hour; IMP = investigational medicinal product; n = number of subjects; popPK = population PK; SD = standard deviation; X = observed data after the incidence of spitting out of IMP dose or regurgitation, which were excluded from the calculated descriptive statistics presented in (B).

Using concentration-time data obtained from the present trial and earlier pediatric PK trials, an updated tapentadol popPK model as well as a joint tapentadol-metabolite popPK model have been successfully developed to characterize the PK profile of tapentadol and its 2 metabolites, tapentadol-O-glucuronide, and tapentadol-O-sulfate in the pediatric population.

The structure and parameter estimates of the tapentadol popPK model after the update were almost identical with those of the previously reported popPK model that was developed based on single-dose data only (PP0075P report GRT, 2018). The developed models were used to perform a model-based PK evaluation.

Primary endpoint

The estimated model-based $AUC_{\tau,ss}$ values ranged from 142 h•ng/mL to 321 h•ng/mL, which were within the range predicted for children aged 2 years to less than 7 years using the popPK model that was developed based on single-dose data only (95th prediction interval [PI] of 138 h•ng/mL to 457 h•ng/mL), without any indication of a higher accumulation than expected for the dosing regimen (Table 1).

The $AUC_{\tau,ss}$ values were also within the targeted steady state exposure range, which was established from the adult therapeutic doses of 50 mg to 100 mg immediate release (IR) every 4 hours (PP0047P report GRT, 2018).

The median AF for tapentadol was estimated to be 1.73.

Table 1: Observed model-based $AUC_{\tau,ss}$ estimates versus predicted $AUC_{\tau,ss}$ estimates versus targeted steady state exposures for tapentadol

	Targeted exposure range [a]	**Predicted (95% PI) [b]**	**Observed [c] (range, n=8)**
$AUC_{\tau,ss}$ (h•ng/mL)	130.7 – 706	138 – 457	142 – 321

a) Targeted steady state exposure range established from the adult therapeutic doses of 50 mg to 100 mg IR every 4 hours.

b) Predicted values for children aged 2 years to less than 7 years based on previous popPK model using single-dose data.

c) Observed model-based estimates for KF5503/75 evaluable subjects (n = 8) based on their observed concentration-time data and the updated tapentadol popPK model.

$AUC_{\tau,ss}$ = area under the concentration-time curve for the dosing interval at steady state; IR = immediate release; n = number of subjects; PI = prediction interval; popPK = population pharmacokinetic; range = minimum to maximum.

Source: pharmacometric report (PA0013R) (Appendix 16.1.14)

Secondary endpoints

The model-based calculated $AUC_{\tau,ss}$ values for tapentadol-O-glucuronide ranged from 4501 h•ng/mL to 7617 h•ng/mL. The median AF for tapentadol-O-glucuronide was estimated to be 1.84, which was close to the estimated value for the tapentadol AF. The model-based calculated $AUC_{\tau,ss}$ values for tapentadol-O-sulfate ranged from 180 h•ng/mL to 590 h•ng/mL. The median AF for tapentadol-O-sulfate was estimated to be 1.28, which was lower than those estimated for tapentadol and tapentadol-O-glucuronide.

Exploratory efficacy

In an exploratory analysis of efficacy, pain intensity was assessed using the FLACC scale, an observational assessment. There was a decrease in post-operative pain intensity after the start of the

tapentadol OS administration. It should be noted, however, that the design of this PK trial (i.e., small number of subjects, lack of a placebo control) limits the possibility to draw conclusions about the efficacy of tapentadol OS based on these data.

Safety results

- A total of 7 treatment-emergent AEs (TEAEs) were reported for 5 subjects. The reported events included nausea in 2 subjects, and events of constipation, regurgitation, vomiting and hyperhidrosis in 1 subject each.
- There were no deaths or serious TEAEs, and no subjects discontinued from IMP or from the trial due to TEAEs.
- Treatment-emergent AEs that were considered to be at least possibly related to IMP by the investigator were reported for 4 subjects (hyperhidrosis, constipation, nausea and vomiting), all of which are known adverse drug reactions (ADRs) to tapentadol OS.
- All TEAEs were mild in intensity, with the exception of 1 moderate event of vomiting, the outcome of which was resolved.
- No clinically meaningful abnormal vital signs or oxygen saturation values were reported for any subject at any assessment, and there were no clinically meaningful changes in physical examination findings following treatment.

Conclusions

- Multiple administrations of tapentadol OS as per approved dosing recommendation (i.e., dose of 1.25 mg tapentadol per kilogram bodyweight every 4 hours) to children aged 2 years to less than 7 years resulted in serum concentrations of tapentadol within the predicted concentration range from the popPK model which was based on single dose PK data.
- Observed model-based $AUC_{\tau,ss}$ estimates for tapentadol were within the predicted exposure range with accumulation no higher than expected for the dosing regimen.
- The concentration-time data obtained in this trial contributed to the update of the tapentadol popPK model and the development of a joint tapentadol-metabolite popPK model to characterize the PK profile of tapentadol and its 2 metabolites, tapentadol-O-glucuronide and tapentadol-O-sulfate in the pediatric population.
- Multiple administrations of tapentadol OS in children aged 2 years to less than 7 years were safe and well tolerated. No new safety concerns were identified.