SDR-CTR-SYN-06

Trial code	KF5503-73
Title of trial	Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of intravenous tapentadol solution for injection for the treatment of post-surgical pain in children aged from birth to less than 2 years, including preterm neonates.
Trial design	Interventional Phase II, non-randomized, multiple-site, open-label, single-dose, intravenous administration trial.
Development phase	Phase II
EudraCT number	2014-002259-24
Universal Trial Number	U1111-1157-3228
Pediatric investigation plan (PIP)	EMEA-000018-PIP01-07
Investigational medicinal product (IMP)	Tapentadol solution for injection.
Indication	Moderate to severe acute post-operative pain.
International coordinating investigator	Dr [redacted]. Anaesthetic Department Sheffield Children's Hospital, Western Bank, Sheffield S10 2TH, United Kingdom.
Trial sites	Spain (5 sites), France (3 sites), United Kingdom (5 sites), Hungary (5 sites), Poland (6 sites).
Sponsor's signatory	Dr [redacted], Head of Clinical Science. Contact number: +49 (0) 241-569-1090
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany.
Trial period	First subject in: 23 Apr 2015 Last subject out: 27 Sep 2018
Previous report (interim)	31 May 2017

Objectives

Primary objective

The primary objective of the trial was to collect serum concentration data of tapentadol and its major metabolite tapentadol-O-glucuronide after the administration of a single dose of intravenous tapentadol solution for injection (tapentadol IV) in children aged from birth to less than 2 years, including preterm neonates, after a qualifying procedure (either a surgical or medical procedure in preterm neonates) that routinely produces moderate to severe acute pain requiring opioid treatment.

The concentration data was to be used to characterize the pharmacokinetic parameters of tapentadol using a population pharmacokinetic approach. This was to enable data-based recommendations for the use of tapentadol in children of different ages.

The dose recommendation for use in clinical practice, which will be made based on the population pharmacokinetic analysis, is not in the scope of this report.

Secondary objectives

The secondary objectives of the trial were to evaluate the safety and tolerability of a single dose of tapentadol IV in the population studied and to explore the effect of tapentadol IV on moderate to severe pain that, in the opinion of the investigator, requires treatment with an opioid, using validated age-appropriate scales.

Investigational medicinal product

Tapentadol solution for injection (CG5503/R331333; tapentadol IV), 1 mg/mL solution in 2 mL glass ampoules.

Batch number: 11556G003, collective batch numbers E128087-01 (expiration date 07/2017) and E128087-03 (expiration date 07/2017, after partial re-labeling the expiration date was extended to 07/2018).

Batch number: N0005, collective batch number E128087-04 (expiration date 03/2022).

The IMP was a single intravenous dose of tapentadol solution for injection (1 mg/mL) given over 1 hour.

Dosing is based on gestational and postnatal age:

Gestational age	Postnatal age	Dose
≥32 weeks	≥7 days	0.4 mg/kg
	<7 days	0.3 mg/kg
31 weeks	≥14 days	0.4 mg/kg
	7 days to <14 days	0.3 mg/kg
30 weeks	≥21 days	0.4 mg/kg
	14 days to <21 days	0.3 mg/kg
26 weeks to <30 weeks	≥6 weeks	0.4 mg/kg
	4 weeks to <6 weeks	0.3 mg/kg
24 weeks to <26 weeks	≥8 weeks	0.4 mg/kg
	6 weeks to <8 weeks	0.3 mg/kg

Trial treatments

Tapentadol IV was given as a single dose after the qualifying procedure.

Trial population

Subjects who were selected had undergone a qualifying procedure (either a surgical or medical procedure in preterm neonates) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

The subjects were male or female aged from birth to less than 2 years, including preterm neonates, and not obese with a minimum body weight of 1.5 kg.

The main exclusion criteria were previous exposure to tapentadol, receiving another medication that was disallowed, and a concomitant disease or disorder that in the opinion of the investigator could have affected or compromised the subject's safety during the trial.

The trial population comprised evaluable subjects in the following 4 age subgroups:

- Age subgroup 1: a targeted enrollment number of 8 evaluable subjects aged 6 months to less than 2 years.
- Age subgroup 2: a targeted enrollment number of 8 evaluable subjects aged 1 month to less than 6 months.
- Age subgroup 3: a targeted enrollment number of 8 evaluable subjects from birth (must be ≥37 weeks gestational age) to less than 1 month.
- Age subgroup 4: a targeted enrollment number of 8 evaluable preterm born subjects from birth to a postmenstrual age of ≤41 weeks. Subjects had to have a gestational age between 24 weeks and <37 weeks.

The trial sequentially recruited subjects in each of the age subgroups, starting with subjects in age subgroup 1, and moving to the next age subgroup once the targeted exposure was verified.

Summary of the trial procedures and assessments

For each subject, the trial included the following:

Enrollment Period (Visit 1; Day -28 to Day 1):

The Enrollment Period started before or after a qualifying procedure. It included the enrollment evaluations covering the time up to allocation to IMP.

Treatment and Evaluation Period (Visit 2; Day 1 up to 15 hours)

The Treatment and Evaluation Period included the administration of a single dose of tapentadol IV followed by safety assessments, pain intensity assessments, and blood sampling for the determination of the serum concentrations of tapentadol and its main metabolites. Subjects were carefully observed, especially during the first 5 hours after taking IMP.

End of Treatment Visit (Visit 3; Day 1 or Day 2) or at discontinuation

Following safety and pain assessments, subjects were discharged from the site according to the site routine procedures.

Follow-up Visit (Day 10 to Day 14)

A site visit or the subject's parent(s) or legal guardian(s) were contacted by telephone for the assessment of adverse events and the use of concomitant medication/therapies.

Trial performance

Protocol amendments implemented

There were 7 protocol amendments.

Clinical hold or early termination of the trial

The trial was not put on clinical hold. The trial was not terminated early.

Trial size

A population pharmacokinetic model was built using data from children aged 3 years to less than 18 years from 2 single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R331333PAI2005]). This model was used as the basis the for sample size calculation.

The trial was prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of the primary pharmacokinetic parameters (apparent clearance and apparent volume of distribution) for each age subgroup. The simulations suggested that a targeted enrollment number of 32 subjects with 3 pharmacokinetic samples per subject (8 subjects per subgroup) at specific time points was sufficient to meet a power criterion of at least 80%.

Summary of the statistical methods

Descriptive and graphical methods were used in the exploratory data analyses. For continuous variables, descriptive statistics included the number of observations, arithmetic mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequency counts and percentages were used to summarize the results.

Summary of the modeling and simulation methods

The serum concentrations of tapentadol, tapentadol-O-glucuronide, and tapentadol-O-sulfate were used in order to fit a population pharmacokinetic model.

The population pharmacokinetic model was used to calculate population pharmacokinetic parameters (e.g., typical population clearance and volume of distribution of tapentadol, tapentadol-O-glucuronide, and tapentadol-O-sulfate). The predictions obtained from the physiological based pharmacokinetic model that was used to determine the doses for this trial were retrospectively compared against the observations in order to confirm the predictive ability of the physiological based pharmacokinetic model. The retrospective analysis is not within the scope of this report.

The inclusion of tapentadol-O-sulfate (in addition to tapentadol-O-glucuronide) in the population pharmacokinetic model became possible after data was collected in this trial given that the bioanalytical analysis method for sulfate could be improved and results could be used for population pharmacokinetic analysis. The integration of sulfate conjugation pathway in the final model allowed a more comprehensive understanding of the correlation between biological maturation function and tapentadol metabolism in pediatrics.

The exposure of subjects to tapentadol was evaluated on an ongoing basis where the subjects' serum concentrations were compared with the observed serum concentrations obtained from older children in previous trials. Additionally, area under the concentration-time curve (AUC) was estimated using the structural elements from the tapentadol pediatric population pharmacokinetic model, the individual serum concentrations and subjects' demographics. These AUCs were then compared to the expected adult range after administration of therapeutic doses of oral tapentadol IR. The pediatric AUCs were expected to lie above the 2.5 percentile corresponding to the 50 mg oral tapentadol IR dose in adults (130.7 ng*h/mL) and below the 97.5 percentile of the 100 mg oral tapentadol IR dose (706 ng*h/mL). These evaluations were made before moving to the next younger age subgroup.

Summary of results

Subject disposition

A total of 46 subjects were enrolled and 40 of these subjects were allocated to tapentadol IV, for the final analysis. There were 6 subjects enrolled but not allocated; 4 subjects did not meet the inclusion and exclusion criteria and the parents of 2 subjects withdrew consent.

Two subjects were allocated but discontinued the trial before receiving tapentadol IV as inclusion criteria were not met or exclusion criteria were met. A total of 38 subjects completed the trial.

The analysis populations are given in the following table.

Frequency table of analysis populations – all allocated subjects

Population	Age subgroup 1 N (%)	Age subgroup 2 N (%)	Age subgroup 3 N (%)	Age subgroup 4 N (%)	Overall N (%)
Allocated subjects	10 (100)	12 (100)	9 (100)	9 (100)	40 (100)
Safety Set	10 (100)	11 (91.7)	9 (100)	8 (88.9)	38 (95.0)
Full Analysis Set	10 (100)	11 (91.7)	9 (100)	8 (88.9)	38 (95.0)
Pharmacokinetic Set	10 (100)	11 (91.7)	9 (100)	8 (88.9)	38 (95.0)

Age subgroups:

- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months
- subgroup 3: 0 months to <1 month
- subgroup 4: preterm

N = number of subjects.

Demographics

In the Safety Set, there were 28/38 male subjects (73.7%) and 10/38 female subjects (26.3%), and all subjects were White. The mean (SD) age was 423.0 (158.4) days in age subgroup 1, 95.2 (41.8) days in age subgroup 2, 15.3 (6.4) days in age subgroup 3, and 35.0 (37.7) days in age subgroup 4.

Pharmacometrics

An integrated pharmacokinetic model was developed to quantify the tapentadol and its metabolites (tapentadol-O-glucuronide and tapentadol-O-sulfate) in subjects aged from birth to less than 2 years, including preterm neonates. The pharmacokinetic models of tapentadol and its metabolites were successfully joined into a single pharmacokinetic model with the first order metabolite formation rate constants.

The final population pharmacokinetic model developed for the pediatric population following intravenous administration of tapentadol appropriately described tapentadol, tapentadol-O-glucuronide, and tapentadol-O-sulfate concentrations-time profiles in the population studied. The population pharmacokinetic model allowed for data driven dose recommendations for the repeated dosing of tapentadol intravenous infusion in subjects from birth to less than 2 years, including

preterm neonates. The dose recommendations itself will not be part of the ICTR, but will be reported separately.

Tapentadol pharmacokinetic parameters stratified by age subgroup

Parameter		Age subgroup 1 (N = 10)	Age subgroup 2 (N = 11)	Age subgroup 3 (N = 9)	Age subgroup 4 (N = 8)
CL (L/h)	Mean	14.4	9.73	5.65	4.25
	SE	0.307	0.481	0.230	0.355
	RSE (%)	2.13	4.94	4.07	8.35
	95% PI	(12.6 - 15.2)	(7.45 - 11.6)	(5.04 - 6.7)	(3.13 - 5.67)
V (L/h)	Mean	67.8	41.3	27.5	19.3
	SE	5.58	2.83	2.91	1.84
	RSE (%)	8.23	6.87	10.6	9.53
	95% PI	52.7 - 106	27.3 - 55.8	17.3 - 43.9	13.8 - 27.2
C_{max} SD (ng/mL)	Mean	60.1	56.0	49.5	46.6
	SE	3.53	4.3	3.14	5.85
	RSE (%)	5.88	7.68	6.35	12.6
	95% PI	44.4 - 79.8	33.5 - 72.5	37.0 - 66.3	20.5 - 68.3
$t_{1/2}$ (h)	Median	2.95	2.71	3.35	3.12
	SE	0.239	0.259	0.275	0.468
	RSE (%)	7.37	8.62	8.20	14.1
	95% PI	2.72 - 4.85	2.09 - 4.72	2.26 - 4.67	2.03 - 5.78
AUC_{0-24h} (ng.h/mL)	Mean	308	264	259	225
	SE	13.5	9.31	7.25	15.9
	RSE (%)	4.38	3.53	2.80	7.08
	95% PI	247 - 371	217 - 307	223 - 291	157 - 288

Age subgroups:

- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months
- subgroup 3: 0 months to <1 month
- subgroup 4: preterm

AUC_{0-24h} = area under the curve from 0 hours to 24 hours after a single dose; CL = clearance of tapentadol; C_{max} SD = maximum concentration after a single dose; N = number of subjects; PI = prediction interval; RSE = relative standard error; SD = single dose; SE = standard error; $t_{1/2}$ = elimination half-life; V = volume of distribution of tapentadol.

Efficacy

In an exploratory analysis of efficacy, pain was assessed using the Face, Legs, Activity, Cry, Consolability scale (FLACC), an observational assessment. There was a decrease in post-operative pain after the start of the tapentadol IV administration. The median pain intensity levels assessed using the FLACC decreased from 4.5, 5.0, 4.0, and 3.5 at baseline to zero by 1 hour after the start of

the administration of tapentadol IV in age subgroup 1, age subgroup 2, age subgroup 3, and age subgroup 4, respectively.

The median pain scores remained 0.0 in age subgroup 1 and age subgroup 2 or increased to maximum 2.0 in age subgroup 3 or to a maximum of 0.5 in age subgroup 4 during the 15-hour treatment period.

Safety and tolerability

Overall, 11 of 38 treated subjects (28.9%) experienced 20 treatment emergent adverse events (TEAEs). There were 3 TEAEs reported in 1 subject (10.0%) in age subgroup 1, 4 TEAEs reported in 3 subjects (27.3%) in age subgroup 2, 10 TEAEs in 5 subjects (55.6%) in age subgroup 3, and 3 TEAEs in 2 subjects (25%) in age subgroup 4. No subject reported more than 3 TEAEs.

The reported TEAEs included vomiting (in 4 subjects), oxygen saturation decreased (in 5 subjects), anaemia neonatal (in 2 subjects), pyrexia (in 2 subjects), and in single subjects, vaccination site injury, infectious pleural infusion, sepsis, weight decreased, nervousness, pneumothorax, and rash macular. No TEAEs were considered by the investigators to be related to the administration of tapentadol IV.

Post-treatment non-TEAEs were reported in 1 subject, 6 subjects, 3 subjects, and 6 subjects in age subgroup 1, 2, 3, and 4, respectively. There was 1 post-treatment serious non-TEAE (aspiration) in a subject of age subgroup 3.

There were no deaths, other serious (treatment emergent) adverse events, or adverse events leading to discontinuation.

There were no other changes in vital signs, oxygen saturation, clinical laboratory tests, or electrocardiogram (ECG) evaluations that could raise a safety concern in the trial.

Hematological and clinical chemistry parameters generally showed small but not clinically relevant changes. Larger changes were seen for alanine aminotransferase and aspartate aminotransferase. Variations in laboratory parameters were expected in this population of young children after the qualifying procedure. The changes from baseline did not indicate a particular trend in the time course of any parameter.

Mean and median systolic and diastolic blood pressures, pulse rates, and respiratory rates were decreased at almost all time points after baseline. Oxygen saturations were stable or slightly decreased at most time points. There were 2 subjects in age subgroup 3 and 1 subject in age subgroup 4 with oxygen saturations below 92% on continuous pulse oximetry. One of the subjects in age subgroup 3 had 3 events of decreased oxygen saturation reported as TEAEs. Two events occurred 5 minutes and 13 minutes after the start of tapentadol IV with reported oxygen saturations of 76% to 77%. The third TEAE reported for decreased oxygen saturation (45% to 47%) in this subject occurred 10 hours and 55 minutes after the start of tapentadol IV. A second subject in age subgroup 3 had 4 episodes of decreased oxygen saturation between 83% and 89%, with 1 event reported as a TEAE occurring 14 hours and 30 minutes after the start of tapentadol IV. One subject in age subgroup 4 had 1 episode of decreased oxygen saturation (87%) reported as TEAE that occurred 45 minutes after the start of tapentadol IV. None of these events were considered to be related to IMP by the investigator.

One subject in age subgroup 2 had prolongation of the QT interval corrected according to Fridericia (QTcF interval) at Visit 3. The QTcF was 437 ms at Visit 1 and 453 ms at Visit 3 (normal defined as ≤449 ms). This was considered to be not clinically relevant by the investigator.

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Treatment emergent adverse events by Primary System Organ Class and Preferred Term occurring in more than 1 subject in the trial – Safety Set

Primary System Organ Class **Preferred Term**	**Age subgroup 1**	**Age subgroup 2**	**Age subgroup 3**	**Age subgroup 4**	**Overall**
Number of subjects	N = 10 n (%)	N = 11 n (%)	N = 9 n (%)	N = 8 n (%)	N = 38 n (%)
All system organ classes	1 (10.0)	3 (27.3)	5 (55.6)	2 (25.0)	11 (28.9)
Blood and lymphatic system disorders	0	0	2 (22.2)	0	2 (5.3)
- Anaemia neonatal	0	0	2 (22.2)	0	2 (5.3)
Gastrointestinal disorders	1 (10.0)	1 (9.1)	1 (11.1)	1 (12.5)	4 (10.5)
- Vomiting	1 (10.0)	1 (9.1)	1 (11.1)	1 (12.5)	4 (10.5)
General disorders and admin. site conditions	1 (10.0)	1 (9.1)	0	0	2 (5.3)
- Pyrexia	1 (10.0)	0	0	0	1 (2.6)
- Vaccination site injury	0	1 (9.1)	0	0	1 (2.6)
Infections and infestations	0	0	2 (22.2)	0	2 (5.3)
- Infectious pleural effusion	0	0	1 (11.1)	0	1 (2.6)
- Sepsis	0	0	1 (11.1)	0	1 (2.6)
Investigations	0	1 (9.1)	2 (22.2)	1 (12.5)	4 (10.5)
- Oxygen saturation decreased	0	0	2 (22.2)	1 (12.5)	3 (7.9)
- Weight decreased	0	1 (9.1)	0	0	1 (2.6)
Number of events	E = 3 e (%)	E = 4 e (%)	E = 10 e (%)	E = 3 e (%)	E = 20 e (%)
All system organ classes	3 (100)	4 (100)	10 (100)	3 (100)	20 (100)
Blood and lymphatic system disorders	0	0	2 (20.0)	0	2 (10.0)
- Anaemia neonatal	0	0	2 (20.0)	0	2 (10.0)
Gastrointestinal disorders	1 (33.3)	1 (25.0)	1 (10.0)	1 (33.3)	4 (20.0)
- Vomiting	1 (33.3)	1 (25.0)	1 (10.0)	1 (33.3)	4 (20.0)
General disorders and admin. site conditions	2 (66.7)	1 (25.0)	0	0	3 (15.0)
- Pyrexia	2 (66.7)	0	0	0	2 (10.0)
- Vaccination site injury	0	1 (25.0)	0	0	1 (5.0)
Infections and infestations	0	0	2 (20.0)	0	2 (10.0)
- Infectious pleural effusion	0	0	1 (10.0)	0	1 (5.0)
- Sepsis	0	0	1 (10.0)	0	1 (5.0)
Investigations	0	1 (25.0)	4 (40.0)	1 (33.3)	6 (30.0)
- Oxygen saturation decreased	0	0	4 (40.0)	1 (33.3)	5 (25.0)
- Weight decreased	0	1 (25.0)	0	0	1 (5.0)

All subjects and TEAEs are presented if more than 1 subject experienced an TEAE within the primary System Organ Class.

Age subgroups: subgroup 1:

- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months

- subgroup 3: 0 months to <1 month
- subgroup 4: preterm

admin. = administration; N = number of subjects; n = number of subjects with TEAE; E = total number of TEAEs; e = number of TEAEs; TEAE = treatment emergent adverse event.

Limitations of the trial

This trial was primarily designed to evaluate the pharmacokinetic profile of tapentadol in young children. Therefore, the design of the trial (i.e., small number of subjects, and a single-dose trial lacking a comparator or control with the allowance of concomitant analgesic medications) limits the possibility to draw conclusions about the efficacy of tapentadol (assessed exploratively using the age-specific FLACC pain scale) in the population under study. The safety profile 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. Despite the limitations of the trial (small sample size, different pathology in different age subgroups), there is overall no clinically notable difference in the safety parameters between age subgroups.

Conclusion

- A single, weight and age-adjusted, dose of tapentadol IV administered to pediatric subjects (in subjects from birth to less than 2 years of age, including preterm neonates) produced serum concentrations of tapentadol that are within the range observed in adults after single-dose administration of therapeutic doses of tapentadol immediate release (IR) 50 mg to 100 mg.
- Serum concentrations of the main metabolite (tapentadol-O-glucuronide) were generally lower when compared to adult data.
- The final population pharmacokinetic model for pediatric population following intravenous administration of tapentadol appropriately described tapentadol, tapentadol-O-glucuronide, and tapentadol-O-sulfate concentrations-time profiles in subjects from birth to less than 2 years of age, including preterm neonates.
- Although limitations of the trial design caution against over-interpretation, a notable clear decrease in post-operative pain was observed following the start of the tapentadol IV administration using an observational pain assessment (FLACC).
- Tapentadol IV in subjects from birth to less than 2 years of age, including preterm neonates, was generally well tolerated.
- The safety profile in the studied population was consistent with the known safety profile for tapentadol observed in other pediatric trial subjects and adults. No new adverse drug reaction was identified.
- Considering the limitations of the trial design, there was overall no clinically notable difference in safety parameters between age subgroups.

Publications based on this trial

Not applicable.