PROTOCOL

Tapentadol (code numbers CG5503 and R331333, respectively) is being developed under a Licensing agreement between Ortho-McNeil Pharmaceutical Inc., Janssen Research & Development, L.L.C., and Grünenthal GmbH that was executed in February 2003, the United States rights to which were subsequently acquired by Depomed, Inc. in April 2015. Subsequent to investigational new drug (IND) and new drug application (NDA) acquisition, Depomed Inc. has further transferred sponsor regulatory obligations for this trial to Grünenthal.

This trial will be conducted in accordance with United States (U.S.) Food and Drug Administration Investigational New Drug regulations (CFR Part 312) and the European Directive 2001/20/EC of the European Parliament and of the council of 04 Apr 2001; Directive 2001/83/EC of the European Parliament and of the council of 06 Nov 2001 and Directive 2005/28/EC of the European Parliament and of the council of 08 Apr 2005.

Trial numbers:	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.
EudraCT number:	2012-004359-35
IND number:	108134
Sponsor:	Grünenthal GmbH, 52099 Aachen, Germany.
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. [a]
Trial sites:	Multi-site trial. A list of sites will be maintained.
Trial design:	This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution.
Investigational medicinal products:	Tapentadol oral solution. Placebo.

a) Contact detail changes during the course of the trial will be documented.

EudraCT = European Union drug regulating authorities clinical trials; IND = investigational new drug.

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Publication number: [redacted]

a) Contact detail changes during the course of the trial will be documented.

Version	Date	DMS version:	Valid for
Original	16 Sep 2013	DMS version 2.0	All countries
Amendment 01	27 Nov 2013	DMS version 3.0	All countries
Amendment 02	14 Oct 2014	DMS version 4.0	All countries
Amendment 03	16 Apr 2015	DMS version 5.0	All countries
Amendment 04	23 Jun 2015	DMS version 6.0	All countries
Amendment 05	27 Oct 2015	DMS version 7.0	All countries
Amendment 06	19 Aug 2016	DMS version 9.0	All countries
Amendment 07	24 Mar 2017	DMS version 10.0	All countries

1 PROTOCOL SYNOPSIS

Trial objectives:

This protocol is part of a pediatric development program that fulfills differing requirements of the Pediatric Committee of the European Medicines Agency (EU PDCO) and the Food and Drug Administration of the United States of America (US FDA). For the EU PDCO, to assess the efficacy and safety of tapentadol in the treatment of acute pain, subjects between 2 years and less than 18 years old will be evaluated. For the US FDA, subjects between birth and less than 17 years old will be evaluated.

The clinical hypothesis of this trial is that tapentadol oral solution reduces the total amount of supplemental opioid analgesic medication used over 12 hours (primary objective for US FDA) or 24 hours (primary objective for EU PDCO) following initiation of investigational medicinal product (IMP), compared to placebo, in children and adolescents 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 is considered as the secondary efficacy objective in the other, for the different age range, as described below.

Subjects can be treated for up to 72 hours, and efficacy and safety information will also be collected throughout this time period.

Primary objectives:

For EU PDCO: To evaluate the efficacy of tapentadol oral solution, based on the total amount of supplemental opioid analgesic medication used over 24 hours following initiation of IMP, in children and adolescents aged 2 years to less than 18 years who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

For US FDA: To evaluate the efficacy of tapentadol oral solution, based on the total amount of supplemental opioid analgesic medication used over 12 hours following initiation of IMP, in children and adolescents aged from birth to less than 17 years who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

For both EU PDCO and US FDA: To evaluate the safety of tapentadol oral solution in children and adolescents aged 2 years to less than 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.

Secondary objectives:

To assess the efficacy of tapentadol oral solution using multiple subjective and objective measures of the subject's response to treatment (see secondary endpoints).

Definition of endpoints:

All endpoints compare the results in the group of subjects treated with tapentadol oral solution to the group treated with placebo. As applicable and appropriate for the individual endpoint, these endpoints will be analyzed in the age ranges of 2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA.

The primary efficacy endpoint for the EU PDCO is considered a secondary efficacy endpoint for the US FDA and vice versa.

The primary efficacy endpoints are:

- EU PDCO: The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 24 hours after first IMP intake.
- US FDA: The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours after first IMP intake.

The secondary efficacy endpoints are:

- The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours (EU PDCO) or within the first 24 hours (US FDA) after first IMP intake.
- The total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP.
- Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged 2 years to less than 18 years old (EU PDCO).
- Changes from baseline in pain intensity over the Treatment Period using age-appropriate pain scales (Face, Legs, Activity, Cry, Consolability [FLACC] scale for ages birth to less than 6 years or in older children who are not able to report their pain using the other scales, Faces Pain Scale–Revised [FPS-R] for ages 6 years to less than 12 years, and visual analog scale [VAS] for ages 12 years to less than 18 years).
- Clinical Global Impression of Change (CGIC) by investigator/clinician after completion of double-blind IMP treatment.
- Patient Global (overall) Impression of Change (PGIC) by subject/parent/legal guardian after completion of double-blind IMP treatment.
- Time to first and time to second nurse controlled analgesia (NCA)/patient controlled analgesia (PCA) after the first dose of IMP.
- Time from first dose of IMP until IMP treatment discontinuation due to lack of efficacy.

Safety endpoints:

- Percentage of subjects with treatment emergent adverse events (TEAEs).
- Percentages of subjects who develop abnormal:
  - Vital signs.
  - Laboratory parameters.
  - 12-lead electrocardiogram (ECG) parameters.
- Changes from baseline in vital signs parameters.
- Sedation scores using the University of Michigan Sedation Scale.
- Changes from baseline in safety laboratory parameters.
- Changes from baseline in 12-lead ECG parameters.
- Percentage of subjects discontinuing the trial due to TEAEs and drug-related adverse events.
- Suicidal ideation/behavior in subjects aged 6 years or older using the Columbia Suicide Severity Rating Scale (C-SSRS) scores before IMP and at the end of the trial.

Trial design:

This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution.

Trial population:

The trial population will comprise male and female subjects aged from birth to less than 18 years old who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment via NCA/PCA. Examples of surgeries suitable for this trial include, but are not limited to, spinal fusions, cleft palate repair, Nuss procedures, scoliosis repair, nephrectomy, pyeloplasty, and orthopedic procedures such as club foot repair, leg lengthening, open reduction and internal fixation of long bone fractures. Subjects must remain hospitalized until the End of Treatment Visit.

The trial enrollment will be initiated in a staggered approach, starting with enrollment of an older age group until pharmacokinetic data are available in younger age groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years will be recruited. Subjects from birth to less than 2 years of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups.

The trial population must comply with the inclusion and exclusion criteria given in Section 1.3.

Course of the trial:

By definition, Enrollment Period is synonymous with Screening Period and allocation is synonymous with randomization.

The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may 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). A flow diagram of the trial is provided in Section 1.1 and a schedule of events in Section 1.2.

Trial treatments:

The subject will undergo a scheduled surgery. This surgery is not part of the trial, but would be performed as per standard of care. Subjects may start enrollment before or after surgery.

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

When the subject is able to tolerate liquids, meets the inclusion criteria, and does not meet any exclusion criterion, the subject will be allocated/randomized to IMP (tapentadol oral solution or placebo) using an interactive voice/web response system (IVRS/IWRS). Doses of IMP will be given at intervals explained below.

The first dose of IMP is given when IMP is available on the ward and the investigator determines it is medically appropriate for the subject to receive the IMP.

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

After the first dose of IMP (see table below), NCA/PCA will be 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.

Subjects must be carefully observed, especially during the first hour after the initiation of IMP.

Dosing with IMP will be stopped if:

- A switch to exclusively oral opioid analgesic medication is indicated according to the local standard of care.
- Opioid analgesic medication is no longer needed.
- IMP has been administered for 72 hours.

Investigational medicinal products

The 2 IMPs are:

- Tapentadol 4 mg/mL oral solution and tapentadol 20 mg/mL oral solution.
- Placebo.

The dosing regimen is as follows:

Age of subject	Dose for the first 24 hours	Dose after the first 24 hours	Body weight	Tapentadol oral solution or placebo
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
Birth to <30 days old	0.1 mg/kg	0.1 mg/kg or 0.075 mg/kg	-	4 mg/mL

Each dose of tapentadol oral solution (or equivalent for placebo) will not exceed 100 mg (i.e., subjects weighing 80 kg or more will receive a maximum dose of 100 mg [5 mL of the 20 mg/mL solution]).

The IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If the subject is sleeping at the time of the scheduled dose, they must be woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP must be taken as soon as possible after the subject is awake.

The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level.

Dose reduction after 24 hours

The dose of IMP may be reduced after 24 hours if there is a reduced need for analgesia according to the investigator's judgment, as follows:

- Age 6 months or more: 1.0 mg/kg.
- Age 30 days to less than 6 months: 0.3 mg/kg.
- Age birth to less than 30 days old: 0.075 mg/kg.

Stratification

Allocation/randomization to IMP will be stratified by 7 age groups (birth to <30 days, 30 days to <6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years, 17 years to <18 years) and by use of morphine or hydromorphone as supplemental opioid analgesia.

Concomitant medications/therapies:

Allowed prior and concomitant medications

Unless explicitly prohibited, all prior and concomitant medications are allowed.

Benzodiazepines may be used to treat muscle spasms or anxiety, consistent with local standard of care. They should be used with caution as they may potentiate central nervous system depression that may occur with tapentadol or other opioids.

Medications for the treatment of adverse events are allowed according to the investigator's judgment and post-operative standard of care. For example, clinically relevant respiratory depression may be treated with naloxone, and nausea/vomiting can be treated with antiemetics, which may also be given prophylactically according to the standard of care.

If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously.

In exceptional cases, if a subject has unbearable pain despite using NCA/PCA, an additional bolus (defined as a clinician bolus) of morphine or hydromorphone may be administered. The clinician bolus can be given either using the NCA/PCA pump system or by an intravenous bolus injection.

The opioid given as a clinician bolus or if the NCA/PCA intravenous line fails must be the same as that used in the NCA/PCA pump system.

Prohibited medication from 14 days before allocation/randomization to IMP until 24 hours after the last administration of IMP

- Monoamine oxidase inhibitors.
- Strong enzyme inducing drugs (e.g., rifampicin, phenobarbital, St John's Wort [hypericum perforatum]).
- Neuroleptics, anticonvulsants (except for gabapentin used in association with surgery), antiparkinsonian drugs, and all serotonergic drugs including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, triptans, and St. John's Wort (hypericum perforatum).
- Methadone.

Prohibited medication from 6 hours before allocation/randomization to IMP until 4 hours after the last administration of IMP

- Long-acting opioids.
- Medication used for sedation (as noted above, benzodiazepines may be used to treat muscle spasms or anxiety).
- Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia.

Prohibited medication/therapy from time of allocation/randomization to IMP until 4 hours after the last administration of IMP

- Opioids (other than protocol defined morphine, hydromorphone, or IMP).
- Continuous positive airway pressure or mechanical ventilation.

Restrictions for the mother of a newborn or breastfeeding mother

- For monoamine oxidase inhibitors, neuroleptics, anticonvulsants, antiparkinsonian drugs, methadone, and all serotonergic drugs including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, and triptans:
  - Prepartum intake by a mother of a newborn subject is prohibited in the 14 days prior to the subject's allocation/randomization to IMP.
  - The intake of these medications by the breastfeeding mother of a subject is prohibited from 14 days prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.
- For opioid medication (including tapentadol formulations) and medication used for sedation:
  - The intake of opioid medication (including tapentadol formulations) and medication used for sedation by the breastfeeding mother of a subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.
  - The intake of opioid medication (including tapentadol formulations) and medication used for sedation taken prepartum by the mother of a newborn subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP.

Trial duration:

Each subject is expected to be in the trial for up to about 42 days (up to 28 days for enrollment, and a treatment and follow-up period of up to 14 days).

Dosing of IMP will be for up to 72 hours.

Sample size rationale:

The sample size determination was based on the primary efficacy endpoint variable for the respective Full Analysis Sets. A linear relationship is 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 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) results in a sample size of 106 tapentadol-treated subjects and 53 placebo-treated subjects.

Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.

Completion of trial enrollment

The trial enrollment for the EU PDCO set (see Section 14.2.1 for the definition of the analysis populations) will complete when the following criterion is met:

- At least 159 treated subjects in the age range 2 years to less than 18 years of age (EU PDCO).

The trial enrollment for the US FDA set will complete when the following 2 criteria are met:

- At least 159 treated subjects in the age range birth to less than 17 years of age (US FDA).
- 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses (US FDA). Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size.

An additional objective of the study is to meet a US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age who have been exposed to tapentadol for at least 48 hours. As medically appropriate, every effort will be made to enroll subjects in this trial to meet this objective.

Reporting

Two reports will be prepared for the trial. The first report will be prepared after the date of the last contact with the last subject according to the protocol for the EU PDCO set (last subject out - EU PDCO). The second report will be prepared after the date of the last contact with the last subject according to the protocol for the US FDA set (last subject out - US FDA).

Blood sampling:

The total blood volume drawn per subject will not exceed approximately 15 mL for subjects aged 2 years and older or 2.4 mL/kg for subjects aged less than 2 years during the trial (even when additional blood is drawn for a pharmacokinetic analysis if a serious adverse event occurs).

Key data collected:

Demographic data, background data, and other subject characteristics:

- Date of signing the informed consent/assent form, sex, age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months [i.e., 60 days] to less than 2 years, and days for subjects aged less than 2 months [i.e., less than 60 days] – the day of birth is counted as day 1), race/ethnicity, height, and weight. The body mass index (BMI) will be calculated automatically.
- Prior and concomitant medications and therapies, excluding anesthetics and medication used during the surgery.
- The trade name, date, time, dose, and route of administration of opioid and non-opioid analgesic medication given post-operatively for pain before the first IMP dose. The detailed recording of these medications is limited to after surgery, for a period of (maximum) 24 hours before the first IMP dose.
- Clinically relevant medical and surgical history.
- The indication, the type of surgical procedure, the date of surgery, the start time and completion time of surgery.
- Pain intensity scores (FLACC in subjects from birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R in subjects aged 6 years to less than 12 years old, and VAS in subjects aged 12 years to less than 18 years old) before each NCA/PCA activation, whenever possible, after the first dose of IMP.

Safety:

- Adverse events.
- Safety laboratory.
- Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.
- 12-lead ECG.
- Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Reporting of clinically relevant values arising from continuous monitoring of respiratory rate and heart rate as adverse events.
- Oxygen saturation (by pulse oximetry), including values below 92% for at least 60 seconds.
- Physical examination.
- C-SSRS score in subjects aged 6 years or older.
- University of Michigan Sedation Scale score.

Efficacy:

- Dose and time of administration of IMP.
- Trade name, dose, and time of each administration of NCA/PCA supplemental opioid analgesia from first dose of IMP up to the End of Treatment Visit.
- Trade name, dose, and time of each administration of intravenous morphine or hydromorphone given if the NCA/PCA line fails, or a clinician bolus is given.
- Global impression of change using CGIC (by investigator/clinician) and PGIC (completed by the subject or parent/legal guardian).
- Acceptability and palatability of IMP in subjects aged 2 years to less than 18 years old.
- Pain intensity scores before and after first dose of IMP, before each subsequent dose of IMP, and at the End of Treatment Visit (FLACC in subjects from birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R in subjects aged 6 years to less than 12 years old, and VAS in subjects aged 12 years to less than 18 years old).
- The trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication. The detailed recording of these medications is limited to after surgery (starting up to 24 hours before first IMP dose) up to End of Treatment Visit.
- Time from the first dose of IMP to treatment discontinuation due to lack of efficacy.

Statistical methods:

The primary efficacy analysis will be based on the respective Full Analysis Set. The primary null hypothesis to be tested for the trial is that the tapentadol group is not different from the placebo group for the primary efficacy endpoint. The alternative hypothesis is that the tapentadol group is different from the placebo group for the primary efficacy endpoint. For the primary efficacy endpoint, descriptive statistics will be presented by treatment group and the endpoint will be analyzed using an analysis of variance model (ANOVA), which includes treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Treatment effects will be estimated based on least-squares means of the difference. The 95% confidence intervals and p-value will be presented for tapentadol compared with placebo. The test for the primary efficacy analysis will be 2-sided at a 0.05 level of significance. Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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, as applicable for the EU PDCO set and US FDA set) and by method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.

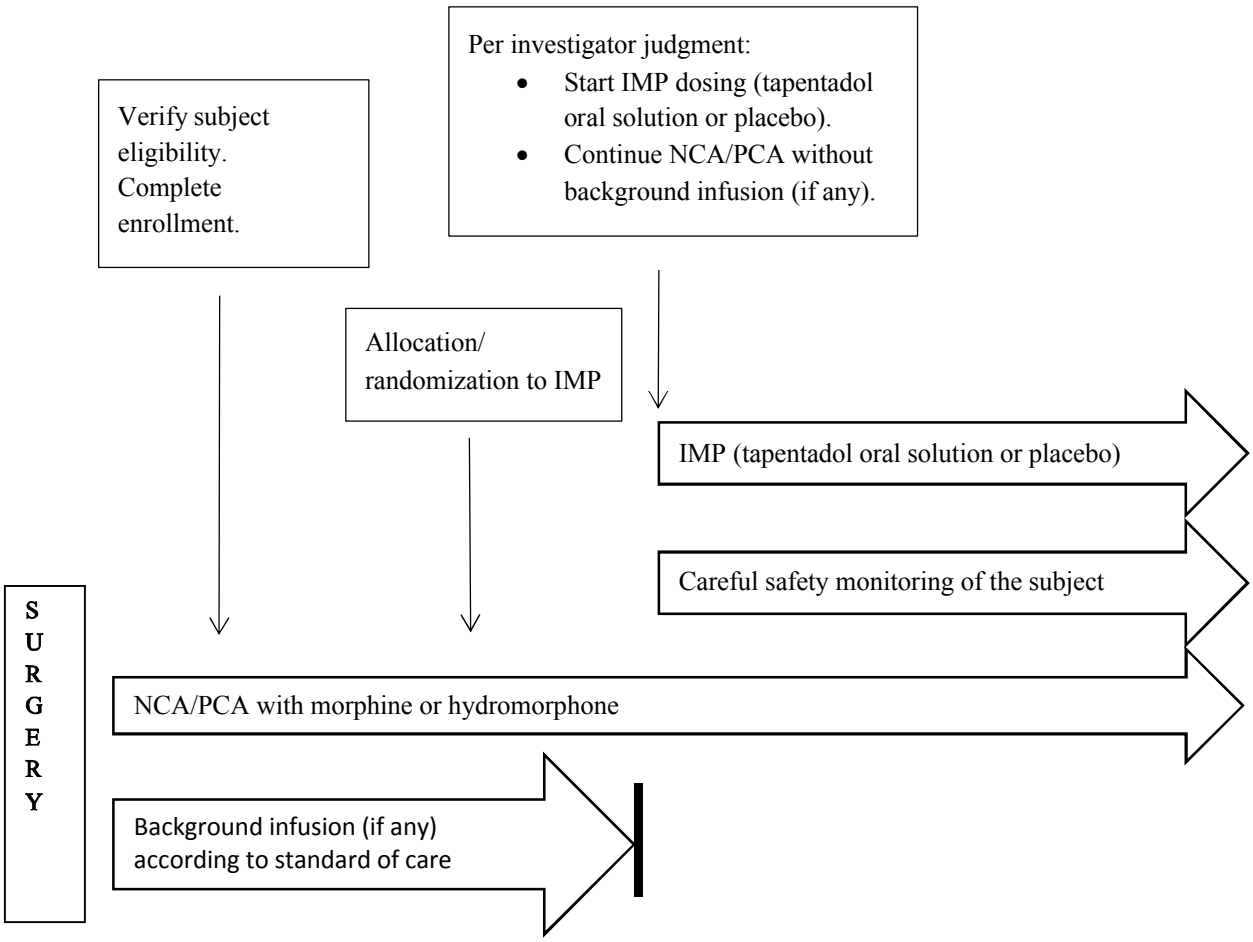
Each secondary endpoint will be analyzed using appropriate statistical methods. There will be no multiplicity adjustments for any of the secondary endpoints.

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

Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings will be 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 will be provided for the sedation scores.

Changes in physical examination findings compared to Visit 1 will be summarized by body system and results will be listed. The C-SSRS results will be listed.

1.1 Flow diagram summary of the trial



NCA = Nurse controlled analgesia; PCA = Patient controlled analgesia; IMP = Investigational medicinal product.

Figure 1: Immediate post-operative timeline

1.2 Schedule of events

Period:	**Enrollment**		**Treatment and evaluation**					**Follow-up**
Visit:	**1**		**2**				**3** [a]	**4** [b]
Time:	**≤28 days before allocation/ randomization**		**First dose Day 1**		**Subsequent doses**		**End of Treatment**	**Day 10 to Day 14**
			Before	**After**	**Before**	**After**		
	Any time	After surgery						
Obtain informed consent/assent [c]	X							
Record date of signing the informed consent/assent form, sex, race/ethnicity, and height.	X [e]							
Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight) [d]		X						
Record age at time of allocation/randomization [z]		X						
Record clinically relevant medical/surgical history	X [e]							
Record details about the surgery		X [f]						
Perform a physical examination	X [e]						X [g]	
Record intake of prior/concomitant medication and therapies, as appropriate [h]	X		X	<----------	----------	----------	---------->	X
Detailed recording of analgesics [i]		X		X	X		X	
Record C-SSRS [j]		X					X	
Continuous heart- and respiratory-rate recording for 24 hours after first IMP [k]			<----------	----------	----------	----------	---------->	
Record vital signs [l]		X [m]	X [n]		X [n]		X	
Record sedation score			X [n]		X [n]			
Continuous oxygen saturation measurement until 4 hours after the last administration of IMP [o]			<----------	----------	----------	----------	---------->	
Record oxygen saturation		X [m]	X [n]		X [n]		X	
Record 12-lead electrocardiogram		X					X	
Take blood for safety laboratory		X [p]					X	
Perform a pregnancy test	X [q]							
Check inclusion/exclusion criteria		X						
Allocate subject to IMP		X						
Stop background infusion (if any) of opioids at time of first IMP dose			X					
Detailed recording of NCA/PCA and background infusion (if any) [r]		X		<----------	----------	----------	---------->	
				no background infusion				
Administer IMP (record time and dose) [s]			X		X			
Record pain intensity [u]			X [n]	X [v]	X [n]		X	
Record pain intensity before each NCA/PCA activation [u, t]				<----------	----------	----------	---------->	
Record palatability and acceptability [w]				X			X	
Global impression of change [x]							X	

Period:	**Enrollment**	**Treatment and evaluation**					**Follow-up**
Visit:	**1**	**2**				**3** [a]	**4** [b]
Time:	**≤28 days before allocation/ randomization**	**First dose Day 1**		**Subsequent doses**		**End of Treat-ment**	**Day 10 to Day 14**
		Before	**After**	**Before**	**After**		
Perform and document drug accountability						X	
Assess and record adverse events [y]	<----------						---------->
Assess discontinuation criteria (Table 1)		X		X		X	
Dispense subject trial card	X						

Day 1 is defined as the day of first administration of IMP. Trade names should be given in preference to generic names when recording medication in the CRF. The generic name may be used if the trade name is not available.

a) To be performed between 4 hours and 24 hours after the last administration of IMP, or if the subject is prematurely discontinued from the trial. The visit must be performed before discharge from hospital.

b) Can be performed by phone.

c) Subjects from whom assent is requested after surgery will be asked to give assent when they are properly stable and able to give assent according to the investigator's judgment.

d) The body mass index will be calculated automatically.

e) May be extracted from the hospital charts if already available according to the standard of care.

f) Includes the date of surgery, the indication, type of surgical procedure, start time and completion time of surgery.

g) Record that a full examination has been performed and record changes to Visit 1 only.

h) Record all medications, including opioid and non-opioid analgesics but excluding anesthetics and medication used during the surgery (Section 12.1.2). This includes the recording of prohibited medication used by breastfeeding mothers and prohibited prior medication used by mothers of a newborn subject.

i) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.2).

j) In subjects aged 6 years or older. The administration of the C-SSRS "children's baseline" must be performed after surgery. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. The initials of the interviewer are to be recorded. The C-SSRS will only be used at a trial site if its use has not been rejected by the responsible ethics committee.

k) Record clinically relevant values as adverse events.

l) Respiratory rate, systolic and diastolic blood pressure, and pulse rate.

m) Directly before allocation/randomization to IMP.

n) Directly before IMP (i.e., within 10 minutes).

o) Using pulse oximetry. Record values below 92% for at least 60 seconds (excluding technical failures or artifacts).

p) When the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.

q) For female subjects if aged 12 years or older, or post-menarchal, or sexually active. Within 48 hours prior to allocation/randomization to IMP.

r) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.1). NCA/PCA is with morphine or hydromorphone in accordance with the standard of care at the site. Detailed information on use will be recorded at times consistent with the memory of the NCA/PCA pump. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails, or a clinician bolus is given.

s) IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If the subject is sleeping at the time of the scheduled dose they must be woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP must be taken as soon as possible after the subject is awake. After 24 hours, the investigator may decrease the dose of IMP to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia.

t) Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.

u) The different pain scales are recorded in different age ranges: FLACC – birth to less than 6 years or in older children who are not able to report their pain using the other scales; FPS-R – 6 years to less than 12 years old; VAS – 12 years to less than 18 years old.

v) Between 30 minutes and 60 minutes after IMP. Subjects do not need to be woken for this assessment.

w) In subjects aged 2 years to less than 18 years old.

x) Clinical Global Impression of Change completed by investigator/clinician, and Patient Global (overall) Impression of Change by subject if capable of completing the questionnaire (or parent/legal guardian).

y) Adverse events are to be recorded from the time after signing the informed consent form/assent form. Adverse events are to be recorded and assessed at the time when they occur. A blood sample for analysis of serum concentrations of tapentadol needs to be drawn if there is a serious adverse event.

z) Years for subjects aged 2 years and older, months for subjects aged 2 months (i.e., 60 days) to less than 2 years, and days for subjects aged less than 2 months (i.e., less than 60 days).

CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; FPS-R = Faces Pain Scale–Revised; FLACC = Face, Legs, Activity, Cry, and Consolability (scale); IMP = investigational medicinal product (tapentadol oral solution or placebo); NCA = Nurse controlled analgesia; PCA = Patient controlled analgesia; VAS = visual analog scale.

1.3 Inclusion/exclusion criteria

1.3.1 Inclusion criteria

Subjects are eligible for the trial if all the following apply:

Inclusion criteria	Rationale for criterion
1. Informed consent, and if applicable assent, given according to local regulations.	Legal and ethical requirement.
2. Male or female subject aged from birth (≥37 weeks gestational age) to less than 18 years.	Standardization of the trial population. Safety.
3. A female subject must be pre-menarchal, or surgically incapable of childbearing, or sexually abstinent, or if a female subject is sexually active, then she must be practicing an effective method of birth control (e.g., prescription hormonal contraceptives, intra-uterine devices used according to the product's instruction, double-barrier methods) before trial entry and throughout the trial.	Safety.
4. A female subject must have a negative pregnancy test if aged 12 years or older, or is post-menarchal, or is sexually active.	Safety.
5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after first dose of IMP. Subjects must remain hospitalized until the End of Treatment Visit.	Standardization of the trial population.
6. Subject has 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/randomization to IMP and subject is expected to require this morphine or hydromorphone by NCA/PCA after starting IMP.	Standardization of the trial population.
7. Subject is able to tolerate liquids at the time of allocation/randomization to IMP.	Standardization of the trial population.

Note: Subjects will only receive IMP if documentation is available showing that they comply with these inclusion criteria.

1.3.2 Exclusion criteria

Subjects are not eligible for the trial if any of the following applies:

Exclusion criteria	Rationale for criterion
1. Subject, parent or the legal representative is an employee of the investigator or trial site, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial site, or family member of the employees or the investigator.	Good clinical practice (GCP).
2. Subject has been previously exposed to tapentadol.	Ethics and interference with trial assessments.
3. Subject has received an experimental drug or used an experimental medical device within 28 days before allocation/randomization to IMP, or within a period less than 10 times the drug's half-life, whichever is longer.	Safety.
4. Subject has a history or current condition of any one of the following: • 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 episode(s) of unconsciousness of more than 24 hours.	Safety and interference with trial assessments.
5. Subject has a history or current condition of any one of the following: • Moderate to severe renal or hepatic impairment. • Abnormal pulmonary function or clinically relevant respiratory disease (e.g., acute or severe bronchial asthma, hypercapnia).	Safety and interference with trial assessments.
6. Subject has a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection, febrile seizure, paralytic ileus) that in the opinion of the investigator may affect or compromise subject safety during the trial participation.	Safety.
7. Subject has history of suicidal ideation or behavior.	Safety.
8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). or Subject weight is less than 2500 gm.	Standardization of the trial population.
9. Subject has a clinically relevant history of hypersensitivity, allergy, or contraindication to the supplemental opioid analgesic medication or tapentadol, or the excipients (see the investigator's brochure), or naloxone.	Safety.
10. Subject is not able to understand and comply with the protocol as appropriate for the age of the subject or subject is cognitively impaired in the investigator's judgment such that they cannot comply with the protocol.	Ethics and interference with trial assessments.
11. Subject has a history of alcohol and/or substance abuse in the investigator's judgment based on subject's history and physical examination.	Safety.
12. Subject is taking prohibited concomitant medication. For details, see the synopsis section Concomitant medications/therapies.	Standardization of the trial population and safety.
13. Subject has received a long-acting opioid for the treatment of pain following surgery within 6 hours of allocation/randomization to IMP.	Interference with trial assessments.

Exclusion criteria	Rationale for criterion
14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject aged 6 months to less than 18 years old is excluded if the: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • Total bilirubin is >2-times upper limit of normal (except if the cause is due to Gilbert's syndrome). • Glomerular filtration rate <60 mL/min (calculated according to Schwartz et al. 1984). A subject aged from birth to less than 6 months old is excluded if:.: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • There is pathological jaundice in the opinion of the investigator. • Glomerular filtration rate (calculated according to Schwartz et al. 1984) is: – <20 mL/min/1.73 m^2 for subjects <1 week post-partum. – <30 mL/min/1.73 m^2 for subjects 1 week to 8 weeks post-partum. – <50 mL/min/1.73 m^2 for subjects >8 weeks post-partum to <6 months old.	Safety.
15. Subject has: • Clinically relevant abnormal ECG. • Signs of pre-excitation syndrome. • Brugada's syndrome. • QT or QTc interval >470 ms for children aged 6 years to less than 18 years old. • QT or QTc interval >460 ms for children aged from birth to less than 6 years old.	Safety.
16. 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/randomization to IMP.	Standardization of the trial population.
17. Subject has post-operative clinically unstable systolic and diastolic blood pressure, heart rate, respiratory depression, or clinically unstable upper or lower airway conditions (in the investigator's judgment), or a saturation of peripheral oxygen (SpO_2) <92% at the time of randomization (allocation/randomization to IMP).	Safety.
18. Female subject is breastfeeding a child.	Safety.
19. Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP.	Safety.
20. The mother of a newborn subject or the breastfeeding mother of a subject was administered a prohibited medication (see Restrictions for the mother of a newborn or breastfeeding mother).	Standardization of trial population.

Note: Subjects will only receive IMP if documentation is available showing that they do not meet any of these exclusion criteria.

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3 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

Abbreviation	Explanation
ANOVA	Analysis of variance model
BMI	Body mass index
C-SSRS	Columbia–Suicide Severity Rating Scale
CGIC	Clinical Global Impression of Change
CL/F	Apparent clearance after oral administration
CRF	Case report form(s)
CMH	Cochran–Mantel–Haenszel (test)
DMC	Data monitoring committee
ECG	Electrocardiogram
US FDA	Food and Drug Administration of the United States of America
FLACC	Face, Legs, Activity, Cry, Consolability (scale)
FPS-R	Faces Pain Scale–Revised
GCP	Good clinical practice
IEC	Independent ethics committee
IMP(s)	Investigational medicinal product(s)
IR	Immediate-release
IRB	Institutional review board
IVRS/IWRS	Interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Nurse controlled analgesia
PCA	Patient controlled analgesia
EU PDCO	Pediatric Committee (of the European Medicines Agency)
PGIC	Patient Global (overall) Impression of Change
PR	Prolonged-release
QTc	Corrected QT interval (ECG)
QTcF	Corrected QT interval using the Fridericia correction (ECG)
SOP(s)	Standard operating procedure(s)
TEAE	Treatment emergent adverse event
TRF	Tamper resistant formulation
VAS	Visual analog scale
V/F	Apparent volume of distribution of the central compartment

Note: Système International d'Unités units and standard pharmacokinetic, hematological and biochemical abbreviations are not listed.

Definition of terms

Term	Definition
Allocated subjects	Enrolled subjects who are allocated (randomized) to IMP.
Applicable regulatory requirement(s)	Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where the trial is conducted.
Clinician bolus	An additional bolus of morphine or hydromorphone given either using the NCA/PCA pump system or by an intravenous bolus injection. The clinician bolus can only be given in exceptional cases if a subject suffers unbearable pain despite using NCA/PCA.
Discontinuation	The act of concluding the participation of an enrolled subject in a trial prior to completion of all activities required by the protocol.
End of the trial	The trial-related end of the trial is defined as the date of last subject out. The subject-related end of trial is defined as date of last contact with the subject according to the protocol.
Enrolled subjects	Informed consent/assent given according to local regulations, and subject given a subject identification number by the IVRS/IWRS.
Enrollment failures	Enrolled subjects who were not allocated to IMP.
First subject allocated	First subject that was allocated to IMP, a synonym for “first subject entered”.
First subject in	Date of first enrolled subject.
Investigational medicinal product (IMP)	A generic term describing the preparations under investigation in this trial, i.e., tapentadol oral solution and placebo.
Last subject out - EU PDCO	Date of last contact with the last subject according to the protocol for the EU PDCO set.
Last subject out - US FDA	Date of last contact with the last subject according to the protocol for the US FDA set.
Screened subjects	Screened subjects are subjects undergoing screening. Screening is any activity concerning subjects who could potentially be enrolled into the trial before the informed consent form is signed.
Treated subjects	Subjects with at least 1 administration of IMP.
Treatment period completers	Two sets of treatment period completers will be defined for subjects in accordance with the time points of the primary endpoint, i.e., 12 hours and 24 hours. Treatment period completers are defined for each of these sets as subjects who do not discontinue the treatment period before 12 hours and 24 hours, respectively.
Trial completers	Trial completers are defined as treatment period completers who have completed the Follow-up Visit. For purposes of compliance with a US FDA request, completers beyond 24 hours and up to 72 hours will be tracked and data reported.

Day 1 is defined as the day of first administration of IMP.

By definition, Enrollment Period is synonymous with Screening Period, and allocation is synonymous with randomization.

End of surgery is defined as the time the subject leaves the operating room.

An allocation/randomization failure is a subject who was allocated to IMP but was discharged from hospital or the trial without taking IMP.

4 ETHICS

This trial will be conducted according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

4.1 Independent ethics committee(s) or institutional review board(s)

The relevant independent ethics committee(s) (IEC) or institutional review board(s) (IRB) for this trial will be provided with all documents required so that the IEC/IRB responsibilities can be fulfilled. Any updates thereof will be provided according to GCP and applicable regulatory requirements.

Trial activities will only start after approval from the relevant IRB/IEC is available.

Documentation of all involved IEC/IRBs will be maintained according to GCP and applicable regulatory requirements.

4.2 Subject information and informed consent

Before any trial-related procedure is performed, freely given informed consent/assent covering all parts of the trial must be obtained.

The informed consent/assent discussion, the information sheet (if used) and the informed consent/assent form provided to the parent(s) or legal guardian(s) or, if applicable the subject, must adhere to GCP and applicable regulatory requirements. Unless agreed otherwise, the sponsor's information sheet (if used) and informed consent/assent form must be used. Prior to use, these documents must be approved by the relevant IEC/IRB.

The parent(s) or legal guardian(s) of the subject, if applicable, and/or the subject, will be informed as soon as possible if new information becomes available that may be relevant to their willingness to continue participation in the trial. The communication of this information will be documented.

If subjects, or parent(s) or legal guardian(s), withdraw their consent for participation in the trial, the investigator must inform the sponsor in writing.

Subjects (if old enough according to local laws), or parent(s) or legal guardian(s) of the subject defined according to local laws, must sign an informed consent form indicating that the signatory understands the purpose of the trial, the risks and benefits of the procedures required for the trial, and for a parent or legal guardian, give permission for their child's participation in the trial. An assent form should be signed by the child in adherence to local regulations. Subjects from whom assent is requested after surgery will be asked to give assent when they are properly stable and able to give assent according to the investigator's judgment.

As the inclusion of exclusively minors is foreseen for this trial, the subject has to be informed about the trial taking into consideration the age of the subject using an appropriate information sheet for the age of the subject and thorough explanation by qualified staff. The opinion of the minor has to be taken into account when deciding about participation in the trial, and an assent form signed as appropriate/applicable for the age of the subject.

All communication with the child or adolescent must be done by staff having experience dealing with minors.

4.3 Informing the subject's healthcare provider

In applicable countries, and only if the subject, parent, or legal guardian agrees in writing in the informed consent form and assent form as applicable, the subject's healthcare provider (e.g., general practitioner), if the subject is treated by a healthcare provider, will be informed about the subject's participation in the trial at trial enrollment. The opinion of the subject, subject's parent(s), and/or legal guardian(s) must be taken into consideration. The opinion and action is to be documented in the case report form (CRF) and on the informed consent form/assent form as applicable for the age of the subject.

The healthcare provider will be informed about the trial code, the investigator's name, and a contact (telephone) number at the trial site. Any communication with the healthcare provider will be documented in the subject's medical records.

5 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

5.1 Investigators and trial site personnel

5.1.1 Investigators

The investigator, in general, is the person responsible for the conduct of the trial at the trial site and the safety of the trial subjects.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as an investigator/principal investigator will be required to sign a declaration of their responsibilities (the "Investigator Confirmation Sheet") before any trial-related procedure is performed.

A coordinating investigator will be defined who is responsible for the coordination of multiple trial sites in multiple countries.

Curriculum vitae and/or other relevant documents confirming the qualifications of the investigator are required by the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials and experience with subject care.

Documentation of all involved investigators will be maintained according to GCP and applicable regulatory requirements.

5.1.2 Trial site personnel assigned trial-related duties

The principal investigator may define personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision.

The principal investigator must maintain a signed list of appropriately qualified persons to whom he or she delegates significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list. The delegation of tasks has to comply with international and local regulations.

When personnel or responsibility changes are made, the relevant documentation must be updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions will be maintained according to GCP and applicable regulatory requirements.

5.2 Contract research organizations

Contract research organizations (commercial, academic or other, e.g., central laboratory facilities, trial supply management provider, diary provider) may be contracted by the sponsor to perform trial-related duties and functions. The extent of the delegation will be documented. All involved contract research organizations will be required to have implemented quality control and quality assurance processes, and to support the sponsor's quality control and quality assurance measures.

Documentation of all involved contract research organizations will be maintained according to GCP and applicable regulatory requirements.

5.3 The sponsor and sponsor's personnel

Grünenthal GmbH, 52099 Aachen, accepts the responsibility to be the sponsor of this clinical trial.

The sponsor will designate appropriately qualified personnel to give advice on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained.

5.4 Data monitoring committee

An independent data monitoring committee (DMC) will be established to oversee and evaluate safety data and serum concentration data (tapentadol and tapentadol-O-glucuronide), as applicable.

The DMC members will neither be employees of the sponsor or collaborator nor be directly involved in the ongoing pediatric trials with tapentadol. Further details describing the data to be assessed and operational aspects of the DMC will be given in a charter which will be issued before the first subject is enrolled in this trial.

Based on the reviewed data, the DMC may recommend the implementation of additional measures or dose changes. The final decision on how to further proceed with the trial will be made by the sponsor or collaborator on the basis of the DMC recommendation.

6 INTRODUCTION AND TRIAL BACKGROUND

6.1 Background to the investigational medicinal product

Tapentadol is a centrally acting analgesic agent. Tapentadol has been pharmacologically characterized as both a mu-opioid receptor agonist and an inhibitor of noradrenaline reuptake. Non-clinical data suggest that both mechanisms contribute to its analgesic effects. Tapentadol is a pure enantiomer that acts directly on the central nervous system and metabolites were shown not to contribute to the analgesic activity.

6.2 Relevant non-clinical and clinical data

For a detailed summary of relevant non-clinical and clinical experience, see the current edition of the investigator's brochure.

Non-clinical pharmacology

In various animal models of acute, chronic, inflammatory, and neuropathic pain, tapentadol exerted potent antinociceptive effects. This broad antinociceptive profile reflects its combined mode of action (mu-opioid receptor agonist and an inhibitor of noradrenaline reuptake). Both opioid and non-opioid properties are relevant for the management of clinical pain.

Effects in humans

Tapentadol has been given to adults as an oral solution, intravenous solution, immediate-release (IR) tablets or capsules, and as prolonged-release (PR) tablets (including a tamper resistant formulation [TRF]). To date, tapentadol has been administered to children aged 2 years to less than 18 years in the pediatric clinical program. The oral solution has been given to these children as a single dose in 2 pharmacokinetic trials (KF5503/68 and KF5503/59).

Pharmacodynamics in adults

Tapentadol showed dose-dependent effects in a model for mu-opioid receptor agonist activity (pupil diameter) and in an experimental pain model (pain somatosensory evoked potentials following CO_2 [carbon dioxide] laser stimulation) in doses ranging from tapentadol IR 50 mg to 200 mg.

Tapentadol IR prolonged the orocecal transit time in a dose dependent manner, but the effect with tapentadol IR 43 mg was less pronounced than with morphine IR 30 mg.

Pharmacokinetics in adults

Tapentadol was rapidly and completely absorbed after oral administration of tapentadol IR. Mean absolute bioavailability after single-dose administration (fasting) was approximately 32%, most probably due to an extensive first-pass metabolism. Peak serum concentrations of tapentadol were observed at approximately 1.25 hours (tapentadol IR) and approximately 3 hours to 6 hours (tapentadol PR or tapentadol TRF) post-dose. The tapentadol terminal half-life was approximately 4 hours (tapentadol IR) and approximately 5 hours to 6 hours (tapentadol PR). The serum protein binding of tapentadol was approximately 20%.

After oral administration, approximately 70% (comprising 55% as a glucuronide and 15% as a sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. A total of 3% of the drug was excreted in urine as unchanged drug.

In humans, tapentadol is mainly metabolized via phase 2 conjugation, and only a small amount is metabolized via phase 1 oxidative pathways. No metabolite contributes to the analgesic activity. As glucuronidation is a high capacity/low affinity system, clinically relevant interactions at the level of phase 2 metabolism are unlikely. Since in-vitro investigations showed that tapentadol does not inhibit or induce cytochrome P450 enzymes, clinically relevant interactions mediated by the cytochrome P450 system are also considered unlikely.

After intravenous administration, tapentadol was widely distributed throughout the body with a volume of distribution (V_z) of 540 L. The terminal half-life was approximately 4.1 hours and total clearance was 1530 ± 177 mL/min. Systemic exposure to tapentadol (area under the concentration-time curve; AUC) and accumulation factors following multiple dosing were found to be consistent

with single-dose data. Steady-state was attained approximately 16 hours to 20 hours after the first administration.

Systemic exposure (maximum concentration of analyte [C_{max}] and AUC) to tapentadol showed dose-proportional increases over the therapeutic dose range. The accumulation ratio of tapentadol based on the maximum serum concentrations at steady-state ($C_{max,ss}$) was consistent with linear pharmacokinetics and close to the theoretically expected value.

The pharmacokinetics of an oral solution was similar to those of the immediate-release tablet formulation.

After oral dosing, AUC and C_{max} of tapentadol were higher in subjects with mild and moderate hepatic impairment compared to healthy subjects. The rate of formation of tapentadol-O-glucuronide decreased with increasing liver impairment.

After oral dosing, AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired function). In contrast, increasing exposure (i.e., AUC) to tapentadol-O-glucuronide was observed with increasing degrees of renal impairment.

In drug-drug interaction trials studying the possible influence of paracetamol, naproxen, acetylsalicylic acid, and probenecid on tapentadol glucuronidation, there were no clinically relevant effects on tapentadol serum concentrations. Also, there were no clinically relevant effects on the absorption of tapentadol in interaction trials of tapentadol with metoclopramide and omeprazole.

Pharmacokinetics in children

A population pharmacokinetic model was developed by means of the non-linear mixed effect approach using the data available from 2 single-dose pharmacokinetic trials in children aged 2 years to less than 18 years (KF5503/68 and KF5503/59). A 1 compartment model was found to describe the data adequately. The pharmacokinetic parameters of the allometrically scaled base model were as follows: CL/F = 172 $L.h^{-1}$, V/F = 677 L (the CL/F and V/F are typical estimates for a subject with a body weight of 45 kg), first order absorption rate constant (Ka) = 2.01 h^{-1}, time delay between drug administration and beginning of absorption (T_{LAG}) = 0.247 h. The modeled pharmacokinetic parameters in children aged 2 years to less than 18 years old are in line with the corresponding modeled pharmacokinetic parameters in adults. The coefficients of weight on CL/F and V/F were estimated to be 0.635 and 0.853, respectively. The inter-individual variabilities on CL/F, V/F, and Ka were 22.4%, 17.3%, and 145.3%, respectively.

The addition of data from KF5503/72, i.e., adding data from children aged birth to less than 2 years, resulted in minor changes to the model (comprising children from birth to 18 years old) and was best described by incorporation of an E_{max} type maturation function. The pharmacometric parameters changed to: CL/F = 155 $L.h^{-1}$, V/F = 533 L (the CL/F and V/F are typical estimates for a subject with a body weight of 32.6 kg), Ka = 2.44 h^{-1}, T_{LAG} = 0.267 h, with the coefficients of weight on CL/F and V/F being estimated as 0.562 and 0.827, respectively. The maturation function, which describes the age at which half the maximum CL/F in the data set was estimated as 39 weeks. The inter-individual variabilities on CL/F, V/F, and Ka remained virtually the same.

Safety in Phase I trials in adults (tapentadol intravenous, tapentadol oral solution, tapentadol IR, and tapentadol PR including TRF)

As studied in single- and multiple-dose Phase I trials, tapentadol IR (single-dose: ≤200 mg and multiple-dose: ≤175 mg orally every 6 hours) and tapentadol PR (single-dose: ≤300 mg and

multiple-dose: ≤250 mg orally twice daily) were safe; no maximum tolerated dose was reached. The adverse event profile was consistent with that of centrally-acting analgesics. The most frequent TEAEs were dizziness, headache, somnolence, nausea, fatigue, vomiting, and dry mouth. Most TEAEs were mild or moderate in intensity. Overall, there were no clinically relevant treatment-related or dose-related effects on laboratory parameters, vital signs, or ECG parameters.

No effects on the QT interval and other ECG parameters were shown after multiple therapeutic (100 mg) and supra-therapeutic (150 mg) doses of tapentadol IR in a thorough QT trial. Similarly, tapentadol had no relevant effect on heart rate, PR interval, QRS duration, and T-wave or U-wave morphology. In a second thorough QT trial, multiple oral administration of 86 mg or 172 mg tapentadol PR did not cause corrected QT (QTc) prolongation.

A dedicated abuse liability trial conducted in non-dependent healthy recreational users of opioids showed a similar abuse liability profile to that of hydromorphone at estimated equianalgesic doses.

Safety results from trials in which tapentadol was given as an oral solution or intravenously were generally consistent with those observed with tapentadol IR with the exception of a stronger influence on the respiratory system after intravenous administration.

Safety in Phase II trials in children (tapentadol oral solution)

In a single dose trial (KF5503/68) of 66 children undergoing dental, ear, nose, or throat surgery, there were no deaths. There was 1 serious adverse event (post-operative bleeding 6 days after a tonsillectomy), and 6 subjects were discontinued due to an adverse event (vomiting, which was also considered a stopping criteria). In a second trial (KF5503/59 [R33133PAI2005]) of similar design, but which included a greater variety of surgical procedures, in 45 children, there were no deaths, serious adverse events, or discontinuations due to an adverse event.

Safety Phase II and Phase III in adults (tapentadol IR)

Adverse drug reactions, the most common (≥10% subjects) being nausea, dizziness, vomiting, somnolence, and headache, were observed with tapentadol IR treatment in the dose range of 50 mg to 100 mg, and are as expected for a centrally-acting analgesic. Most adverse drug reactions reported with tapentadol IR were of mild or moderate intensity. Apart from withdrawal classified as mild in most cases, prolonged use of tapentadol IR (for up to 90 days) was not associated with a change in the safety profile of tapentadol IR. With prolonged use, the incidence of nausea and vomiting decreased with time, whereas constipation remained at the same level.

Safety Phase II and Phase III in adults (tapentadol PR)

Adverse drug reactions, the most common (≥10% subjects) being nausea, dizziness, somnolence, headache, and constipation observed with tapentadol PR treatment in the dose range of 50 mg to 250 mg twice daily, are as expected for a centrally-acting analgesic.

Safety experience from post-marketing data in adults

The total cumulative post-authorization patient exposure to tapentadol (IR and PR) since the first launch in Jul 2008 up to 20 May 2016 was 314 million patient treatment days with an estimated average daily dose for tapentadol IR of 280 mg. In the time period from first launch to 20 May 2016, 7556 spontaneous, medically confirmed cases were received, reporting tapentadol either as the suspect, co-suspect, or suspect-interacting drug. Among the 7556 cases, there were 188 cases with a fatal outcome, 2195 serious nonfatal cases, and 5173 not serious cases. Age was reported in 3687 cases and ranged from 0 years to 100 years. The cases involved 3690 female

patients and 2243 male patients (the sex was not reported or was reported as unknown in 1623 cases). Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, somnolence, vomiting, and headache.

Two important potential risks (serotonin syndrome with concomitant use of serotonergic medications, and suicidal ideation and behavior) were included in the reference safety information and the risk management plan of tapentadol. Currently, neither clinical nor post-authorization safety data provide sufficient evidence to include these potential risks as adverse drug reactions of tapentadol.

Efficacy of tapentadol IR

The efficacy of tapentadol IR was shown in all Phase III trials, encompassing several different pain models, including a visceral pain model, for all doses employed in the trials, i.e., 50 mg, 75 mg, and 100 mg taken every 4 hours to 6 hours. These trials examined subjects with moderate to severe pain following abdominal hysterectomy, bunionectomy, hip replacement (the treatment duration was 3 days for all 3 indications), and in subjects with pain due to end-stage degenerative joint disease (10 days of treatment in an outpatient population).

Tapentadol IR showed a rapid onset of action (ranging from 24 minutes to 46 minutes) that was at least as fast as the onset observed for the active comparators oxycodone IR and morphine IR.

The efficacy of tapentadol IR in the dose range of 50 mg to 100 mg every 4 hours to 6 hours in trials with an active comparator appeared similar to that of oxycodone IR in the dose range of 10 mg to 15 mg every 4 hours to 6 hours in trials of pain following bunionectomy (3 trials), hip replacement (1 trial), and end-stage degenerative joint disease (1 trial). Tapentadol IR 75 mg and morphine IR 20 mg had similar efficacy in the trial of pain following abdominal hysterectomy (1 trial).

Efficacy of tapentadol PR

Efficacy of tapentadol PR (100 mg to 250 mg twice daily) for the treatment of moderate to severe chronic pain was demonstrated in 3 representative pain conditions: 2 trials in chronic painful osteoarthritis, 1 trial in chronic low back pain, and 2 trials in painful diabetic peripheral neuropathy.

7 TRIAL OBJECTIVES

This protocol is part of a pediatric development program that fulfills differing requirements of the EU PDCO and the US FDA. For the EU PDCO, to assess the efficacy and safety of tapentadol in the treatment of acute pain, subjects between 2 years and less than 18 years old will be evaluated. For the US FDA, subjects between birth and less than 17 years old will be evaluated.

The clinical hypothesis of this trial is that tapentadol oral solution reduces the total amount of supplemental opioid analgesic medication used over 12 hours (primary objective for US FDA) or 24 hours (primary objective for EU PDCO) following initiation of IMP, compared to placebo, in children and adolescents 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 is considered as the secondary efficacy objective in the other, for the different age range, as described below.

Two reports will be prepared for the trial. The first report will be prepared after the last subject out of the EU PDCO set. The second report will be prepared after the last subject out of the US FDA set.

Subjects can be treated for up to 72 hours, and efficacy and safety information will also be collected throughout this time period.

Primary objectives:

For EU PDCO: To evaluate the efficacy of tapentadol oral solution, based on the total amount of supplemental opioid analgesic medication used over 24 hours following initiation of IMP, in children and adolescents aged 2 years to less than 18 years who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

For US FDA: To evaluate the efficacy of tapentadol oral solution, based on the total amount of supplemental opioid analgesic medication used over 12 hours following initiation of IMP, in children and adolescents aged from birth to less than 17 years who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

For both EU PDCO and US FDA: To evaluate the safety of tapentadol oral solution in children and adolescents aged 2 years to less than 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.

Secondary objectives:

To assess the efficacy of tapentadol oral solution using multiple subjective and objective measures of the subject's response to treatment (see secondary endpoints, Section 8.1).

8 TRIAL DESIGN

This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution.

Trial duration

Each subject is expected to be in the trial for up to about 42 days (up to 28 days for enrollment, and a treatment and follow-up period of up to 14 days). Dosing of IMP will be for up to 72 hours.

8.1 Definition of endpoints

All endpoints compare the results in the group of subjects treated with tapentadol oral solution to the group treated with placebo. As applicable and appropriate for the individual endpoint, these endpoints will be analyzed in the age ranges of 2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA.

The primary efficacy endpoint for the EU PDCO is considered a secondary efficacy endpoint for the US FDA and vice versa.

The primary efficacy endpoints are:

- EU PDCO: The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 24 hours after first IMP intake.
- US FDA: The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours after first IMP intake.

The secondary efficacy endpoints are:

- The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours (EU PDCO) or within the first 24 hours (US FDA) after first IMP intake.
- The total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP.
- Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged 2 years to less than 18 years old (EU PDCO).
- Changes from baseline in pain intensity over the Treatment Period using age-appropriate pain scales (FLACC scale for ages birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R for ages 6 years to less than 12 years, and VAS for ages 12 years to less than 18 years).
- CGIC by investigator/clinician after completion of double-blind IMP treatment.
- PGIC by subject/parent/legal guardian after completion of double-blind IMP treatment.
- Time to first and time to second NCA/PCA after the first dose of IMP.
- Time from first dose of IMP until IMP treatment discontinuation due to lack of efficacy.

Safety endpoints:

- Percentage of subjects with TEAEs.
- Percentages of subjects who develop abnormal:
  - Vital signs.
  - Laboratory parameters.
  - 12-lead ECG parameters.
- Changes from baseline in vital signs parameters.
- Sedation scores using the University of Michigan Sedation Scale.
- Changes from baseline in safety laboratory parameters.
- Changes from baseline in 12-lead ECG parameters.
- Percentage of subjects discontinuing the trial due to TEAEs and drug-related adverse events.
- Suicidal ideation/behavior in subjects aged 6 years or older using the C-SSRS scores before IMP and at the end of the trial.

8.2 Trial rationale

Although there is a lack of controlled clinical trials investigating the use of opioids for pain relief in the pediatric population, opioids are often used off-label as analgesics in this population. Given this lack of information on the use of strong analgesics in children and adolescents, confirmatory trials have been requested by the EU PDCO and US FDA. The design of this trial reflects the joint requirements of both authorities.

Tapentadol is approved in various regions of the world, such as Australia, Canada, the European Union, and the United States, for the relief of acute pain in adults with an immediate-release formulation, and as an oral solution in the European Union and United States. Tapentadol IR was shown to be efficacious and well-tolerated in adults for the treatment of acute pain. The better gastrointestinal tolerability profile compared to that of oxycodone may make tapentadol a better alternative for use in children.

This trial is designed to assess the efficacy and safety of multiple doses of a tapentadol oral solution in children aged from birth to less than 18 years. The efficacy will be evaluated by assessing the opioid sparing effect in subjects treated with tapentadol compared to subjects treated with placebo.

Based on the known efficacy of tapentadol in adults, it is assumed that this efficacy will also be present in children and adolescents. Thus, it is expected that subjects treated with tapentadol will require less supplemental opioid analgesic medication (given via NCA/PCA) for additional pain control than children in the placebo group who, because they should not experience more pain than they would if not enrolled in a clinical trial, are expected to require more supplemental opioid analgesia. Overall, there should be no difference in the intensity of pain measured between the 2 treatment groups. Hence, the opioid sparing effect (i.e., lower expected use of supplemental opioid analgesic in the tapentadol treatment group than in the placebo-treated group) can be considered a surrogate for more direct measures of analgesia, such as changes in pain intensity. The use of NCA/PCA will allow subjects on placebo to receive analgesia.

8.3 Special agreements with regulatory authorities

This protocol is part of a pediatric development program that fulfills differing requirements of the EU PDCO and the US FDA. The complete clinical program for the use of tapentadol in children and adolescents is designed to characterize the efficacy, tolerability, safety, and pharmacokinetics of tapentadol in different pediatric age groups.

8.4 Discussion of the trial design

This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution.

Choice of population and sites

The age ranges selected for the trial conform to the requirements for development of medicines in children (see Section 8.3). The types of surgery allowed are restricted to those that are expected to produce pain severe enough to require opioid analgesic treatment via NCA/PCA. Examples of surgeries suitable for this trial include, but are not limited to, spinal fusions, cleft palate repair, Nuss procedures, scoliosis repair, nephrectomy, pyeloplasty, and orthopedic procedures such as club foot repair, leg lengthening, open reduction and internal fixation of long bone fractures. Subjects must remain hospitalized until the End of Treatment Visit.

Multiple sites in multiple countries will be required for the recruitment of required subjects in the specified time.

See Section 14.1 for the sample size rationale.

Comparator and use of NCA/PCA

In this double-blind trial, the efficacy of tapentadol oral solution, compared to placebo, will be evaluated based on the amount of supplemental opioid analgesic medication required to achieve adequate pain relief. All subjects will receive supplemental opioid analgesic medication (via NCA/PCA) for additional pain control during the period of administration of IMP. Morphine or hydromorphone (via NCA/PCA) are allowed as supplemental opioid analgesic medication. Both are frequently used in the clinical setting chosen for this trial, i.e., post-operative pain. Hence, due to the use of NCA/PCA as per usual routine, children should not be subjected to more pain than they would otherwise experience in the selected post-operative setting.

This trial will compare the amount of supplemental opioid analgesic medication given by NCA/PCA used in the tapentadol oral solution and placebo groups. The expectation is that the level of use of supplemental opioid analgesic medication will be higher in the placebo group than in the tapentadol oral solution group.

A subject will be discontinued from the trial if their pain is not controlled by the IMP plus NCA/PCA, requiring treatments other than those defined in the protocol.

Blinding

The trial is double-blinded to prevent bias. The EU PDCO set will be locked and unblinded before recruitment of the under 2 year olds in the US FDA set is completed. All subjects in the EU PDCO set (which includes completed subjects aged 2 years or older in the US FDA set) will remain locked after the analysis for the first report. Subjects under 2 years old in the US FDA set will remain blinded, as independent randomization lists are used for subjects aged less than 2 years old.

Dosing

The main metabolic pathway for tapentadol in adults is glucuronidation, which is a system known to be immature for the first 2 years of life (Benedetti et al. 2007, Edginton et al. 2006). However, the clearance of morphine and paracetamol, both of which undergo glucuronidation, is expected to be near the level of adults by the age of 3 years (Anderson and Holford 2009). Thus, it is not expected that there will be major differences in the pharmacokinetic profile of tapentadol in children aged above 3 years compared with adults. Since Phase 1 oxidative routes only make a minor contribution to the overall elimination of tapentadol, ontogeny of the cytochrome P450 family of enzymes is not expected to have any effect on the overall pharmacokinetic profile of tapentadol in adolescents.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. A total of 3% of the drug is excreted in urine as unchanged drug. Renal function has been predicted to reach 90% of adult function between the ages of 1 year and 2 years (Rhodin et al. 2009, Hayton 2002).

Data from a multiple dose trial in healthy adult subjects (HP5503/13) using tapentadol film coated tablets indicated that the pharmacokinetics of tapentadol at steady-state can be predicted from single dose pharmacokinetics. An accumulation factor for AUC in the range of 1.4 to 1.7 was observed which agreed well with the theoretical ratio of approximately 1.7 based on the dosing interval and terminal half-life. This provides evidence for time-independent pharmacokinetics for tapentadol. By analogy to adults, it is expected that the pharmacokinetics of tapentadol in children will be predictable and time independent after both single and multiple dosing.

Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for tapentadol oral solution. The data from 2 dedicated single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R33133PAI2005]) were used for the population pharmacokinetic model and served as a basis for dose selection in the current trial for children aged 2 years to less than 18 years old. The doses for children aged from birth to less than 2 years are predicted from additional pharmacokinetic sampling in children of the same age group.

Simulations were performed to identify tapentadol doses that would produce total exposures (i.e., serum AUC for tapentadol) in pediatric subjects that are similar to those reported in adults. The approved adult therapeutic dose range that is generally associated with efficacy and good tolerability in adults, 50 mg to 100 mg, was used for comparison. These simulations showed that tapentadol doses of 1.25 mg/kg every 4 hours in subjects aged 2 years to less than 18 years old are expected to produce exposures similar to those after administration of 50 mg to 100 mg every 4 hours, given as an immediate-release formulation in adults. The median steady state simulated AUCs after a 50 mg, 75 mg, and 100 mg dose in adults are 217 ng.h/mL, 325 ng.h/mL, and 433 ng.h/mL, respectively. In comparison, the median simulated steady state AUC in subjects aged 2 years to 17 years old receiving 1.25 mg/kg is 306 ng.h/mL.

The population pharmacokinetic model used for the pediatric dose simulations was updated with exposure data obtained from children aged birth to less than 2 years (KF5503/72), the simulations were then redone to determine the appropriate dose for the age group 6 months to less than 2 years. The simulations specified that the dose of 1.25 mg/kg would give similar exposures as that observed in the age group 2 years to less than 18 years. For the younger groups, a lower dose is required.

Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged 6 months to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the investigator's judgment of the effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. For children aged 1 month to less than 6 months, and birth to less than 1 month old, doses of 0.5 mg/kg and 0.1 mg/kg, respectively, are expected to produce similar exposures as that observed in the age group 6 months to less than 18 years.

The maximum single dose for this trial is 100 mg because this is the maximum approved dose for adults.

Pain measurements

To measure pain intensity, 3 pain intensity scales will be used to cover the different age-related abilities to report pain. These assessments are discussed in Section 12.4. In addition, the investigator/delegate or subject will record a pain intensity score prior to each NCA/PCA activation, whenever possible (as requested by the US FDA). Pain intensity data collected for this purpose, i.e., directly before each NCA/PCA activation, will be used only for the purpose of exploratory descriptive analysis.

Blood sampling

The total withdrawn blood volume in this trial is given in Section 11.7, and this will not exceed the maximum safe blood loss that is recommended in a pediatric population (e.g., EMEA ad hoc working party 2008).

Safety

The safety of tapentadol oral solution in the studied population will be assessed by evaluating the safety parameters listed in Section 12.3.

8.5 Benefit/risk analysis

Benefits

Tapentadol has been shown to be effective for the treatment of moderate to severe pain in adults (Section 6.2). Data on the efficacy of tapentadol in children are preliminary and limited. It is not expected that the efficacy of tapentadol in children will deviate notably from that observed in adults.

Risks

Lack of efficacy

Tapentadol may not be as efficacious in children as in adults. In addition, some subjects will receive placebo. The risk of lack of efficacy with tapentadol, or no efficacy with placebo, is mitigated as all subjects in this trial will have access to supplemental opioid analgesic medication using NCA/PCA. Due to the chosen trial design, subjects are not expected to experience undue pain.

Safety - background procedures

All subjects will undergo a surgical procedure. The surgical procedure and anesthesia have inherent risks. However, these surgical procedures and the need for opioid treatment are independent of participation in this trial.

Risks to subjects also include discomfort, inconvenience, and the number and volume of blood samples required by this trial protocol. These risks will be minimized by:

- Limiting the number of venipunctures.
- Possibly obtaining blood samples at the same time as routine blood sampling.
- Permitting the use of analgesic patches, creams, etc., to reduce pain due to venipuncture.
- Use of laboratories with expertise in handling, monitoring, and analyzing biologic samples using small volumes.
- Involving trial site staff experienced with treating children.

Safety - tapentadol

A potential risk to subjects in this trial is the exposure to tapentadol, with possible side effects.

Although there is a tapentadol oral solution available for the adult population, the assessment of risk for the tapentadol oral solution for use in children is mainly based on the much greater experience with the solid oral formulations tapentadol IR and tapentadol PR (and a related tamper resistant formulation). This experience is considered to be applicable to the tapentadol oral solution as well.

The safety profile of tapentadol has been well characterized through a completed clinical program in adults and post-marketing experience is now available. Furthermore, it is not expected that the safety profile of tapentadol will deviate notably from that in adults based on the pharmacodynamic and pharmacokinetic properties of tapentadol already observed in KF5503/68 and KF5503/59 (R33133PAI2005).

Safety - tapentadol multiple dosing

To optimize exposure to tapentadol, a weight-adjusted treatment dose of tapentadol oral solution was chosen (see Section 8.4). Multiple oral dose administration of tapentadol in children is not expected to have an additional inherent risk above that seen in the adult population.

Safety - monitoring

To assure proper safety surveillance, the subjects will be kept in a monitored and well controlled environment as generally recommended when opioid-naïve subjects are treated with strong opioids. Subjects will be monitored for adverse events throughout the trial, and experts in pediatric investigations will be chosen to conduct the trial. Measures will be taken to ensure that all subjects will be closely supervised for anticipated side effects known to occur with opioids or with tapentadol. Subjects will be confined to the trial site until completion of Visit 3 (End of Treatment Visit) assessments.

Safety - selection of sites

The chosen investigative trial sites and the investigators will have experience in the care of patients following pediatric surgery and the trial sites will be properly prepared to conduct a clinical trial. The trial site staff will be trained in the use of the scales and instruments included in this trial to ensure that trial procedures and evaluations are carried out according to GCP, and in accordance with standard medical practice.

Safety - general

This trial has been designed to protect the interests of the subjects, including minimizing the risk to subjects and ensuring compliance with the recommendations made by an EMEA ad hoc working

party (2008) regarding the amount of blood to be drawn as well as the monitoring of children in a controlled environment (post-operative setting that provides intensive monitoring).

Data monitoring committee

A DMC will oversee this trial. For more details about the planned monitoring by the DMC, see Section 5.4.

Conclusion

The efficacy of tapentadol is expected to be similar in children to that seen in adults. The risks associated with the trial, and the risks associated with the administration of tapentadol, are adequately addressed by the mitigation procedures. The overall risk-benefit assessment is considered to be such that the trial can be ethically performed.

9 SUBJECT ENROLLMENT AND TRIAL DISCONTINUATION

9.1 Subject enrollment procedure

Before the informed consent form and, if applicable, the assent form, is signed, the subjects may be screened to identify subjects who could potentially be enrolled into the trial. If a subject is identified to be potentially eligible, the subject, parent(s), or legal guardian(s) will be asked by the investigator to give consent for the subject's enrollment in the trial as described in Section 4.2. If allowed by applicable regulatory requirements, the investigator will keep a subject screening log and a subject identification and enrollment log.

The trial enrollment will be initiated in a staggered approach. Enrollment starts with an older age group until pharmacokinetic data are available in younger age groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years are to be recruited. The recruitment of subjects aged 6 months to less than 2 years is allowed following Amendment 05 and the recruitment of subjects aged from birth to less than 6 months of age is allowed following Amendment 07, based on pharmacokinetic and safety data gathered from a separate trial in the same age groups. Allocation/randomization to IMP will be stratified by 7 age groups and by use of morphine or hydromorphone as supplemental opioid analgesia (Section 10.3).

9.2 Inclusion/exclusion criteria

9.2.1 Inclusion criteria

Subjects are eligible for the trial if all the following apply:

Inclusion criteria	Rationale for criterion
1. Informed consent, and if applicable assent, given according to local regulations.	Legal and ethical requirement.
2. Male or female subject aged from birth (≥37 weeks gestational age) to less than 18 years.	Standardization of the trial population. Safety.
3. A female subject must be pre-menarchal, or surgically incapable of childbearing, or sexually abstinent, or if a female subject is sexually active, then she must be practicing an effective method of birth control (e.g., prescription hormonal contraceptives, intra-uterine devices used according to the product's instruction, double-barrier methods) before trial entry and throughout the trial.	Safety.
4. A female subject must have a negative pregnancy test if aged 12 years or older, or is post-menarchal, or is sexually active.	Safety.
5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after first dose of IMP. Subjects must remain hospitalized until the End of Treatment Visit.	Standardization of the trial population.
6. Subject has 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/randomization to IMP and subject is expected to require this morphine or hydromorphone by NCA/PCA after starting IMP.	Standardization of the trial population.
7. Subject is able to tolerate liquids at the time of allocation/randomization to IMP.	Standardization of the trial population.

Note: Subjects will only receive IMP if documentation is available showing that they comply with these inclusion criteria.

9.2.2 Exclusion criteria

Subjects are not eligible for the trial if any of the following applies:

Exclusion criteria	Rationale for criterion
1. Subject, parent or the legal representative is an employee of the investigator or trial site, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial site, or family member of the employees or the investigator.	Good clinical practice (GCP).
2. Subject has been previously exposed to tapentadol.	Ethics and interference with trial assessments.
3. Subject has received an experimental drug or used an experimental medical device within 28 days before allocation/randomization to IMP, or within a period less than 10 times the drug's half-life, whichever is longer.	Safety.
4. Subject has a history or current condition of any one of the following: • 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 episode(s) of unconsciousness of more than 24 hours.	Safety and interference with trial assessments.
5. Subject has a history or current condition of any one of the following: • Moderate to severe renal or hepatic impairment. • Abnormal pulmonary function or clinically relevant respiratory disease (e.g., acute or severe bronchial asthma, hypercapnia).	Safety and interference with trial assessments.
6. Subject has a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection, febrile seizure, paralytic ileus) that in the opinion of the investigator may affect or compromise subject safety during the trial participation.	Safety.
7. Subject has history of suicidal ideation or behavior.	Safety.
8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). or Subject weight is less than 2500 gm.	Standardization of the trial population.
9. Subject has a clinically relevant history of hypersensitivity, allergy, or contraindication to the supplemental opioid analgesic medication or tapentadol, or the excipients (see the investigator's brochure), or naloxone.	Safety.
10. Subject is not able to understand and comply with the protocol as appropriate for the age of the subject or subject is cognitively impaired in the investigator's judgment such that they cannot comply with the protocol.	Ethics and interference with trial assessments.
11. Subject has a history of alcohol and/or substance abuse in the investigator's judgment based on subject's history and physical examination.	Safety.
12. Subject is taking prohibited concomitant medication. For details, see Section 10.6.4.	Standardization of the trial population and safety.
13. Subject has received a long-acting opioid for the treatment of pain following surgery within 6 hours of allocation/randomization to IMP.	Interference with trial assessments.

Exclusion criteria	Rationale for criterion
14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject aged 6 months to less than 18 years old is excluded if the: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • Total bilirubin is >2-times upper limit of normal (except if the cause is due to Gilbert's syndrome). • Glomerular filtration rate <60 mL/min (calculated according to Schwartz et al. 1984). A subject aged from birth to less than 6 months old is excluded if: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • There is pathological jaundice in the opinion of the investigator. • Glomerular filtration rate (calculated according to Schwartz et al. 1984) is: – <20 mL/min/1.73 m^2 for subjects <1 week post-partum. – <30 mL/min/1.73 m^2 for subjects 1 week to 8 weeks post-partum – <50 mL/min/1.73 m^2 for subjects >8 weeks post-partum to <6 months old.	Safety.
15. Subject has: • Clinically relevant abnormal ECG. • Signs of pre-excitation syndrome. • Brugada's syndrome. • QT or QTc interval >470 ms for children aged 6 years to less than 18 years old. • QT or QTc interval >460 ms for children aged from birth to less than 6 years old.	Safety.
16. 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/randomization to IMP.	Standardization of the trial population.
17. Subject has post-operative clinically unstable systolic and diastolic blood pressure, heart rate, respiratory depression, or clinically unstable upper or lower airway conditions (in the investigator's judgment), or a saturation of peripheral oxygen (SpO2) <92% at the time of randomization (allocation/randomization to IMP).	Safety.
18. Female subject is breastfeeding a child.	Safety.
19. Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP.	Safety.
20. The mother of a newborn subject or the breastfeeding mother of a subject was administered a prohibited medication (see Section 10.6.4).	Standardization of trial population.

Note: Subjects will only receive IMP if documentation is available showing that they do not meet any of these exclusion criteria.

9.3 Trial discontinuation or discontinuation of a subject from investigational medicinal product

9.3.1 Reasons for discontinuation of a subject

The investigator must discontinue subjects from the trial for the compulsory reasons given in Table 1. If the reason is given as optional, then the investigator may decide to stop the participation of the subject in the trial if the benefit/risk ratio is not favorable for the continued participation of the subject. The evaluation of optional reasons for discontinuation must be documented by the investigator in the CRF.

Table 1: Reasons for compulsory and optional discontinuation of subjects from trial participation (discontinuation criteria)

	Discontinuation	
Reason	**Compulsory**	**Optional**
Adverse event		
• There is any relevant deterioration in the health of the subject that could alter the benefit/risk assessment for the subject, including adverse events, safety laboratory parameters, vital signs, or other safety parameters (e.g., ECG).		X
• A confirmed QT or QTc interval >470 ms for children aged 6 years to less than 18 years old.	X	
• A confirmed QT or QTc interval >460 ms for children aged from birth to less than 6 years old.	X	
• Clinically relevant change in liver parameters after dosing if the result is confirmed by 1 additional laboratory assessment (see Section 19.7):		
– Alanine transaminase or aspartate transaminase is >5 times above the upper limit of normal.		
– Alanine transaminase or aspartate transaminase is >3 times above upper limit of normal and total bilirubin >2 times above upper limit of normal or international normalized ratio (INR) >1.5 times above the upper limit of normal (without documented pathological screening value or without pharmacological anticoagulation with vitamin K antagonists).	X	
Death	X	
Lack of efficacy		
• The subject has pain needing other treatments than defined in the protocol to control it.	X	
Pregnancy	X	
Enrollment failure	X	
Protocol deviation		
• The subject is non-compliant with requirements of the trial.		X
• Participation in another investigational trial.	X	
• The subject or mother of a newborn or breastfeeding mother has taken prohibited medication/therapy (see Section 10.6.4).		X
• The subject continues or starts a background infusion of opioid medication after the first dose of IMP.	X	
Lost to follow-up	X	
Technical reasons		
• Technical or logistical grounds (e.g., important technical equipment fails).		X

	Discontinuation	
Reason	**Compulsory**	**Optional**
Withdrawal of informed consent	X	
Trial terminated by the sponsor	X	

Further trial procedures should be performed as scheduled including Visit 3 (End of Treatment Visit) and Visit 4 (Follow-up Visit).

9.3.2 Procedure for the handling of prematurely discontinued subjects

The investigator must inform the sponsor within 24 hours about any discontinuation of a subject. In case of death or any other serious adverse event, the sponsor or the sponsor's authorized delegate must be informed according to the requirements defined in the corresponding protocol section about notification of serious adverse events. Where applicable, the relevant IEC/IRB must be informed with a detailed written explanation. Also, any technical devices issued must be collected.

The following information must be documented for all discontinued subjects:

- Demographic data.
- Reason for discontinuation.
- Status of all new and ongoing adverse events (both serious and non-serious). Any adverse event should be followed up until it reaches a satisfactory resolution, or becomes stable, or can be explained by other causes, or clinical judgment indicates that further evaluation is not warranted.

For treated discontinued subjects, the following should be done in addition:

- Ensure return of partially used and unused medication kits.
- Final drug accountability must be performed.
- All data captured until discontinuation as required at all attended visits, including the recording of concomitant medication taken until the day of discontinuation.

If the subject/parent/legal guardian agrees:

- Perform all tests as defined for Visit 3 (End of Treatment Visit) and Visit 4 (Follow-up Visit).

All efforts should be made to collect data from subjects who are discontinued because of clinically relevant changes in liver parameters so that a valid causality assessment can be made.

9.3.3 Premature termination or suspension of the trial

The relevant IEC/IRB, the regulatory authorities, or the sponsor or the sponsor's authorized delegate alone or in conjunction have the power to make a binding decision to prematurely terminate or suspend the trial at any or all trial sites. In addition, for an individual trial site, this decision can be made by the principal investigator.

The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigator(s), the relevant IEC/IRB, the regulatory authorities, the sponsor/the sponsor's authorized delegate, and the DMC, as applicable).

In addition, the investigator must promptly inform the subjects, ensure appropriate follow-up for any enrolled subjects, and provide the relevant IEC/IRB and the sponsor or the sponsor's authorized delegate, as applicable, with a detailed written explanation of the termination or suspension.

The coordinating investigator has to be informed immediately if the trial is prematurely terminated or suspended.

9.3.3.1 Criteria to terminate or suspend the whole trial

A suspension or discontinuation of this trial will be considered based on clinically relevant changes of safety laboratory parameters, 12-lead ECG parameters, or serious adverse events.

A risk benefit committee organized by the sponsor will convene to decide on further action, which could include immediate stopping of the trial.

The DMC may recommend stopping the trial, but the final decision will rest with the sponsor and collaborator.

The trial may be restarted following a thorough evaluation by the sponsor and collaborator.

10 TREATMENTS

10.1 Investigational medicinal product

10.1.1 Identity and composition – tapentadol oral solution (test)

Name:	Tapentadol oral solution
Substance code:	CG5503/R331333
Substance name:	Tapentadol hydrochloride
Active component(s):	Tapentadol
Dose (strength):	Tapentadol 4 mg/mL and 20 mg/mL oral solutions
Manufacturer:	Grünenthal GmbH, Aachen, Germany.

For further information about the identity and composition of tapentadol oral solution, see the current investigator's brochure and the clinical supply specification.

10.1.2 Identity and composition – placebo (comparator)

Name:	Placebo
Substance name:	Placebo
Active component(s):	Not applicable
Dose (strength):	Not applicable
Manufacturer:	Grünenthal GmbH, Aachen, Germany.

The placebo formulation contains the same excipients as tapentadol oral solution 4 mg/mL (i.e., citric acid monohydrate, sucralose, raspberry flavor, sodium benzoate, and purified water).

10.1.3 Preparation

The IMP will be supplied as a liquid in 100 mL bottles intended for multiple use per subject. A dosing syringe for oral use (either a syringe supplied by the sponsor or a suitable sponsor-approved alternative, as defined in Section 10.2.1 and in the Investigational Product Preparation Instructions supplied by the sponsor) must be used for IMP administration.

10.1.4 Packaging and labeling

For detailed information about the packaging and labeling, see the clinical supply specification.

The IMP will be labeled according to local requirements in local languages with booklet labels or single panel labels if applicable.

10.1.5 Delivery, storage and disposal

The sponsor or designee is responsible for supplying the investigator with IMP. These will not be delivered until all required documentation (IEC/IRB approval, authority approval, signed contract and protocol, curriculum vitae) is present at the sponsor or designee.

Further storage conditions will be specified on the labeling of the IMPs.

For countries in which tapentadol has been classified as a controlled or scheduled substance, all local requirements for the handling, storage, and distribution of opioid analgesics will be followed.

Controls will be implemented at the trial site to ensure documented compliance with these requirements.

10.1.6 Special requirements

Due to the scheduling status of tapentadol, the investigator may need country-specific approval for handling tapentadol in accordance with the applicable regulations for narcotics.

10.2 Administration of trial treatments

10.2.1 Dose

The doses to be administered are given in Table 2.

The maximum individual dose of tapentadol oral solution (or equivalent for placebo) is 100 mg, i.e., subjects weighing 80 kg or more will receive a maximum dose of 100 mg (5 mL of the 20 mg/mL solution).

The “to be used” oral solution stock (4 mg/mL or 20 mg/mL) will depend on the subject’s body weight. The subject’s weight will be recorded before the first dose of IMP. The weight should be measured after surgery if the surgery notably changes the weight of the child.

Dosing charts will be provided by the sponsor.

Table 2: Determination of tapentadol dose and oral solution concentration

Age of subject	Dose for the first 24 hours	Dose after the first 24 hours	Body weight	Tapentadol oral solution or placebo
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
Birth to <30 days old	0.1 mg/kg	0.1 mg/kg or 0.075 mg/kg	-	4 mg/mL

The IMP does not require preparation unless very small volumes would need to be administered, in which case the IMP may be suitably diluted. This may be necessary, for example, for subjects less than 6 months old. The investigators will be supplied with instruction sheets for the preparation of the IMP.

Volumes of 1 mL or less will be given using a 1 mL syringe with 0.05 mL graduations. Volumes of more than 1 mL will be given using a 5 mL syringe with 0.1 mL graduations.

10.2.2 Total dosing time and dosing interval

The IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If the subject is sleeping at the time of the scheduled dose, they must be woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP must be taken as soon as possible after the subject is awake.

The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level.

The dose of IMP may be reduced after 24 hours if there is a reduced need for analgesia according to the investigator's judgment, as follows:

- Age 6 months or more: 1.0 mg/kg.
- Age 30 days to less than 6 months: 0.3 mg/kg.
- Age birth to less than 30 days old: 0.075 mg/kg.

Dosing with IMP will be stopped if:

- A switch to exclusively oral opioid analgesic medication is indicated according to the local standard of care.
- Opioid analgesic medication is no longer needed.
- IMP has been administered for 72 hours.

10.2.3 Administration

The route of IMP administration is oral. Subjects will be encouraged to take a small drink (approximately 25 mL of e.g., water or juice) after dosing to help ensure all medication is completely swallowed.

The IMP may be administered through, for example, a nasogastric tube (according to standard of care). The use of a nasogastric tube will be documented in the CRF. An interaction study of tapentadol with polyurethane, silicone, and polyvinyl chloride (PVC) tubes showed no interactions

or degradation of tapentadol, so the compound can be considered to be compatible with this method of dosing.

The administration must not be repeated if the subject vomits or regurgitates a complete dose. If only part of the dose is swallowed before vomiting or regurgitation, the remainder of the dose may be administered at the investigator's discretion. Vomiting and/or regurgitation must be recorded as an adverse event.

10.3 Method of assigning subjects to treatment groups (allocation/randomization)

An IVRS/IWRS will be used to assign a subject number at the Enrollment Visit (Visit 1) and to support the drug supply chain management processes of distribution and return.

Subjects who comply with all inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to 1 of the 2 treatment arms in a 2:1 tapentadol oral solution to placebo ratio.

Computer-generated randomization will be implemented by using permuted blocks of treatments and stratified by predefined age groups (birth to <30 days, 30 days to <6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years, 17 years to <18 years) and supplemental opioid used (morphine versus hydromorphone).

Randomization numbers will be allocated in ascending order within each age group, and by ascending age group.

The investigators must log into the system using their own user identification number and a password. The investigator will enter the subject's number and other information required by the system to obtain the medication number of the IMP package for the subject.

10.4 Blinding and unblinding

10.4.1 Methods of blinding

Randomization and blinding will be done in accordance with the sponsor's standard operating procedures (SOPs).

There are 4 randomization lists for this trial; 1 randomization list for each of the 3 youngest age groups (birth to <30 days, 30 days to <6 months, 6 months to <2 years), each stratified by supplemental opioid used (morphine versus hydromorphone), and 1 randomization list for the older age groups stratified by age group (2 years to <6 years, 6 years to <12 years, 12 years to <17 years, 17 years to <18 years) and supplemental opioid use. Unblinding can be performed for 1 or more of these lists individually.

10.4.2 Methods of unblinding

The investigator, the responsible department of the sponsor, the responsible drug safety department, and contract research organization will receive appropriate methods for unblinding of single cases, i.e., via the IVRS/IWRS.

Personnel in the sponsor's departments of clinical trials supply will be unblinded during the trial according to the sponsor's SOPs for randomization and unblinding during the trial. Once the EU PDCO set has completed recruitment and data for these subjects is locked, unblinding will be

performed for those subjects aged 2 years and older. The additional age groups under 2 years old will be unblinded at the end of the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial.

Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after data is locked. Unblinding will be initiated by the sponsor's department of biostatistics according to the sponsor's SOPs for randomization and unblinding.

Data will be unblinded for the DMC (Section 5.4).

10.4.3 Identification of investigational medicinal products

The blinding code may be broken if it is necessary and in that subject's interest in order to identify the IMPs given, e.g., if knowing the identification of the treatment arm would lead to the investigator treating the subject differently.

In addition, within drug safety, the blinding code may be broken for regulatory reporting, medico-scientific assessment of adverse events, or on request of the qualified person for pharmacovigilance.

For every subject whose blinding code was broken, the following information must be documented on an "unblinding an individual subject form":

- The reason for, the date, and time of unblinding.
- The person performing the unblinding.
- The person(s) informed of the treatment allocation/randomization must be identified.

In order to maintain the double-blind nature of the trial, the allocation/randomization of IMPs for the subject must not be communicated further unless required for the surveillance of the subject or if necessary for urgent risk to benefit re-evaluation and/or measures for urgent risk minimization.

If required by local regulations, it may be that the IEC/IRB or the coordinating investigator needs to be informed.

10.5 Other medication

10.5.1 Supplemental opioid analgesic medication

Intravenous morphine or hydromorphone (supplemental opioid analgesic medication) will be administered by a controlled infusion pump using NCA/PCA for additional pain control during the period of IMP administration.

The placement or replacement of the catheter and the settings for the NCA/PCA system will be predefined by the investigator and medically qualified staff according to the site's standard of care. The settings include the doses of morphine/hydromorphone administered and lock-out times, which may be overridden as required. The device will be triggered by the subject, nurse, or treating physician. It is important for the sites to monitor subjects to ensure that they are using the device properly.

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

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

No background infusion is allowed after the first dose of IMP.

After the first dose of IMP (see Table 2), NCA/PCA will be 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.

The supplemental opioid analgesic medication must be purchased by the trial site unless otherwise agreed upon with the sponsor.

If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously.

In exceptional cases, if a subject has unbearable pain despite using NCA/PCA, an additional bolus (defined as a clinician bolus) of morphine or hydromorphone may be administered. The clinician bolus can be given either using the NCA/PCA pump system or by an intravenous bolus injection.

10.6 Allowed and prohibited prior/concomitant medications

10.6.1 Prior medications

Restrictions apply to prior medication use (see Section 10.6.3 and Section 10.6.4).

10.6.2 Concomitant medications

Subjects will be instructed to only use allowed concomitant medications during the trial.

If, in the interests of the subject's safety, the administration of prohibited concomitant medications is required, the sponsor should be informed in advance (or promptly after the instance).

For information about potential interactions with concomitant medications, see the current investigator's brochure.

Medication according to standard medical knowledge should be initiated in emergency situations.

10.6.3 Allowed prior and concomitant medications

Unless explicitly prohibited, all prior and concomitant medications are allowed.

Benzodiazepines may be used to treat muscle spasms or anxiety, consistent with local standard of care. They should be used with caution as they may potentiate central nervous system depression that may occur with tapentadol or other opioids.

Medications for the treatment of adverse events are allowed according to the investigator's judgment and post-operative standard of care. For example, clinically relevant respiratory depression may be treated with naloxone, and nausea/vomiting can be treated with antiemetics, which may also be given prophylactically according to the standard of care.

If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously.

In exceptional cases, if a subject has unbearable pain despite using NCA/PCA, an additional bolus (defined as a clinician bolus) of morphine or hydromorphone may be administered. The clinician bolus can be given either using the NCA/PCA pump system or by an intravenous bolus injection.

The opioid given as a clinician bolus or if the NCA/PCA intravenous line fails must be the same as that used in the NCA/PCA pump system.

The trade name of the medication, dose, and time will be recorded in the CRF.

10.6.4 Prohibited prior and concomitant medications/therapy

Prohibited medication from 14 days before allocation/randomization to IMP until 24 hours after the last administration of IMP

- Monoamine oxidase inhibitors.
- Strong enzyme inducing drugs (e.g., rifampicin, phenobarbital, St John's Wort [hypericum perforatum]).
- Neuroleptics, anticonvulsants (except for gabapentin used in association with surgery), antiparkinsonian drugs, and all serotonergic drugs including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, triptans, and St. John's Wort (hypericum perforatum).
- Methadone.

Prohibited medication from 6 hours before allocation/randomization to IMP until 4 hours after the last administration of IMP

- Long-acting opioids.
- Medication used for sedation (as noted above, benzodiazepines may be used to treat muscle spasms or anxiety).
- Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia.

Prohibited medication/therapy from time of allocation/randomization to IMP until 4 hours after the last administration of IMP

- Opioids (other than protocol defined morphine, hydromorphone, or IMP).
- Continuous positive airway pressure or mechanical ventilation.

Restrictions for the mother of a newborn or breastfeeding mother

- For monoamine oxidase inhibitors, neuroleptics, anticonvulsants, antiparkinsonian drugs, methadone, and all serotonergic drugs including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, and triptans:
  - Prepartum intake by a mother of a newborn subject is prohibited in the 14 days prior to the subject's allocation/randomization to IMP.
  - The intake of these medications by the breastfeeding mother of a subject is prohibited from 14 days prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.
- For opioid medication (including tapentadol formulations):
  - The intake of opioid medication (including tapentadol formulations) and medication used for sedation by the breastfeeding mother of a subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.

- The intake of opioid medication (including tapentadol formulations) and medication used for sedation taken prepartum by the mother of a newborn subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP.

10.7 Documentation of drug accountability

The investigator is obliged to keep documentation of the receipt, inventory, use, and destruction or return of unused, used, or partially used packages of trial treatment(s). The documentation must include trial treatment name, dates, quantities, subject numbers, batch/serial numbers or other identification numbers, expiration dates, and the means to identify the subject to whom it was given.

In addition to records in the documentation, e.g., source documents and CRF, the investigator must maintain documentation of drug accountability, i.e., separate records of the subject's numbers, date of dispensing, and amount of trial treatment(s) dispensed to each subject and returned by each subject, and the return date. The drug accountability log contains the source data for drug accountability.

The bottles of oral solution (tapentadol or placebo) will be weighed to determine the amount used. The instructions for weighing will be given separately. The weighing scales used must be appropriately calibrated and verified. Instructions for drug accountability will be given in the drug accountability log.

Before the unused and residual IMPs and other medications supplied to the investigator are returned or destroyed, the investigator must allow the sponsor's representative to perform drug reconciliation. The entries in the documentation will be compared with the returned and residual trial treatment(s), and the administration/intake as documented in the CRF, with clarification of any discrepancies or inconsistencies.

11 TRIAL PROCEDURES

See Section 1.1 for a flow diagram summary of the trial and Section 1.2 for a tabular schedule of events.

Unless otherwise specified, all recordings are in the CRF.

11.1 Course of the trial

The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may 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).

11.1.1 Enrollment Period (Visit 1)

During this period, the general suitability of the subjects for the trial will be assessed. Subjects will be considered to be trial participants when enrolled.

The duration of this period will be as per standard of care for the concerned surgery, but the start of enrollment is not to exceed 28 days before allocation/randomization to IMP.

The subject will undergo a scheduled surgery. This surgery is not part of the trial, but would be performed as per standard of care. Subjects may start enrollment before or after surgery.

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

The Enrollment Period will be completed when the subject is allocated to IMP using IVRS/IWRS. The following procedures will be performed during this period:

- Obtain informed consent/assent (see Section 4.2). Subjects from whom assent is requested after surgery will be asked to give assent when they are properly stable and able to give assent according to the investigator's judgment.
- Record date of signing the informed consent/assent form, sex, race/ethnicity, and height. The data may be extracted from the hospital charts if already available according to the standard of care.
- Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight). The BMI will be calculated automatically.
- Record clinically relevant medical and surgical history. The data may be extracted from the hospital charts if already available according to the standard of care.
- Record details about the surgery (the date of surgery, the indication, the type of surgical procedure, the start time and completion time of surgery). Surgery should be performed according to the usual standard of care at the site.
- Perform a physical examination. The data may be extracted from the hospital charts if already available according to the standard of care; in this case, the physical examination need not be repeated for the trial.
- Record prior medication and therapies, as appropriate (excluding anesthetics and medication used during the surgery). This includes the recording of prohibited medication used by breastfeeding mothers and prohibited prior medication used by mothers of a newborn subject.
- Complete the C-SSRS "children's baseline" questionnaire if the subject is aged 6 years or older. The C-SSRS will be explained and demonstrated at the time of the informed consent procedure. The administration of the C-SSRS must be performed after surgery. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. Referrals to mental health professionals will be made as determined by the investigator. Record the initials of the interviewer.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) after surgery directly before allocation/randomization to IMP.
- Record oxygen saturation after surgery directly before allocation/randomization to IMP.
- Record a 12-lead ECG. This must be performed after surgery.
- Take blood for both local and central (children aged 2 years or older) or local (children younger than 2 years old) safety laboratory investigations when the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.

- Perform a pregnancy test in female subjects if aged 12 years or older, or post-menarchal, or sexually active, within 48 hours prior to allocation/randomization to IMP.
- Assess and record adverse events occurring after signing the informed consent/assent form.
- Evaluate suitability for participation according to the inclusion/exclusion criteria.
- Dispense subject trial card.

When the subject is able to tolerate liquids, meets the inclusion criteria, and does not meet any exclusion criterion, the subject will be allocated/randomized to IMP (tapentadol oral solution or placebo) using IVRS/IWRS.

- Record age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months [i.e., 60 days] to less than 2 years, and days for subjects aged less than 2 months [i.e., less than 60 days] – the day of birth is counted as day 1).

11.1.2 Treatment and Evaluation Period (Visit 2 and Visit 3)

11.1.2.1 Visit 2

Visit 2 starts once the subject has been allocated to IMP.

Before first dose of investigational medicinal product

- Record the following details about opioid analgesic medication given by NCA/PCA and given by background infusion (if any) after surgery. The recording is for a maximum of 24 hours before the first IMP dose:
  - The trade names of the opioid analgesic medications used.
  - The routes of administration.
  - The times of each administration for NCA/PCA.
  - The doses of each administration for NCA/PCA.
  - The doses of the background infusion.
  - The times of starting and stopping the background infusion.
  - The lockout time.
- Record the trade name, date, time, dose, dose unit, formulation, and route of administration of opioid and non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events for analgesic medication (Section 1.2).
- Record intake of other concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed), excluding anesthetics and medication used during the surgery. This includes the recording of prohibited medication used by breastfeeding mothers.
- Record the following directly before (i.e., within 10 minutes) administration of IMP:
  - Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
  - Sedation score (see Section 12.3.10).
  - Oxygen saturation.
  - Pain intensity (see Section 12.2.5).
- Assess and record adverse events (adverse events are to be recorded and assessed at the time when they occur).

- Assess discontinuation criteria (Table 1, Section 9.3.1).
- Start or continue continuous monitoring of heart rate and respiratory rate. This is to be continued for 24 hours after the first administration of IMP.
  - Record clinical relevant values as adverse events.
- Start or continue continuous measurement of oxygen saturation by pulse oximetry. This is to be continued until 4 hours after the last administration of IMP.
  - Record values below 92% for at least 60 seconds (excluding technical failures or artifacts).

Administration of first dose of investigational medicinal product (Day 1)

The subject will only receive IMP if the SpO_2 does not drop below 92% for a period of ≥60 seconds in the 10 minutes before IMP administration.

The first dose of IMP is given when IMP is available on the ward and the investigator determines it is medically appropriate for the subject to receive the IMP. The time between allocation to IMP and first administration should be kept as short as possible.

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

The IMP will be administered as an oral solution as described in Section 10.2.

- Record dose and time of administration of IMP.

Dosing with IMP will be stopped if:

- A switch to exclusively oral opioid analgesic medication is indicated according to the local standard of care.
- Opioid analgesic medication is no longer needed.
- IMP has been administered for 72 hours.

After the first dose of investigational medicinal product

After the first dose of IMP, NCA/PCA will be 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. Subjects must be carefully observed, especially during the first hour after the initiation of IMP.

- Administer supplemental opioid analgesic medication as required (by NCA/PCA, see Section 10.5.1). Record the following at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2):
  - The trade names of the supplemental opioid analgesic medications used.
  - The times of each administration.
  - The doses of each administration.
  - The lockout time.
  - The trade name of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails, or a clinician bolus is given.

- Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.
- Record pain intensity within 30 minutes to 60 minutes after the first dose of IMP only (see Section 12.2.5). Subjects do not need to be woken for this assessment.
- Record the palatability and acceptability of the oral solution after the first dose of IMP in subjects aged 2 years to less than 18 years old.
- Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). This includes the recording of prohibited medication used by breastfeeding mothers.
- Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events (Section 1.2). The same details of any additional opioid medication used inadvertently must be collected.
- Assess and record adverse events (adverse events are to be recorded and assessed at the time when they occur).

Before subsequent doses of investigational medicinal product

The subject will only receive IMP if the SpO_2 does not drop below 92% for a period of ≥60 seconds in the 10 minutes before IMP administration.

The following procedures will be performed before the administration of each subsequent dose of IMP:

- Record the following directly before (i.e., within 10 minutes) administration of IMP:
  - Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
  - Sedation score (see Section 12.3.10).
  - Oxygen saturation.
  - Pain intensity (see Section 12.2.5).
- Record the following details about the use of supplemental opioid analgesic medication (by NCA/PCA) at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2):
  - The trade names of the supplemental opioid analgesic medication used.
  - The times of each administration.
  - The doses of each administration.
  - The lockout time.
  - The trade names of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails, or a clinician bolus is given.
- Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.

- Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). This includes the recording of prohibited medication used by breastfeeding mothers.
- Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events (Section 1.2). The same details of any additional opioid medication used inadvertently must be collected.
- Assess and record adverse events (adverse events are to be recorded and assessed at the time when they occur).
- Assess discontinuation criteria (Table 1, Section 9.3.1).

11.1.2.2 Administration of investigational medicinal product

- Record dose and time of administration of each dose of IMP.

11.1.2.3 Visit 3 (End of Treatment Visit)

Visit 3 will be performed between 4 hours and 24 hours after the last administration of IMP, or if the subject is prematurely discontinued from the trial. The visit must be performed before discharge from hospital.

The following procedures will be performed:

- Perform a physical examination (record that a full examination has been performed and only record changes to Visit 1).
- Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events (Section 1.2). The same details of any additional opioid medication used inadvertently must be collected.
- Record intake of other concomitant medication and therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). This includes the recording of prohibited medication used by breastfeeding mothers.
- Complete the C-SSRS questionnaire “children’s since last visit” if the subject is aged 6 years or older. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. Record the initials of the interviewer.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Record oxygen saturation.
- Record a 12-lead ECG.
- Take blood for safety laboratory (to be sent to the central laboratory for children aged 2 years or older or local laboratory for children younger than 2 years old).
- Record pain intensity (see Section 12.2.5). Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.

- Record the palatability and acceptability of the oral solution in subjects aged 2 years to less than 18 years old.
- Record global impression of change by investigator/clinician (CGIC) and subject (PGIC) if capable of completing the questionnaire (or parent/legal guardian).
- Perform and document drug accountability.
- Assess and record adverse events (adverse events are to be recorded and assessed at the time when they occur).
- Assess discontinuation criteria (Table 1, Section 9.3.1).

The subjects will be discharged from the site according to site routine.

11.1.3 Follow-up Visit (Visit 4; Day 10 to Day 14)

This visit may be performed by telephone.

The following procedures will be performed at the Follow-up Visit:

- Record intake of concomitant medication and therapies as appropriate.
- Assess and record adverse events.

11.2 Examination hierarchy and time windows

Non-invasive procedures (including completion of questionnaires) should generally be performed first. Blood samples for safety laboratory should be taken after all non-invasive procedures have been completed. The order that procedures are performed may deviate due to local circumstances and a change in the order does not constitute, per se, a protocol deviation.

Time windows for procedures are given, where applicable, in the schedule of events (Section 1.2).

11.3 Conditions during the trial

11.3.1 Medical care

For any adverse events, a causal or symptomatic treatment according to standard medical practice will be performed if deemed necessary by the investigator. The medical care given to, and medical decisions made on behalf of, the subjects will always be the responsibility of a qualified physician.

See the guidance for the investigator given in the investigator's brochure for precautions and emergencies, e.g., for the management of overdose, relevant for this trial.

11.3.2 General restrictions

Subjects must be willing to adhere to the following conditions and restrictions during the course of the trial to be eligible for participation:

- Subjects must remain at the trial site for at least 4 hours after the last administration of IMP.
- Subjects may not drink beverages containing alcohol until the Visit 3 (End of Treatment Visit) has been completed.

11.3.3 Counseling of female subjects of childbearing potential

All female subjects who are capable of childbearing, who are post-menarchal or sexually active, should be counseled on the need to practice medically acceptable methods of birth control during the trial and on the importance of avoiding pregnancy.

Sexually active girls must use one of the following acceptable methods of birth control:

- Hormonal contraceptives.
- Intra-uterine devices used according to the product's instruction.
- Double-barrier methods (condom and occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository). A female condom and a male condom should not be used together as friction between the two can result in either product failing.

All female subjects of childbearing potential will be counseled to contact the investigator or site staff immediately if pregnancy is suspected within 30 days after the last dose of IMP.

11.4 Subject trial cards

Subjects who are enrolled in the trial will receive a "subject trial card". The trial card will list the following information:

- Name of the subject and the name(s) of the parent(s) or legal guardian and a statement that the subject is currently participating in a clinical trial.
- Trial code.
- Dates of the trial periods.
- Name of investigator.
- Contact (telephone) number at the trial site.

11.5 Provisions of any additional care of subject after trial termination

After completion of the End of Treatment Visit (Visit 3), subjects will be treated by their physicians according to the specific standard treatment at the site concerned.

11.6 Handling of low enrollment

Sites with a low recruitment rate and/or which persistently deviate from the protocol may be required by the sponsor/coordinating investigator/contract research organization to stop further recruitment at once or to cease participation in the trial. A low recruitment rate is defined as no subject allocated to IMP within 8 weeks of IMP availability at the site.

11.7 Overview of blood sampling in this trial

Blood sampling

Blood samples may be collected using a central venous line or an indwelling cannula (e.g., with a Mandrin) inserted either during surgery or shortly thereafter or by venipuncture according to the standard of care at the site.

Repeat or unscheduled samples may be taken for safety reasons. For details of steps taken to reduce the risk to the subjects regarding blood sampling, please see Section 8.5.

The approximate amount of blood drawn for this trial is given in Table 3. Local laboratories can use microsampling, especially for subjects aged <2 years old, so these blood volumes may be lower.

Table 3: Approximate volume of blood to be collected from each subject

Assessment	Approximate blood volume per sample	Number of samples		Approximate total blood volume per test [a]	
		2 years to <18 years	<2 years [b]	2 years to <18 years	<2 years
Clinical chemistry	2 mL	2 for central, 1 for local	2 for local	6 mL	4 mL
Hematology	2 mL	2 for central, 1 for local	2 for local	6 mL	4 mL
Total				12 mL	8 mL

The volume of blood taken may be individually variable due to flushing, resampling etc.

a) Calculated as number of samples multiplied by amount of blood per sample.

b) For subjects with a low body weight, blood sampling for clinical chemistry and hematology may be limited to a subset of clinical chemistry evaluations only to keep the total blood volume drawn low.

The volume of blood drawn from subjects who participate in the trial will not exceed the recommended limits (Section 8.4).

For subjects aged 2 years and older, the total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even if additional blood is drawn for a pharmacokinetic analysis if a serious adverse event occurs) (Table 3).

For subjects aged less than 2 years old, blood sampling for clinical chemistry and hematology should be performed such that blood volumes taken do not exceed 0.8 mL/kg body weight for each sampling time point, and 2.4 mL/kg in total (EMEA ad hoc working party 2008).

For subjects less than 6 months old with a low body weight, such that the drawing of sufficient blood sample volumes for both clinical chemistry and hematology are precluded, the tests may be limited to a subset of clinical chemistry evaluations only (the tests to be performed are alanine transaminase and aspartate transaminase, alkaline phosphatase, and creatinine [with calculation of the glomerular filtration rate]). Local site-specific guidelines must also be adhered to. Other chemistry and hematology values from samples taken for the standard of care may be used to supplement the safety laboratory profile.

12 DATA COLLECTION

The following data collected for this trial will be recorded/documented in the CRF.

12.1 Collection of subject characteristics data

12.1.1 Demographic data

Demographic data to be collected and recorded for this trial includes date of signing the informed consent/assent form, sex, age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months [i.e., 60 days] to less than 2 years, and days for subjects aged less than 2 months [i.e., less than 60 days] – the day of birth is counted as day 1),

race/ethnicity, height, and weight. The BMI will be calculated automatically by the IVRS/IWRS or electronic CRF.

12.1.2 Prior and concomitant medications

All medication requiring prescriptions (including oral contraceptives) and/or over-the-counter medication used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded, excluding anesthetics and medication used during the surgery.

All additions to or changes after enrollment must be recorded. Any change in dosage (analgesics only), regimen, or route, must be recorded as a new entry.

Trade names should be given in preference to generic names when recording medication. The generic name may be used if the trade name is not available.

Prohibited medication used by the mother of a newborn or breastfeeding mother will be recorded.

12.1.2.1 Opioid analgesic medication given by NCA/PCA and background infusion

The following details about opioid analgesic medication given by NCA/PCA and by background infusion (if any) after surgery will be recorded. The recording is from up to 24 hours before first dose of IMP until the End of Treatment Visit:

- The trade names of the opioid analgesic medications used.
- The routes of administration.
- The times of each administration for NCA/PCA.
- The doses of each administration for NCA/PCA.
- The doses of the background infusion.
- The times of starting and stopping the background infusion.
- The lockout time.

12.1.2.2 Detailed information for other analgesic (opioid and non-opioid) medication

The trade name, date, time, dose, dose unit, formulation, and route of administration of analgesic medication will be recorded, irrespective of the indication. The detailed recording of these medications is limited to after surgery (starting up to 24 hours before first IMP dose) until the End of Treatment Visit, as indicated in the schedule of events (see Section 1.2).

12.1.3 Prior and concomitant therapies

All therapies used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded.

12.1.4 Medical and surgical history

The clinically relevant medical and surgical history of the subject per investigator's opinion is required to be documented.

12.1.5 Surgery

The following details about the surgical procedure will be recorded: date of surgery, the indication, type of surgical procedure, and start time and completion time of surgery.

12.1.6 Other data

The times of starting and stopping the continuous monitoring of pulse oximetry, respiration rate, and heart rate will be recorded. If the IMP is given via a nasogastric tube, this will be documented.

Pain intensity scores (see Section 12.2.5 for a description of the pain intensity scales) will be collected before each NCA/PCA activation, whenever possible.

12.2 Collection of efficacy data

During the trial, the evaluations described in Section 12.2.1 to Section 12.2.5 will be performed at the time points indicated in the schedule of events (see Section 1.2). Where appropriate, information related to the rationale for these evaluations is in Section 12.4.

12.2.1 Amount of supplemental opioid used

The details of the supplemental opioid analgesic medication used (see Section 12.1.2.1) will be recorded at times consistent with the memory of the NCA/PCA pump from the first dose of IMP, as indicated in the schedule of events (see Section 1.2).

Details of intravenous morphine or hydromorphone used if the NCA/PCA line fails, or a clinician bolus is given will also be recorded.

12.2.2 Amount of non-opioid analgesic medication used

Detail of the administration of non-opioid analgesic medication will be recorded as given in Section 12.1.2.2, irrespective of the indication.

12.2.3 Global impression of change

12.2.3.1 Patient Global (overall) Impression of Change

The PGIC will be assessed at the End of Treatment Visit (Visit 3) as specified in Section 1.2 if the subject is capable of completing the questionnaire (the parent/legal guardian may complete the questionnaire on behalf of the subject – it will be documented if help was given) (Section 1.2).

Subjects verbally rate their impression of overall status with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) (Section 19.8).

12.2.3.2 Clinical Global Impression of Change

The CGIC will be assessed at the End of Treatment Visit (Visit 3) as specified in Section 1.2.

The investigators will rate the subject's global improvement and satisfaction with the treatment on a 7-point scale that ranges from "very much improved" to "very much worse" with "no change" as the mid-point (Section 19.8). The CGIC (Schneider et al. 1997) was chosen as a complementary assessment of analgesic efficacy.

Inter-rater reliability will be assessed for the CGIC as part of site training.

12.2.4 Palatability and acceptability of IMP

Responses for palatability and acceptability will be evaluated in subjects aged 2 years to less than 18 years old on 5-point hedonic scales in combination with a verbal rating and documented (Guinard 2001), unless the subject is administered the IMP by a nasogastric tube.

Palatability will be assessed by asking the following question “How does the medication taste?”. The verbal rating is from really good, good, a bit good/a bit bad, bad, and really bad.

Acceptability will be assessed by asking the following question “Swallowing the medication is ...”. The verbal rating is really easy, easy, a bit easy/a bit difficult, difficult, and really difficult (Section 19.6).

12.2.5 Pain intensity

The investigator or deputy will record the results of the pain measurements in the subject’s medical file before recording the data.

Documentation of the pain scales actually used will be maintained.

Subjects will continue using the same pain scale that they started with even if they change age group during the trial. The pain scales will be used in the following age groups:

- FLACC – birth to less than 6 years or in older children who are not able to report their pain using the other scales.
- FPS-R – 6 years to less than 12 years old.
- VAS – 12 years to less than 18 years old.

The sites will be supplied with a manual on how to implement the pain scales.

12.2.5.1 Face, Legs, Activity, Cry, and Consolability scale

The FLACC scale is a measurement used to assess pain in this trial for children aged from birth to less than 6 years, or in subjects unable to communicate their pain (Merkel et al. 1997). The scale has a range of 0 to 10, with 0 representing no pain, calculated from 5 criteria (relating to the face, legs, activity, crying, and consolability) that are each assigned a score of 0, 1 or 2 (see example in Section 19.2). The investigator will record the results of these measurements in the subject’s questionnaire before recording the data in the CRF. The total score will not be captured by the CRF but will be calculated during the analysis of the trial. Inter-rater reliability will be evaluated for the FLACC as part of site training.

12.2.5.2 Faces Pain Scale - revised

The FPS-R will be recorded in children aged 6 years (if possible) to less than 12 years (see example in Section 19.3). The FPS-R is a validated self-reported 6-point scale with 0 representing no pain and 10 representing very much pain. Facial representations are used to indicate how much the pain hurts. The investigator or designee will record the results of these measurements in the subject’s medical file before recording the data. It will be documented if help was given by a parent/legal guardian.

12.2.5.3 Visual analog scale

For children aged 12 years to less than 18 years, the pain intensity will be assessed by use of a VAS (see example in Section 19.4). The subject will be asked to draw a single line to indicate the current level of pain intensity at the time of assessment on a 100 mm long VAS. The scoring is the distance in millimeters across the scale. The investigator will record the results of these measurements in the subject’s medical file before recording the data. It will be documented if help was given by a parent/legal guardian.

12.3 Collection of safety data

The following safety data will be collected:

- Adverse events.
- Safety laboratory.
- Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.
- 12-lead ECG.
- Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Reporting of clinically relevant values arising from continuous monitoring of respiratory rate and heart rate as adverse events.
- Oxygen saturation (by pulse oximetry), including values below 92% for at least 60 seconds.
- Physical examination.
- C-SSRS score in subjects aged 6 years or older.
- University of Michigan Sedation Scale score.

Clinically relevant values (investigator's judgment) will be recorded as adverse events.

12.3.1 Adverse events

All adverse events will be documented from the time of enrollment (i.e., the time the informed consent form is signed) up to the time of the last protocol scheduled contact has occurred, i.e., date of last visit/contact (can be a phone call, e.g., in case of withdrawal).

All adverse events will be classified as non-TEAEs or TEAEs by the sponsor or sponsor's designee.

Definition of adverse events

An adverse event is any untoward medical occurrence, i.e., any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, in a subject enrolled in a clinical trial. Pre-existing diseases or conditions occurring before enrollment are not considered to be adverse events unless there is an untoward change in intensity, frequency, or quality after enrollment. Lack of efficacy per se is not considered to be an adverse event.

Pregnancy

A newly diagnosed pregnancy of an enrolled female subject will not be considered an adverse event itself unless it is suspected that the trial treatment interacted with a contraceptive method. In this case, the pregnancy will be considered a TEAE. A congenital anomaly as an outcome of this pregnancy will be considered a serious TEAE.

All newly diagnosed pregnancies of enrolled female subjects will be reported to the sponsor's Drug Safety Department within 24 hours after first knowledge. These pregnancies will be documented using a pregnancy reporting form with all available information provided and followed up to determine the outcome post-parturition.

All pregnant subjects will be discontinued from the trial/trial treatment.

Definition of non-treatment emergent adverse events

All adverse events occurring after enrollment and prior to the administration of an IMP are defined as non-TEAEs. Non-TEAEs are also those adverse events occurring after start of trial treatment, but

beyond the therapeutic reach (i.e., the number of days after treatment completion that a subject is still considered to be potentially affected by IMP as defined in the statistical analysis plan).

Definition of treatment emergent adverse events

All adverse events occurring in a subject administered a trial treatment and which do not necessarily have a causal relationship with this treatment. The therapeutic reach relevant for this determination (i.e., the number of days after treatment completion that a subject is still considered to be potentially affected by IMP) will be defined in the statistical analysis plan. In addition, pre-treatment adverse events which worsen during the treatment period are also considered TEAEs.

Definition of serious adverse events

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered medically important. The medical concepts included in Section 19.1 should be taken into account when applying the seriousness criterion.

An elective hospital admission, e.g., for pre-planned surgery, will not be considered a serious adverse event if documented at enrollment. Short-lasting (<24 hours) hospital admissions, e.g., for clinical check-ups, not meeting any of the other above mentioned criteria will also not be considered as serious adverse events.

Special procedures for serious adverse events

If serious adverse events occur that are not tolerable, the investigator will decide for that subject whether to stop the trial and/or treatment of the subject. The investigator should consider whether discontinuation from the IMP or trial is needed, based on the characteristics of a particular serious adverse event, e.g., if the serious adverse event precludes further safe participation in the trial.

If possible, after all serious adverse events, a blood sample for the central laboratory quantitation of systemic exposure of tapentadol and tapentadol-O-glucuronide should be drawn in close temporal relationship to the serious adverse event.

Definition of unexpected treatment emergent adverse events

Expectedness will be assessed by the sponsor.

An unexpected TEAE is one where the nature or intensity is not consistent with the information in the investigator's brochure.

Furthermore, reports that add significant information about the specificity or severity of a known, already documented adverse reaction constitute unexpected TEAEs. For example, a TEAE more specific or more severe than expected would be considered "unexpected".

Definition of adverse drug reactions

Adverse drug reactions (synonymous with drug-related adverse events) are all untoward and unintended responses to an IMP independent of the dose administered.

All TEAEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression "reasonable causal relationship" means to convey, in general, that there is evidence or argument to suggest a causal relationship. For guidance on the causal relationship, see the section Classification of causation.

A list of adverse drug reactions seen for the IMP is given in the current version of the investigator's brochure.

Classification of causation

The causal relationship of an adverse event to IMP will be classified using the following terminology. The given criteria for each term are for consideration and are neither exhaustive nor required to be fulfilled in total for the selection of the respective term:

Terms for classification of causation	Criteria for the selection of causality classification terms
Conditional/ Unclassified:	Additional data for a proper assessment are under examination.
Unassessable/ Unclassifiable:	The available data cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.
Not related:	Data with sufficient evidence to accept that there is no causal relationship to IMP administration (i.e., there is no temporal relationship to IMP administration or proved other cause).
Unlikely:	Data without sufficient evidence to accept that there is no causal relationship to IMP administration, but also with no evidence or argument to suggest a causal relationship (e.g., the temporal relationship to IMP administration makes a causal relationship improbable, and other drugs, chemicals, or underlying disease(s) provide plausible explanations).
Possible:	Data with limited evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, but the adverse event could also be explained by concurrent disease[s] or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear).
Probable/ likely:	Data with sufficient evidence or argument to suggest a causal relationship (e.g., there is a reasonable time sequence to administration of the drug, the adverse event is unlikely to be attributed to concurrent disease(s) or other drugs or chemicals, and a clinically reasonable response on withdrawal [dechallenge]).
Certain:	Data with clear evidence for a causal relationship (i.e., a clinical event, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, and it cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug [dechallenge] should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, using a satisfactory rechallenge procedure if necessary).

Definition of intensity

The clinical "**intensity**" of an adverse event will be classified as:

Mild:	Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.
Moderate:	Symptoms cause discomfort but are tolerable; they cannot be ignored and affect concentration.
Severe:	Symptoms which affect usual daily activity.

For adverse events where the intensity changes over time, the maximum intensity observed during the whole duration of the adverse event will be documented.

Definition of outcome at the time of last observation

The outcome at the time of last observation (see Section 11.1.3) will be classified as:

- Recovered/Resolved.
- Recovered/Resolved with sequelae.
- Fatal.
- Recovering/Resolving.
- Not recovered/Not resolved.
- Unknown (unknown should only be used, if at the time of the last visit for a subject in a trial, the outcome of the adverse event is unknown to the investigator, e.g., because the subject is lost to follow-up).

In the event of irreversible congenital anomalies, the choice "not resolved" should be used. "Fatal" should only be used when death is possibly related to the adverse event (note: the causal relationship of the IMP to the adverse event is not to be considered for this decision). If there is more than 1 adverse event, only the adverse event leading to death (possibly related) will be attributed with the outcome "fatal".

Documentation of adverse events

The subjects will be questioned about possible adverse events with non-leading questions before administration of the IMP and at regular intervals thereafter as defined in Section 1.2.

All adverse events reported spontaneously by subjects at any time point will also be documented.

All adverse events will be documented in the CRF with the following information where appropriate:

- Description (adverse event verbatim term).
- Start date/time.
- End date/time or continuation.
- Whether adverse event was serious.
- Intensity.
- Outcome.
- Action taken with IMP.
- Countermeasures.
- Causal relationship to IMP.

Follow-up of subjects with an adverse event

Any adverse event or clinically relevant abnormal laboratory or vital sign result will be followed until it reaches a satisfactory resolution, or becomes stable, or can be explained by other causes (e.g., concurrent condition or medication), or clinical judgment indicates that further evaluation is not warranted.

Definition of countermeasures

"**Countermeasures**" will be defined as:

None:	No countermeasure given.
Newly started medication:	A newly started medication or change in dose or route of application of a concomitant medication due to the adverse event (to be listed on the medication chart) that is used as a countermeasure.
Trial discontinuation:	It was necessary to discontinue the subject from the trial due to the adverse event.
Others:	All other countermeasures, e.g., physical therapy, surgery.

Except for none, multiple countermeasures for 1 adverse event can be recorded.

Classification of action taken with investigational medicinal product when an adverse event occurs:

- Drug withdrawn.
- Dose not changed.
- Dose decreased.
- Not applicable.
- Unknown.

Notification of serious adverse events

All serious adverse events (including death, irrespective of cause) during the trial, regardless of their relationship to IMP, must be reported to the sponsor's Drug Safety Department as soon as possible but no later than 24 hours after learning of the event. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

The investigator has to submit a report, called a safety reporting form, which includes a description of the event, the therapy instituted, and trial procedures. The following information must be communicated with the first notification of an adverse event fulfilling the above criteria:

- Trial identifier.
- Subject's identifier (subject number).
- Subject's date/year of birth (if available, see local data protection requirements) or age (at adverse event onset).
- Subject's sex.
- First administration of IMP (date and time, if available).
- Last administration of IMP (date and time, if available).
- Adverse event verbatim term (specific diagnosis, if possible).

- Adverse event onset (date and time, if available).
- A brief description of the event, the course, and the countermeasures taken.
- Intensity.
- Seriousness criterion.
- Outcome.
- Concomitant medication at onset of the event and whether one of the concomitant medications is also suspected to have caused the event.
- Relevant history / preexisting medical conditions.
- Investigator's assessment of the relationship to IMP(s).
- Whether and when blinding was broken.

All additional information concerning the adverse event until trial termination or definite outcome should be communicated per follow-up report without delay.

The immediate and follow-up reports must only identify the subjects using the unique subject identifier.

The investigator is obliged to comply with applicable regulatory requirement(s) related to the reporting of serious adverse events to the regulatory authorities and the relevant IEC/IRB.

Notification of serious adverse reactions

All suspected adverse reactions related to an IMP (the tested IMPs and comparators) that occur in this trial, and that are both unexpected and serious are subject to expedited reporting.

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to all competent authorities in all the member states concerned, FDA, and to the IEC/IRB, and in any case no later than 7 days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 days. All other suspected serious unexpected adverse reactions will be reported to the competent authorities concerned and to the IEC/IRB concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor.

The sponsor will also inform all investigators involved in the clinical trial.

Once a year throughout the clinical trial, the sponsor will provide the member states in whose territory the clinical trial is being conducted and the IEC/IRB with a listing of all suspected serious unexpected adverse reactions which have occurred over this period and a report of the subjects' safety.

In addition, the sponsor will ensure that all serious adverse reactions are reported in compliance with applicable national regulatory requirements.

12.3.2 Safety laboratory

For details regarding blood sampling, including volumes of blood taken, please see Section 11.7.

Blood samples for this trial should, if possible, be taken at the same time as routine blood sampling.

Before allocation/randomization to IMP, the required blood samples may be taken together and separated by the laboratory.

The following tests will be performed unless the weight of the subject precludes full blood sampling, in which case the tests may be limited (see Section 11.7):

Hematology panel	
Hemoglobin	Mean corpuscular volume (MCV)
Hematocrit	Mean corpuscular hemoglobin (MCH)
Red blood cell (RBC) count	Mean corpuscular hemoglobin concentration (MCHC)
Platelet count	
White blood cell (WBC) count with differential count	

Clinical chemistry panel	
Sodium	Lipase (not required for the local laboratory assessment)
Potassium	Triglycerides
Chloride	Total bilirubin
Bicarbonate	Alkaline phosphatase
Blood urea nitrogen (BUN)	Creatine kinase
Creatinine	Lactic acid dehydrogenase (LDH)
Uric acid	Alanine transaminase (ALT)
Calcium	Aspartate transaminase (AST)
Phosphorus	Glucose
Total protein	

Clinical chemistry and hematology – central laboratory (for subjects aged 2 years to less than 18 years)

Blood samples will be drawn for clinical chemistry and hematology for central safety laboratory testing after surgery when the subject is considered clinically stable before allocation/randomization to IMP. A further sample will be taken at the End of Treatment (see schedule of events, Section 1.2).

The samples will be analyzed at a central laboratory. The results of the central laboratory will be transferred electronically to the sponsor.

The trial site will follow the instructions provided in the laboratory manual regarding the specific procedures for collection of all blood samples.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes during the trial in the adverse event section of the CRF. Appropriate action should be taken if necessary.

The glomerular filtration rate will be estimated according to Schwartz et al. 1984.

If the red or white blood cell analyses are clinically relevantly abnormal, the red or white cell morphologies must be reported, respectively.

Clinical chemistry and hematology – local laboratory (all subjects)

Blood samples for clinical chemistry and hematology for the local laboratory will be taken at the same time as the blood sample for the central laboratory before allocation/randomization to IMP for subjects aged 2 years to less than 18 years. For subjects less than 2 years old, only the blood sample for local analysis will be taken.

The results of blood analyzed in a local laboratory for clinical chemistry and hematology will be used for verification of the exclusion criteria. The results of the tests must be available for review before a subject is allocated to IMP. Parameters specified in the exclusion criteria need to be reviewed. This does not preclude the need to take a sample for central laboratory analysis for subjects aged 2 years to less than 18 years.

12.3.2.1 Serum concentrations of tapentadol

A 0.5 mL blood sample for analysis of serum concentrations of tapentadol needs to be drawn if there is a serious adverse event. Instructions for handling the pharmacokinetic samples are given in Section 19.10.

Serum samples will be analyzed to determine concentrations of tapentadol and, optionally, tapentadol-O-glucuronide using a validated liquid chromatography-tandem mass spectrometry bioanalytical assay under the supervision of the department of pharmacokinetics at the sponsor.

12.3.3 Pregnancy test

For female subjects if aged 12 years or older, or post-menarchal, or sexually active, a pregnancy test will be performed within 48 hours prior to allocation/randomization to IMP. This may be done on a serum sample according to local routine, or using a urine dipstick test (either supplied by the sponsor or a local test capable of detecting human chorionic gonadotropin levels of 25 mIU/mL or greater and a sensitivity/specificity of >99%).

12.3.4 Twelve-lead electrocardiogram

Twelve-lead ECGs will be recorded after surgery prior to allocation/randomization to IMP and at End of Treatment. The measured ECG intervals will be RR, PR, QRS, and QT; the corrected [Fridericia] QTcF will be calculated. The investigator will review the 12-lead ECG for clinically relevant abnormalities prior to dosing subjects. The investigator will document all abnormal 12-lead ECG results, with a judgment whether the abnormality is clinically relevant.

12.3.5 Vital signs (respiratory rate, systolic and diastolic blood pressure, and heart rate) and oxygen saturation

Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) and oxygen saturation (by pulse oximetry) will be measured as per standard of care and recorded at the times specified in the schedule of events (see Section 1.2).

12.3.6 Continuous monitoring of respiratory rate and heart rate

Respiratory rate and heart rate will be monitored continuously for 24 hours after the first administration of IMP. The monitoring outside of this time period is according to standard of care.

12.3.7 Continuous monitoring of oxygen saturation

Oxygen saturation will be monitored continuously using pulse oximetry from before the first dose of IMP until 4 hours after the last administration of IMP. If the oxygen saturation falls below 92% for at least 60 seconds (excluding technical failures or artifacts), the lowest value, the length of time the oxygen saturation is below 92%, and vital signs are to be recorded. The event is to be recorded as an adverse event as well. The monitoring outside of this time period is according to standard of care.

12.3.8 Physical examination

The physical examination comprises but is not limited to the general condition, skin, eyes, ears, nose, throat, head, neck, thyroid, heart, lungs, chest (including breasts), abdomen, kidneys, liver, lymphatic system, musculoskeletal system, and neurological system. Attention should be paid to abnormalities which may have a bearing on the conduct of the trial. The physical examinations will be documented.

12.3.9 Columbia–suicide severity rating scale

The C-SSRS (Section 19.5, Oquendo et al. 2003) will be completed at the specified times in Section 1.2 in subjects aged 6 years or older. There are 2 versions, 1 version for children's baseline (used at Enrollment after surgery) and 1 version for children's since last visit (used at End of Treatment Visit). The C-SSRS reports the severity of both suicidal ideation and suicidal behavior. The evaluation will be recorded. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason.

The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation.

The C-SSRS will be administered by a clinician who has been certified to administer the C-SSRS.

The C-SSRS will be explained and shown to the parents/legal guardians prior to use.

The C-SSRS will only be used at a trial site if its use has not been rejected by the responsible ethics committee.

12.3.10 University of Michigan Sedation Scale

The University of Michigan Sedation Scale (Section 19.11) is a validated (Malviya et al. 2002) observational pediatric 5-point sedation scale. It will be used to assist in accurately assessing the depth of sedation before the administration of IMP. The investigator will record the sedation score at the times specified in the schedule of events (see Section 1.2).

12.4 Appropriateness of measurements

During the trial, exploratory subject-reported pain assessments and supplemental analgesic (opioid and non-opioid) medication dosing information will be collected.

In children aged from birth to less than 6 years, or in older children who are not able to report their pain using the other scales, pain intensity will be assessed with the FLACC scale (Merkel et al. 1997). The FLACC scale has been validated for measuring post-operative pain in children with mild to severe cognitive impairment. It has also been validated for the assessment of pain secondary to surgery, trauma, cancer or other painful diseases for all pre-verbal children (including infants).

In children aged 6 years to less than 12 years, pain intensity will be assessed with the FPS-R. The FPS-R scale has been established as a valid, self-reported measure of pain intensity in children aged 4 years to 15 years (Hicks et al. 2001, Miró and Huguet 2004).

In children aged 12 years to less than 18 years, pain intensity will be assessed with a VAS. The VAS pain intensity rating scale (Scott and Huskisson 1976) has been established as a valid, self-reported measure of pain intensity in children aged 8 years to 18 years with juvenile chronic polyarthritis (Scott et al. 1977).

The global impressions of change were chosen as a complementary assessment of analgesic efficacy (Section 12.2.3). It is a recommended and responsive outcome measure for pain-related clinical trials (Dworkin et al. 2005, Farrar et al. 2001).

12.5 Compliance

Compliance is the adherence to all trial-related requirements (including treatments), GCP, and applicable regulatory requirements.

Site compliance will be assured by the implementation of a quality system and the performance of a combination of trial site visits, training, and monitoring visits. Non-compliance will lead to prompt action by the sponsor to secure compliance, and may result in closure of the trial site and notification of the regulatory authorities and/or relevant IEC/IRB.

The IMP will be administered in the controlled environment of a clinical research site, and the direct observation of the administration of IMP by trial staff will ensure compliance with trial requirements. Dose, date, and time of the administration of the IMP will be recorded in the CRF and the source documents.

13 DOCUMENTATION OF TRIAL DATA

13.1 Case report forms

Case report forms for each subject will be provided to the investigator by the sponsor in electronic format to document the trial data.

The investigator will use CRFs to record information required by the protocol to be reported on each trial subject. The investigator will be instructed on how to complete the CRFs.

The investigator will verify that the CRFs are complete, accurate, and compatible with source documents. All CRF entries, corrections, and alterations will be made by the investigator or other authorized personnel under their supervision. Entries will be checked against appropriate source documents by the sponsor.

Electronic case report forms

The data will be processed using a validated system. Access to the system will be protected with a personal user name and password. The users are identified and receive access rights according to their role in the trial. All users will receive training on the CRF, and this training will be documented prior to access rights being granted.

The investigator, the clinical research associate, and designated persons at the site and from other parties involved (e.g., data management) will be able to review all captured data during the trial via a secure internet connection.

After source data verification, the corresponding part of the CRF will be flagged as source data verified. Should subsequent changes be made, this flag will be reversed and source data verification must be repeated.

All entries and modifications to the CRF will be stored with the personal identification of the person who made the changes, a date/time stamp, and the reason for change.

The CRF must be signed electronically by the investigator. Any changes made to the CRF pages after the investigator has signed will require re-signing by the investigator.

13.2 Subject reported outcomes

All subject reported outcomes will stay as source data at the site. The investigator is responsible for the accurate transfer of these data into the CRFs.

13.3 Data management

Data management will be performed by sponsor personnel or by authorized sponsor representatives defined by the sponsor prior to the trial start.

Electronic case report forms

During data entry in the electronic CRF, automatic queries will be raised to clarify missing data, inconsistencies, and incorrect values. After completion of the CRF, further queries will be issued to the investigator to clarify inconsistencies (e.g., resulting from additional electronic validation checks or medical and manual reviews). Resolutions of queries will be made by the investigator or the trial site's designated persons. The query is to be answered directly in the electronic CRF system and the original value will be changed, if necessary.

Coding

Medication names will be coded using the World Health Organization-Drug Dictionary. Medical history terms and adverse events will be coded using MedDRA. As required by the sponsor's SOPs, the version most recently implemented by the sponsor will be used at the time of database lock. Coding will be reviewed by the sponsor's personnel according to standard procedures.

External data

Trial data not recorded in the CRF (e.g., safety laboratory data and 12-lead ECG data) will be reconciled against CRF data (details of reconciliation will be specified separately but may include trial number, site number, patient number, age, dates of visits). All external data will be transferred electronically to the data management center using a secure method at predefined intervals during the trial in a data structure defined by the data management center. At the end of the trial, the contract research organization(s) providing these data will provide the data management center with a final data transfer.

Database lock

There will be 2 data locks for this trial. For the first report, only data for the EU PDCO set will be locked within the electronic CRF, the CRF will not be shut down. Any potential subsequent

unlocking of this set of data will be performed according to the sponsor's SOPs for database unlock. The subjects' data will be locked as soon as all data for the EU PDCO set are considered clean (i.e., all data have been received and entered, all data checks and quality control checks on these data have been performed, and all queries for these data are resolved). The same procedure will apply for the final data lock at the end of the trial.

13.4 Source data

Source data is defined by GCP as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)".

Source data comprise clinical documentation, data, and records (e.g., clinic/hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, and data and records arising from departments such as the pharmacy, laboratory, and medico-technical departments) that describe or record the methods, conduct, or results of the trial, the factors affecting the trial, and the actions taken.

All clinical documentation and data arising from the trial will be kept by the investigator, who has to provide direct access for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents. When this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF are: race/ethnic group, and the result of the estimation of the glomerular filtration rate according to Schwartz et al. 1984.

The nature and location of all source data/clinical documentation will be identified and documented by the investigator to ensure that all sources of original data required to complete the CRF are known to the sponsor and/or trial site personnel and are accessible for verification during trial-related monitoring, audits, relevant IEC/IRB review, and inspection(s).

During trial conduct, vendors are responsible for data security with oversight from the sponsor.

All data captured from all subjects will be sent to the sponsor in human readable form on a read-only compact disc for filing/archiving according to sponsor SOPs.

The investigator will receive all data captured for his or her subjects, in a human readable form, on a read-only compact disc for his or her files.

13.5 Investigator's site file and the trial master file

The investigator is responsible for the timely filing of all essential documents in an investigator's site file and the sponsor is responsible for the timely filing of all essential documents in the trial master file. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the investigator will ensure that all source data/documentation arising from the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation

and verification. The investigator will take measures to prevent accidental or premature destruction of these documents.

The investigator will keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the clinic/hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

14 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

There are different requirements for the EU PDCO and US FDA including the age range of the patient population (EU PDCO: 2 years to <18 years of age, US FDA: birth to <17 years of age) and the timing of the primary efficacy endpoint (EU PDCO: 24 hours, US FDA: 12 hours) that impact the statistical methods and are reflected in the following sections.

As applicable and appropriate for the individual endpoint, the endpoints will be analyzed in the age ranges for the EU PDCO and for the US FDA.

Two reports will be prepared for the trial. The first report will be prepared after the last subject out of the EU PDCO set. The second report will be prepared after the last subject out of the US FDA set. Further details on the reports are given in Section 16.6.

14.1 Sample size rationale

The sample size determination was based on the primary efficacy endpoint variable for the respective Full Analysis Sets. A linear relationship is 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, summarized in Table 4, from previously conducted trials in post-surgical pediatric subjects where supplemental opioid was measured.

Table 4: Differences in amount of supplemental opioid use in previously conducted trials in post-surgical pediatric subjects

Reference	Supplemental opioid use (morphine or morphine-equivalent) in original units	Converted to cumulative use over 24 hours (mg/kg)	Treatment group difference based on cumulative use over 24/12 hours (mg/kg)
Rusy et al. 2010	Placebo: 0.055 ± 0.017 mg/kg per h Gabapentin: 0.046 ± 0.016 mg/kg per h	Placebo: 1.32 ± 0.408 Gabapentin: 1.10 ± 0.384	0.22/0.11
Rugyte and Kokki 2007	Placebo: 0.028 ± 0.0083 mg/kg per h Ketoprofen: 0.020 ± 0.0100 mg/kg per h	Placebo: 0.67 ± 0.20 Ketoprofen: 0.49 ± 0.24	0.18/0.09

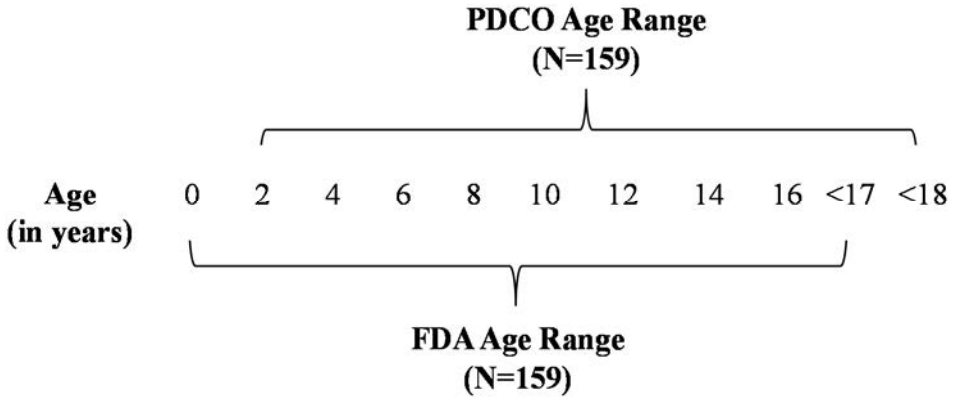
For the current trial, a value of 0.20 mg/kg in 24 hours (0.10 mg/kg in 12 hours) for the between-treatment group difference and a more conservative value of 0.42 mg/kg in 24 hours (0.21 mg/kg in 12 hours) for the standard deviation were considered adequate assumptions. The standardized effect

size based on these values (0.20/0.42 = 0.48) is more conservative than the standardized effect sizes observed in Rusy et al. 2010 (approximately 0.55) or Rugyte and Kokki 2007 (approximately 0.80).

Assuming $\alpha = 0.05$ (two-sided), 80% power ($\beta = 0.2$), and a randomization ratio of 2:1 (tapentadol to placebo) results in a sample size of 106 tapentadol-treated subjects and 53 placebo-treated subjects.

No multiplicity adjustment will be performed.

The target is to have approximately 159 randomized (allocated) subjects treated with IMP in the EU PDCO age range (2 years to less than 18 years of age) and in the US FDA age range (birth to less than 17 years of age) (Figure 2).



N = target number of treated subjects; PDCO = Pediatric Committee (of the European Medicines Agency); FDA = Food and Drug Administration (of the United States of Amrica).

Figure 2: Depictions of regulatory-required age ranges

The treatment of at least 159 subjects with IMP in the EU PDCO age range and US FDA age range is the target for the minimum required number of subjects to meet the statistical power calculation for the primary efficacy endpoints of the trial and regulatory requirements.

Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.

The trial enrollment for the EU PDCO set (see Section 14.2.1 for the definition of the analysis populations) will complete when the following criterion is met:

- At least 159 treated subjects in the age range 2 years to less than 18 years of age (EU PDCO).

The trial enrollment for the US FDA set will complete when the following 2 criteria are met:

- At least 159 treated subjects in the age range birth to less than 17 years of age (US FDA).
- 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses (US FDA). Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size.

An additional objective of the study is to meet a US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age who have been exposed to tapentadol for at least 48 hours. As medically appropriate, every effort will be made to enroll subjects in this trial to meet this objective.

The sample size calculation was performed using the sample size program nQuery v7.0 (Dixon and Massey 1983, O'Brien and Muller 1993) for unequal group sizes and the above assumptions regarding the effect size and the allocation ratio of 2:1 (tapentadol:placebo).

14.2 Analysis of the trial – statistical analysis

The statistical analysis of this trial will be planned, performed, and reported by sponsor personnel or by authorized sponsor delegates, in accordance with sponsor SOPs.

The statistical analysis of this trial will be performed as summarized in this protocol and given in detail in the statistical analysis plan. The statistical analysis plan will be finalized before the first subject in.

14.2.1 Analysis populations (analysis sets)

Safety Set

The Safety Set comprises all treated subjects in the required age ranges for the EU PDCO and US FDA. The overall Safety Set will include all treated subjects in the trial. The EU PDCO Safety Set will include subjects 2 years to less than 18 years of age; the US FDA Safety Set will include subjects from birth to less than 17 years of age. A subject will be considered as treated if administered any amount of IMP.

If by error a subject does not receive the allocated medication, the subject will be evaluated according to the received IMP.

Full Analysis Set

The overall Full Analysis Set includes all subjects that are allocated and treated. The EU PDCO Full Analysis Set will include allocated and treated subjects aged 2 years to less than 18 years old; the US FDA Full Analysis Set will include allocated and treated subjects from birth to less than 17 years of age.

If by error a subject does not receive the allocated medication, the subject will be evaluated as allocated within the Full Analysis Set following the intention-to-treat principle.

Per Protocol Set

The EU PDCO or US FDA Per Protocol Set is a subset of the respective Full Analysis Set, excluding subjects with protocol deviations that may have an impact on the results of the primary efficacy analyses. Further details of the Per Protocol Set definition will be specified in the statistical analysis plan.

14.2.2 General descriptive and graphical methods

Descriptive and graphical methods will be used in the data analyses. Analyses will consider the trial populations, described in Section 14.2.1. For continuous variables, descriptive statistics will include number of observations, arithmetic mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. For categorical variables, frequency counts and percentages will

be used to summarize the results. The main analysis will focus on the treatment; subgroup analyses, e.g., according to age categories, may also be explored as appropriate. For variables collected at multiple visits, descriptive summaries will be provided for each time point.

Baseline measurements are defined as the last evaluation performed immediately before IMP administration, unless otherwise stated.

14.2.3 Analysis of subject characteristics data

Subject characteristics data, and pregnancy tests, will be analyzed as described in Section 14.2.2.

Subjects will be allocated to an age category based on their age recorded at baseline.

Pain intensity scores collected before each NCA/PCA activation will be analyzed descriptively by treatment group.

Prohibited medication used by the mother of a newborn or breastfeeding mother will be listed by subject.

14.2.4 Analysis of subject disposition

Subject disposition data will be analyzed as described in Section 14.2.2.

An allocation/randomization failure is a subject who was allocated to IMP but was discharged from hospital or the trial without taking IMP. Allocation/randomization failures will be listed.

14.2.5 Analysis of efficacy data

14.2.5.1 Primary efficacy endpoint

The primary efficacy endpoints for the EU PDCO and US FDA are the amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours and 24 hours after first IMP intake, respectively. The primary efficacy endpoint that is used in 1 region will be considered as a secondary efficacy endpoint in the other. The primary efficacy endpoints will be summarized using the respective Full Analysis Sets.

For subjects who withdraw from the trial prior to the 12-hour or 24-hour time point due to any other reason than no further need of opioid analgesic medication or switch to exclusively oral opioid analgesic medication, cumulative supplemental opioid analgesia over the respective time period will be based on the observed supplemental opioid use up to the time of the subject's discontinuation. If a subject used a total of X mg/kg of supplemental opioid through Hour T (≤24 hours), cumulative use over 24 hours will be estimated as (X/T)*24 mg/kg. If T is <12 hours, cumulative use over 12 hours will be estimated as (X/T)*12. This extrapolation assumes a constant use (in mg/kg per hour) of supplemental opioid over 24 hours. For subjects who withdraw from the trial due to no further need of opioid analgesic medication or switch to exclusively oral opioid analgesic medication, the cumulative use of supplemental opioid will equal the total amount of supplemental opioid used up to the time of withdrawal. Other imputation methods will be used for sensitivity analyses. These will be described in detail in the statistical analysis plan.

Supplemental opioid analgesia will be expressed in mg/kg of morphine-equivalents. Hydromorphone doses will be multiplied by 5 to obtain the morphine equivalent.

The primary null hypothesis to be tested for the trial is that the tapentadol group is not different from the placebo group for the primary endpoint. The alternative hypothesis is that the tapentadol

group is different from the placebo group for the primary endpoint. For the primary efficacy endpoint, descriptive statistics will be presented by treatment group, and the endpoint will be analyzed using an ANOVA, which includes treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Treatment effects will be estimated based on least-squares means of the difference. The 95% confidence intervals and p-value will be presented for tapentadol compared with placebo. The test for the primary efficacy analysis will be 2-sided at a 0.05 level of significance.

A sensitivity analysis will be performed using the respective Per Protocol Set and analyzed using the same ANOVA model.

The primary endpoint will also be evaluated using Bayesian statistics as a supportive analysis (EU PDCO). The methodology will be described in the statistical analysis plan.

14.2.5.2 Secondary endpoints and subgroup analyses

Unless otherwise noted, all secondary efficacy endpoints will be summarized using the respective Full Analysis Set. There will be no multiplicity adjustments for any of the secondary endpoints.

The amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours or 24 hours after first IMP intake will be a secondary efficacy endpoint for the EU PDCO or US FDA, respectively. The same ANOVA model as defined above for the primary efficacy endpoint will be used to assess treatment group differences. Treatment effects will be estimated based on least-squares means of the difference. The 95% confidence intervals and p-values will be presented for tapentadol compared with placebo.

In addition, the total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours, will be summarized descriptively. The intervals will be >24 to 36 hours, >36 to 48 hours, >48 to 60 hours, >60 to 72 hours, >72 to 84 hours, and >84 to 96 hours. For each interval, only subjects who have their End of Treatment Visit after the start of the interval will be included. If a subject has their End of Treatment Visit during a given interval, the missing data for the remainder of the given interval will be imputed using a similar methodology as for the primary efficacy endpoint, but using only data from within the given interval. The subject will then not be included in the subsequent intervals.

The CGIC and PGIC, both using a 7-point rating scale at the End of Treatment Visit (Visit 3), will be described descriptively.

The acceptability and palatability of IMP will be assessed using 5-point rating scales after the first dose of IMP and at the End of Treatment Visit (Visit 3). The results will be tabulated by treatment group.

Pain intensity scores recorded relative to IMP intake, and at the End of Treatment Visit, with changes from baseline values, will be summarized descriptively over time by treatment group and age categories (respective age-defined pain scale), as well as being listed. Figures will also be produced, where required.

The number and proportion of subjects taking non-opioid analgesic medications (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake will be grouped according to the Anatomical Therapeutic Chemical Classification System (World Health Organization Drug Dictionary coding), and presented in tables by treatment group.

The time to first and time to second NCA/PCA after the first dose of IMP will be summarized descriptively and displayed by treatment group and by treatment group and age categories. Figures will also be produced, where required. Any supplemental opioid analgesic medication given intravenously if the NCA/PCA pump fails and any clinician bolus will be included in this analysis.

The distributions of the time from the first dose of IMP to treatment discontinuation due to lack of efficacy will be evaluated by Kaplan-Meier estimates and compared between the treatment groups using the log-rank test. Subjects who complete the End of Treatment Visit (Visit 3) will be censored at the last observation time point. Subjects who discontinue during the treatment period for reasons other than lack of efficacy will be censored at the time of discontinuation.

Subgroup analyses

Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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, as applicable for the EU PDCO set and US FDA set) and by method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.

14.2.6 Analysis of safety data

The analysis of safety data will be performed for the EU PDCO Safety Set for the EU PDCO report and for the overall Safety Set for the US FDA report.

14.2.6.1 Analysis of adverse events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the most recent version of MedDRA used by the sponsor. All reported adverse events with onset during the treatment period or during the tapentadol therapeutic reach (i.e., TEAEs occurring in the days after treatment completion that a subject is still considered to be potentially affected by IMP as defined in the statistical analysis plan) will be included in the analysis. For each adverse event, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. An adverse event starting before the first dose of IMP and getting worse in intensity during the treatment period will also qualify as a TEAE. The incidence, type, intensity, onset, relationship, treatment, and outcome of TEAEs will be listed and presented descriptively according to treatment group. Serious adverse events will be listed. Subgroup categories (e.g., by age) will be analyzed as appropriate.

The distributions of the time from the first dose of IMP to treatment discontinuation due to an adverse event will be evaluated by time-to-event estimates, including a Kaplan-Meier graphical description. For subjects who complete the End of Treatment Visit (Visit 3), time to discontinuation due to an adverse event will be censored at the end of the treatment period. For subjects who discontinue during the treatment period for reasons other than adverse events, time to discontinuation due to an adverse event will be censored at the time of treatment discontinuation.

Special attention will be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event (e.g., summaries, listings, and narrative preparation may be provided, as appropriate).

14.2.6.2 Analysis of safety laboratory data

Safety laboratory data will be summarized by the type of safety laboratory test. Normal reference ranges and markedly abnormal results (specified in the statistical analysis plan) will be used in the summary of safety laboratory data. Descriptive statistics (only for blood samples analyzed at the central laboratory) will be calculated for each safety laboratory parameter at baseline and at each scheduled time point as described in Section 1.2. Changes from baseline results will be presented descriptively as well as in pre- versus post-treatment cross tabulations (with classes for below, within, and above predefined potentially clinically important ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided.

14.2.6.3 Analysis of electrocardiographic data

The 12-lead ECG variables that will be analyzed are heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF (Fridericia) interval.

The 12-lead ECG measurements will be summarized at each time point of measurement as described in Section 1.2. The change from baseline will be summarized. Changes from baseline results will be presented descriptively as well as in pre- versus post-treatment cross tabulations (with classes for below, within, and above predefined potentially clinically important ranges). A categorical analysis for QT interval and QTcF (Fridericia) interval outliers will be performed as per ICH E14 guidance.

All other clinically important 12-lead ECG abnormalities (e.g., changes in T wave morphology or the occurrence of U waves) will be listed.

14.2.6.4 Analysis of vital signs and oxygen saturation

Descriptive statistics of pulse, respiratory rate, blood pressure (systolic and diastolic) and oxygen saturation (by pulse oximetry) values and change from baseline will be provided at each scheduled time point as described in Section 1.2. Frequency tabulations of clinically-significant abnormalities will be included. Age-specific normal ranges will be detailed in the statistical analysis plan.

14.2.6.5 Analysis of physical examination data

The physical examination findings will be listed per time point as described in Section 1.2.

14.2.6.6 Analysis of Columbia–Suicide Severity Rating Scale

The C-SSRS results will be listed per time point as described in Section 1.2 according to the accepted practice for reporting these data as discussed in Nilsson et al. 2013.

14.2.6.7 Analysis of sedation scores

Descriptive statistics of sedation scores will be provided at each scheduled time point as described in Section 1.2.

14.2.7 Interim analysis

No interim analysis is planned.

14.2.8 Data monitoring committee

A DMC will be supplied a relevant set of data on a regular basis for ensuring their oversight of the subjects' safety and the scientific validity of the trial (see Section 5.4).

15 QUALITY SYSTEM, AUDIT AND INSPECTION

15.1 Quality system

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

The trial documentation must be adequate for the reconstruction of the trial.

15.2 Data quality assurance

The accuracy and reliability of the trial data will be assured by careful clinical research organization/investigator selection and oversight by the performance of a combination of trial site visits, training, monitoring visits, remote verification by the sponsor of appropriate use of electronic tools by the site, data cleaning, and audits.

15.2.1 Clinical research organization/investigator selection

The accuracy and reliability of the trial data will be assured by the selection of suitably qualified and experienced investigators and trial sites, and the introduction of the investigator and associated personnel to protocol requirements and procedures prior to the trial.

15.2.2 Trial site monitoring

Trial site monitoring as defined in GCP will be performed by sponsor personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial. The authorized delegates, applicable SOPs, the frequency of monitoring visits, and the reporting modus, will be defined in writing as required by sponsor SOPs. Monitored sites will be informed about visit outcomes using a follow-up letter.

The investigator(s) will permit monitoring visits at agreed times. Corrections, amendments, or clarifying statements resulting from the monitoring visit will be made by the investigator where necessary.

15.2.3 Audits

Audits as defined by GCP will be performed for this trial. The investigator will permit sponsor personnel or authorized delegates to audit the trial facilities and documentation at agreed times. The auditors will be independent of the trial and its performance.

15.3 Inspections

The investigator, the sponsor, or personnel at other establishments, are obliged to cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The investigator or personnel at other establishments should notify the sponsor as soon as possible about any upcoming regulatory authority inspection.

16 GENERAL CONDITIONS AND AGREEMENTS

16.1 Insurance

If insurance for subjects is required by applicable regulatory requirements in the participating countries, the sponsor will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance.

If insurance for subjects is required by applicable regulatory requirements in the participating countries, the investigator must inform all subjects/parents/legal guardians about this insurance and (if requested) be prepared to explain the relevant terms and conditions of this insurance to the subject.

If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor will inform the investigators who will then inform their subjects/parents/legal guardians about relevant changes, if required.

16.2 Legal regulations

This trial will be carried out in compliance with any applicable regulatory requirements.

Before initiating the trial, if required by the applicable regulatory requirements, the sponsor or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.

This trial will be carried out in compliance with applicable regulatory requirements with respect to the use of narcotics.

16.3 Contracts

Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial site(s) and the sponsor or its local offices or contract research organization or its affiliates authorized by the sponsor, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation, e.g., the “Investigator Confirmation Sheet”, may serve as the basis of such contracts.

In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator’s participation in the trial will be specified in a contract between the investigator and sponsor, if applicable.

16.4 Subject data and data protection

Subject trial data will be stored in a manner maintaining confidentiality in accordance with applicable regulatory requirements.

The investigator is required to ensure that any documents or data given to the sponsor or its representatives do not contain information that would affect the anonymity of the subjects.

The investigator will obtain permission for direct access to subject data from the subject/parent/legal guardian as part of the written informed consent procedure (see Section 4.2).

This gives permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor personnel or its representatives, and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subject's identity and sponsor's proprietary information.

16.5 Publication policy

The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy (e.g., on ClinicalTrials.gov), according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing, and applicable regulatory guidance. The sponsor will post clinical trial information in a lay person understandable form in a freely accessible sponsor internet portal. Due to the preparation of 2 reports, the data presented in the databases may differ.

The results of this trial may also be published as a full publication (e.g., journal publication) or publically disclosed as a poster or presentation at a congress. The sponsor reserves the right to review any proposed presentation of the results of this trial before they are submitted for publication or public disclosure. Neither party (e.g., the sponsor, the coordinating investigator) has the right to prohibit publication or public disclosure unless it can be shown to affect possible patent rights.

In case of discrepancies with other contracts, the provisions of the protocol shall prevail.

16.6 Final report

Two reports for the trial, integrating clinical and statistical results, will be prepared by the sponsor. The first report will be prepared after the last subject out of the EU PDCO set. For the first report the efficacy and safety data will be reported for the EU PDCO set, the subgroup of subjects aged 2 years to less than 18 years old.

The second report will be prepared after the last subject out of the US FDA set. For the second report the safety data will be reported for all subjects in the study; that is the subjects reported in the first report combined with subjects aged less than 2 years old. The second report will include 2 sets of efficacy results; the previously reported results for the EU PDCO set and the efficacy results for the US FDA set.

The coordinating investigator will approve the reports on behalf of the participating investigators.

The sponsor will provide the competent authority and relevant IEC/IRB with summaries of the reports in accordance with applicable regulatory requirements.

The coordinating investigator will be provided with summaries of the reports.

16.7 Approval

16.7.1 Sponsor

This protocol has been approved in accordance with sponsor SOPs.

16.7.2 Coordinating investigator

This protocol has been approved by the international coordinating investigator.

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18 PROTOCOL AMENDMENTS

18.1 Protocol Amendment 01

Amendment rationale

The site of manufacture of the IMP (tapentadol oral solution and placebo) was changed for logistic reasons.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.1.1 Identity and composition – tapentadol oral solution (test) Section 10.1.2 Identity and composition – placebo (comparator)	
Manufacturer: Grünenthal GmbH, Aachen, Germany.	Manufacturer: Janssen Pharmaceutica NV, Beerse, Belgium.

18.2 Protocol Amendment 02

Amendment rationale

This amendment has been enacted for clarification and to comply with US FDA requirements:

- Not all endpoints will be analyzed according to the regional age ranges (2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA). This has been clarified in the text, and will be elucidated in the statistical analysis plan. In addition, the additional analysis of the primary endpoint by predefined narrow age strata has been introduced.
- Based on a request from US FDA, the following data will be collected: when possible, the investigator/delegate or subject will record a pain intensity score prior to each administration of NCA/PCA. Pain data collected for this purpose, i.e., directly before each administration of NCA/PCA, whenever possible, will be used only for the purpose of exploratory analysis.
- The definition of completers has been amended.
- The address of the international coordinating investigator was updated. The operational lead's, and sponsor's medically qualified person and signatories were changed.
- Examples of suitable surgeries have been added to the population descriptions to assist investigators to identify suitable subjects.
- Subjects who are cognitively impaired in the investigator's judgment such that they cannot comply with the protocol are now excluded from participation in the trial.
- The age range of the palatability and taste questionnaire has been extended downwards from 3 years to 2 years as the younger subjects will now start recruitment and are capable of performing the assessment.

- It is no longer necessary that any background infusion to the NCA/PCA is at a "constant" low dose rate.
- The dose of tapentadol oral solution for subjects between 2 years and less than 6 years has now been defined.
- Instructions on whether to use a 1 mL or 5 mL syringe for dosing have been added.
- It has been clarified that dosing should take place as soon as possible after a subject is woken if dosing has been delayed because the subject was sleeping.
- The list of prohibited medication taken within 14 days of allocation/randomization to IMP has been extended to include all serotonergic drugs, including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, triptans, and St. John's Wort (hypericum perforatum) for safety reasons. The time medication for sedation is prohibited has been extended to 6 hours before allocation to IMP. The use of benzodiazepines for muscle cramps and anxiety has been explicitly allowed.
- The use of IMP after 24 hours has been modified to reflect medical practice by allowing its use every 4 hours to 6 hours, and by extending use up to 72 hours to comply with a requirement to assess for at least 48 hours.
- The use of the University of Michigan Sedation Scale has been added for assessing sedation.
- Maximum blood sampling for subjects aged less than 2 years has been defined.
- The time span for recording opioid and non-opioid analgesic medication was redefined to give an adequate coverage for recording these data.
- The length of time the oxygen saturation is below 92% was made consistent across descriptions in the protocol. The phrasing was also aligned in other sections.
- The primary endpoint will also be evaluated using Bayesian statistics as a supportive analysis. The methodology will be described in the statistical analysis plan.
- The information on safety experience from post-marketing data in adults has been updated.

In addition, a number of discrepancies and inconsistencies have been corrected.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Title page:	
International coordinating investigator: Prof Dr [redacted] ~~Sophia Kindergeneeskunde B.V., Dr Molewaterplein 60, 3015 GJ Rotterdam, The Netherlands.~~ [a] Children's National Medical Center, Pharmacology & Physiology, George Washington University School of Medicine and Health Sciences, 111 Michigan Avenue, N.W. Washington, D.C. 20010. United States of America. [a]	**International coordinating investigator:** Prof Dr [redacted] Children's National Medical Center, Pharmacology & Physiology, George Washington University School of Medicine and Health Sciences, 111 Michigan Avenue, N.W. Washington, D.C. 20010. United States of America. [a]

Changes to this protocol include:	
Formerly read:	**Now reads:**
Sponsor's medically qualified person: ~~Dr~~ [redacted]~~, Clinical Leader~~, Janssen Research & Development, LLC Phone: ~~+1 609 730~~ [redacted] [redacted]~~@its.jnj.com~~ [a] **Sponsor's signatory:** ~~Dr~~ [redacted]~~, Clinical Leader,~~ **Operational lead's medically qualified person:** Dr [redacted], Global~~ Late Stage Clinical Development~~ **Operational lead's signatory:** [redacted], Global ~~Late Stage Clinical Development~~,	**Sponsor's medically qualified person:** *Dr* [redacted]*, Clinical Leader,* Janssen Research & Development, LLC Phone: *+1 609-730-*[redacted] [redacted]*@ITS.JNJ.com* [a] **Sponsor's signatory:** *Dr* [redacted]*, Clinical Leader* **Operational lead's medically qualified person:** Dr [redacted], *Head* Global *Clinical Development Strategy* **Operational lead's signatory:** *Dr* [redacted], *Head* Global *Clinical Development Strategy*,
Section 1: Protocol Synopsis – Trial objectives: **Section 7: Trial objectives**	
The clinical hypothesis of this trial is that tapentadol oral solution reduces the total amount of supplemental opioid analgesic medication used over 12 hours or 24 hours following initiation of investigational medicinal product (IMP), compared to placebo, in children and adolescents who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment. The primary efficacy objective for 1 region is considered a secondary efficacy objective in the other.	The clinical hypothesis of this trial is that tapentadol oral solution reduces the total amount of supplemental opioid analgesic medication used over 12 hours *(primary objective for US FDA)* or 24 hours *(primary objective for EU PDCO)* following initiation of investigational medicinal product (IMP), compared to placebo, in children and adolescents 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 is considered as the secondary efficacy objective in the other, *for the different age range, as described below.* *Subjects can be treated for up to 72 hours, and efficacy and safety information will also be collected throughout this time period.*
Section 1: Protocol Synopsis – Definition of endpoints: **Section 8.1: Definition of endpoints**	
All endpoints compare the results in the group of subjects treated with tapentadol oral solution to the group treated with placebo. ~~All~~ endpoints will be analyzed in the age ranges of 2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA. ... **The secondary efficacy endpoints are:** ... • The total amount of supplemental opioid analgesic medication received ~~during treatment with IMP over a maximum period of 48 hours~~ after the first dose of IMP.	All endpoints compare the results in the group of subjects treated with tapentadol oral solution to the group treated with placebo. *As applicable and appropriate for the individual endpoint, these* endpoints will be analyzed in the age ranges of 2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA. ... **The secondary efficacy endpoints are:** ... • The total amount of supplemental opioid analgesic medication received*, assessed in 12 hour intervals from 24 hours to 96 hours* after the first dose of IMP. • The total amount of non-opioid analgesics used

Changes to this protocol include:	
Formerly read:	**Now reads:**
• The total amount of non-opioid analgesics used (irrespective of the indication) during ~~the double-blind IMP~~ treatment period within the first 24 hours (EU PDCO) or within the first 12 hours (US FDA) after the first dose of IMP. • Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged ~~3 years~~ to less than 18 years old (EU PDCO). • Changes from baseline in pain intensity over ~~12 hours, 24 hours, and 48 hours after the first dose of IMP~~ using age-appropriate pain scales (Face, Legs, Activity, Cry, Consolability [FLACC] scale for ages birth to less than 6 years or in older children who are not able to report their pain using the other scales, Faces Pain Scale–Revised [FPS-R] for ages 6 years to less than 12 years, and visual analog scale [VAS] for ages 12 years to less than 18 years). ... **Safety endpoints:** ... • Changes from baseline in vital signs parameters. • Changes from baseline in safety laboratory parameters.	(irrespective of the indication*, e.g., acetaminophen, which can also be given as antipyretic medication*) during the treatment period within the first 24 hours (EU PDCO) or within the first 12 hours (US FDA) after the first dose of IMP. • Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged *2 years* to less than 18 years old (EU PDCO). • Changes from baseline in pain intensity over *the Treatment Period* using age-appropriate pain scales (Face, Legs, Activity, Cry, Consolability [FLACC] scale for ages birth to less than 6 years or in older children who are not able to report their pain using the other scales, Faces Pain Scale–Revised [FPS-R] for ages 6 years to less than 12 years, and visual analog scale [VAS] for ages 12 years to less than 18 years). ... **Safety endpoints:** ... • Changes from baseline in vital signs parameters. • *Sedation scores using the University of Michigan Sedation Scale.* • Changes from baseline in safety laboratory parameters.
Section 1: Protocol Synopsis – Trial population:	
The trial population will comprise male and female subjects aged from birth to less than 18 years old who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.	The trial population will comprise male and female subjects aged from birth to less than 18 years old who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment *via NCA/PCA*. *Examples of surgeries suitable for this trial include, but are not limited to, spinal fusions, cleft palate repair, Nuss procedures, scoliosis repair, nephrectomy, pyeloplasty, and orthopedic procedures such as club foot repair, leg lengthening, open reduction and internal fixation of long bone fractures. Subjects must remain hospitalized until the End of Treatment Visit.*
Section 1: Protocol Synopsis – Trial population: **Section 9.1: Subject enrollment procedure**	
... The trial enrollment will be initiated in a staggered approach, starting with enrollment of an older age group until pharmacokinetic data are available in younger age groups. Initially, subjects aged ~~6 years~~ to less than 18 years will be recruited. Subjects from ~~2 years old to less than 6 years old, and subsequently from~~ birth to less than 2 years of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups.	... The trial enrollment will be initiated in a staggered approach, starting with enrollment of an older age group until pharmacokinetic data are available in younger age groups. Initially, subjects aged *2 years* to less than 18 years will be recruited. Subjects from birth to less than 2 years of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol Synopsis – Course of the trial:	
... The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may be enrolled in the trial either pre- or post-operatively; a Treatment and Evaluation Period (up to ~~48 hours~~); and a Follow-Up Period (10 days to 14 days after the first dose of IMP).	... The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may 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).
Section 1: Protocol Synopsis – Trial treatments: **Section 10.5.1: Supplemental opioid analgesic medication** **Section 11.1.1: Enrollment Period (Visit 1)**	
... At some time after the surgery, the subject must have been started on NCA/PCA with morphine or hydromorphone, with or without a background infusion, according to the standard of care. The background infusion (if any) must be with a ~~constant~~ low dose infusion of the same opioid as that used for the NCA/PCA, i.e., morphine or hydromorphone.	... At some time after the surgery, the subject must have been started on NCA/PCA with morphine or hydromorphone, with or without a background infusion, according to the standard of care. The background infusion (if any) must be with a low dose infusion of the same opioid as that used for the NCA/PCA, i.e., morphine or hydromorphone.
Section 1: Protocol Synopsis – Trial treatments:	
... When the subject is able to tolerate liquids, meets the inclusion criteria, and does not meet any exclusion criterion, the subject will be allocated/randomized to IMP (tapentadol oral solution or placebo) using an ~~integrated~~ voice/web response system (IVRS/IWRS). Doses of IMP will be given at intervals explained below.	... When the subject is able to tolerate liquids, meets the inclusion criteria, and does not meet any exclusion criterion, the subject will be allocated/randomized to IMP (tapentadol oral solution or placebo) using an *interactive* voice/web response system (IVRS/IWRS). Doses of IMP will be given at intervals explained below.
Section 1: Protocol Synopsis – Trial treatments: **Section 11.1.2.1: Visit 2 - Administration of first dose of investigational medicinal product (Day 1)**	
... The first dose of IMP is given when IMP is available on the ward~~, per investigator judgment~~.	... The first dose of IMP is given when IMP is available on the ward *and the investigator determines it is medically appropriate for the subject to receive the IMP.*
Section 1: Protocol Synopsis – Trial treatments: Investigational medicinal products (dosing regimen table) **Section 10.2.1: Dose, Table 2: Determination of tapentadol dose and oral solution concentration**	
... **Age of subject** ~~6 years~~ to <18 years old Birth to <~~6 years~~ old **Dose for ~~the~~ ~~second~~ 24 hours** Footnote: ~~a) The dosing interval is 4 hours (range ±15 minutes) except if the subject is sleeping: Subjects are required to be woken to take the IMP within 6 hours of~~	... **Age of subject** *2 years* to <18 years old Birth to <*2 years* old **Dose *after the first* 24 hours** Footnote: Footnote *a*) The doses for subjects aged less than *2 years* old *(as determined at the time of allocation to IMP)* will

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~the previous dose.~~ Footnote ~~b~~) The doses for subjects aged less than ~~6 years~~ old will be defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.	be defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.
Section 1: Protocol Synopsis – Trial treatments: Investigational medicinal products **Section 10.2.2: Total dosing time and dosing interval**	
... The dosing interval is 4 hours (range ±15 minutes)~~.Within the first 24 hours after the first dose of IMP, if~~ the subject is sleeping at the time of the scheduled dose they must be woken to take the IMP within a maximum of 6 hours after the previous dose. ~~The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented.~~ After 24 hours, ~~the dosing interval may be lengthened up to a maximum of 10 hours, and the IMP dose may remain the same or may be decreased~~ to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia. Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, or after ~~a maximum of 48~~ hours.	... *The IMP will be administered as an oral solution.* The dosing interval is 4 hours (range ±15 minutes). *The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If* the subject is sleeping at the time of the scheduled dose, they must be woken to take the IMP within a maximum of 6 hours after the previous dose. *The dose of IMP must be taken as soon as possible after the subject is awake*. *The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level.* After 24 hours, *the investigator may decrease the dose of IMP* to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia. Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, or 72 hours *after first IMP administration*.
Section 1: Protocol Synopsis – Concomitant medications/therapies: Allowed prior and concomitant medication **Section 10.6.3: Allowed prior and concomitant medication**	
Unless explicitly ~~forbidden~~, all prior and concomitant medications are allowed. Medications for the treatment of adverse events are allowed according to the investigator's judgment and post-operative standard of care. For example, clinically relevant respiratory depression may be treated with naloxone, and nausea/vomiting can be treated with antiemetics~~. Antiemetics~~ may also be given prophylactically according to the standard of care.	Unless explicitly *prohibited*, all prior and concomitant medications are allowed. *Benzodiazepines may be used to treat muscle spasms or anxiety, consistent with local standard of care. They should be used with caution as they may potentiate central nervous system depression that may occur with tapentadol or other opioids.* Medications for the treatment of adverse events are allowed according to the investigator's judgment and post-operative standard of care. For example, clinically relevant respiratory depression may be treated with naloxone, and nausea/vomiting can be treated with antiemetics*, which* may also be given prophylactically according to the standard of care.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol Synopsis – Concomitant medications/therapies: **Section 10.6.4: Prohibited prior and concomitant medication**	
~~**Forbidden**~~ **medication from ~~28 days~~ before allocation/randomization to IMP until 24 hours after the last administration of IMP** ... • Neuroleptics, anticonvulsants (except for gabapentin used in association with surgery), antiparkinsonian drugs, and serotoninergic drugs ~~such as~~ selective serotonin/norepinephrine reuptake inhibitors ~~and~~ tricyclic antidepressants. ~~**Forbidden**~~ **medication from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP** • Long-acting opioids. ~~**Forbidden**~~ **medication from time of allocation/randomization to IMP until 4 hours after the last administration of IMP** ~~• Medication used for sedation.~~ • Opioids (other than morphine, hydromorphone, or IMP).	***Prohibited*** **medication from *14 days* before allocation/randomization to IMP until 24 hours after the last administration of IMP** ... • Neuroleptics, anticonvulsants (except for gabapentin used in association with surgery), antiparkinsonian drugs, and *all* serotoninergic drugs *including* selective serotonin/norepinephrine reuptake inhibitors*,* tricyclic antidepressants*, linezolid, triptans, and St. John's Wort (hypericum perforatum)*. • *Methadone.* ***Prohibited*** **medication from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP** • Long-acting opioids. • *Medication used for sedation (as noted above, benzodiazepines may be used to treat muscle spasms or anxiety).* ***Prohibited*** **medication from time of allocation/randomization to IMP until 4 hours after the last administration of IMP** • Opioids (other than morphine, hydromorphone, or IMP).
Section 1: Protocol Synopsis – Trial duration: **Section 8: Trial design**	
Each subject is expected to be in the trial for up to about 42 days (up to 28 days for enrollment, ~~2 days of~~ treatment~~,~~ and ~~up to 12 days of~~ follow up). Dosing of IMP will be for ~~a maximum of 48~~ hours.	Each subject is expected to be in the trial for up to about 42 days (up to 28 days for enrollment, *and a* treatment and follow-up *period of up to 14 days*). Dosing of IMP will be for *up to 72* hours.
Section 1: Protocol Synopsis – Sample size rationale:	
The trial enrollment will then complete when the following ~~4~~ criteria are met: ... • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses. Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size ~~(i.e., approximately 168 subjects)~~. ~~• 25 subjects in the age range birth to less than 17 years of age (US FDA) have received tapentadol for at least 48 hours.~~ Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.	The trial enrollment will then complete when the following *3* criteria are met: ... • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses *(US FDA)*. Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size. Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168

Changes to this protocol include:	
Formerly read:	**Now reads:**
	subjects will be treated with IMP in this trial. *An additional objective of the study is to meet a US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age who have been exposed to tapentadol for at least 48 hours. As medically appropriate, every effort will be made to enroll subjects in this trial to meet this objective.*
Section 1: Protocol Synopsis – Blood sampling:	
The total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even when additional blood is drawn for a pharmacokinetic analysis ~~when~~ a serious adverse event occurs).	The total blood volume drawn per subject will not exceed approximately 15 mL *for subjects aged 2 years and older or 2.4 mL/kg for subjects aged less than 2 years* during the trial (even when additional blood is drawn for a pharmacokinetic analysis *if* a serious adverse event occurs).
Section 1: Protocol Synopsis – Key data collected: Demographic data, background data, and other subject characteristics: **Section 12.1.1: Demographic data**	
... (years for subjects aged 2 years and older, months for subjects aged 2 months to less than 2 years, and days for subjects aged less than 2 months – the day of birth is counted as day 1), race/ethnicity, height, and weight…	... (years for subjects aged 2 years and older, months for subjects aged 2 months *[i.e., 60 days]* to less than 2 years, and days for subjects aged less than 2 months *[i.e., less than 60 days]* – the day of birth is counted as day 1), race/ethnicity, height, and weight…
Section 1: Protocol Synopsis – Key data collected: Demographic data, background data, and other subject characteristics:	
... • The trade name, date, time, dose, and route of administration of opioid analgesic medication given post-operatively for pain before the first IMP dose. ~~Recording~~ limited to after surgery, for a period of (maximum) 24 hours before the first IMP dose. ... • The indication, the type of surgical procedure, the date of surgery, the start time and completion time of surgery.	... • The trade name, date, time, dose, and route of administration of opioid and non-opioid analgesic medication given post-operatively for pain before the first IMP dose. *The detailed recording of these medications* is limited to after surgery, for a period of (maximum) 24 hours before the first IMP dose. ... • The indication, the type of surgical procedure, the date of surgery, the start time and completion time of surgery. • *Pain intensity scores (FLACC in subjects from birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R in subjects aged 6 years to less than 12 years old, and VAS in subjects aged 12 years to less than 18 years old) before each NCA/PCA activation, whenever possible, after the first dose of IMP.*
Section 1: Protocol Synopsis – Key data collected: Efficacy:	
... • Trade name, dose, and time of each administration of NCA/PCA supplemental opioid analgesia from first dose of IMP ~~until 4 hours after the last administration of IMP~~. ...	... • Trade name, dose, and time of each administration of NCA/PCA supplemental opioid analgesia from first dose of IMP *up to the End of Treatment Visit*. ...

Changes to this protocol include:	
Formerly read:	**Now reads:**
• Acceptability and palatability of IMP in subjects aged ~~3 years~~ to less than 18 years old. • ~~Patient reported outcome for pain~~ (FLACC in subjects from birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R in subjects aged 6 years to less than 12 years old, and VAS in subjects aged 12 years to less than 18 years old). • The trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication. ~~Recording~~ is limited to after surgery (starting up to 24 hours before first IMP dose) ~~until 4 hours after the last administration of IMP~~.	• Acceptability and palatability of IMP in subjects aged *2 years* to less than 18 years old. • *Pain intensity scores before and after first dose of IMP, before each subsequent dose of IMP, and at the End of Treatment Visit* (FLACC in subjects from birth to less than 6 years or in older children who are not able to report their pain using the other scales, FPS-R in subjects aged 6 years to less than 12 years old, and VAS in subjects aged 12 years to less than 18 years old). • The trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication. *The detailed recording of these medications* is limited to after surgery (starting up to 24 hours before first IMP dose) *up to the End of Treatment Visit*.
Section 1: Protocol Synopsis – Key data collected: Safety: **Section 12.3: Collection of safety data**	
... • C-SSRS score in subjects aged 6 years or older.	... • C-SSRS score in subjects aged 6 years or older. • *University of Michigan Sedation Scale score.*
Section 1: Statistical methods:	
... Treatment effects will be estimated based on least-squares means of the difference. The 95% confidence intervals and p-value will be presented for tapentadol compared with placebo. The test for the primary efficacy analysis will be 2-sided at a 0.05 level of significance. ... Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings will be provided for summarizing safety laboratory parameters, 12-lead ECG, vital signs, and oxygen saturation across treatment group.	... Treatment effects will be estimated based on least-squares means of the difference. The 95% confidence intervals and p-value will be presented for tapentadol compared with placebo. The test for the primary efficacy analysis will be 2-sided at a 0.05 level of significance. *Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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 method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.* ... Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings will be provided for summarizing safety laboratory parameters, 12-lead ECG, vital signs, and oxygen saturation across treatment group. *Descriptive statistics will be provided for the sedation scores.*
Section 1: Protocol synopsis - Statistical methods: **Section 14.2.6.1: Analysis of adverse events**	
... The incidence, type, intensity, onset, ~~duration,~~ relationship, treatment, and outcome of TEAEs will be listed and presented descriptively according to treatment group.	... The incidence, type, intensity, onset, relationship, treatment, and outcome of TEAEs will be listed and presented descriptively according to treatment group.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.2: Schedule of events	
Record demographic data [d]	Record *date of signing the informed consent/assent form, sex, race/ethnicity, and height.*
[Added rows]	*Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight).* [d] *Record age at time of allocation/randomization.* [z] *Record sedation score.*
~~Record details~~ of ~~non-opioid~~ analgesics	*Detailed recording* of analgesics
Record age at time of allocation/randomization Record vital signs Record oxygen saturation	[Cross moved to column to coincide with allocation] [Cross moved to column "After surgery"] [Cross moved to column "After surgery"]
~~Record details~~ of NCA/PCA and background infusion (if any).	*Detailed recording* of NCA/PCA and background infusion (if any) [r] [footnote r moved from cross, added <---> and "no background infusion" to columns first dose after and subsequent doses before and after]
Supplemental opioid analgesic medication by NCA/PCA[t]	[line deleted]
[Added row]	*Record pain intensity before each NCA/PC activation*[u,t].
Section 1.2: Schedule of events: Footnotes	
d) ~~Demographic data to be collected and recorded for this trial includes date of signing the informed consent/assent form, sex, age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months to less than 2 years, and days for subjects aged less than 2 months), race/ethnicity, height, and weight.~~ The body mass index will be calculated automatically. ~~The weight should be measured after surgery if the surgery notably changes the weight of the child.~~	d) The body mass index will be calculated automatically.
h) ~~Excluding anesthetics and medication used during the surgery.~~	h) *Record all medications, including opioid and non-opioid analgesics but excluding anesthetics and medication used during the surgery (Section 12.1.2).*
i) Recording limited to after surgery (starting up to 24 hours before first IMP dose) ~~until 4 hours after the last administration of IMP~~.	i) Recording *of detailed information* is limited to after surgery (starting up to 24 hours before first IMP dose) *up to the End of Treatment Visit (Section 12.1.2.2).*
j) In subjects aged 6 years or older. ~~Any~~ refusal to ~~complete~~ the questionnaire must be recorded with the reason.	j) In subjects aged 6 years or older. *The administration of the C-SSRS "children's baseline" must be performed after surgery. A* refusal to *answer the questions in* the questionnaire *that are appropriate for the subject* must be recorded with the reason. *The initials of the interviewer are to be recorded.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
m) ~~Within 2 hours~~ before allocation/randomization to IMP.	m) *Directly* before allocation/randomization to IMP.
o) Using pulse oximetry. Record values ~~under~~ 92% for at least 60 seconds (excluding technical failures or artifacts).	o) Using pulse oximetry. Record values *below* 92% for at least 60 seconds (excluding technical failures or artifacts).
r) Recording is limited to after surgery, for a period of (maximum) 24 hours before the first IMP dose.	r) Recording *of detailed information* is limited to after surgery *(starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.1). NCA/PCA is with morphine or hydromorphone in accordance with the standard of care at the site. Detailed information on use will be recorded at times consistent with the memory of the NCA/PCA pump. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails.*
s) IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). ~~Within the first 24 hours after the first dose of IMP, if~~ the subject is sleeping at the time of the scheduled dose they must be woken to take the IMP within a maximum of 6 hours after the previous dose. ~~The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented.~~ After 24 hours, ~~the dosing interval may be lengthened up to a maximum of 10 hours, and the IMP dose may remain the same or may be decreased~~ to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia.	s) *The* IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). *The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If* the subject is sleeping at the time of the scheduled dose they must be woken to take the IMP within a maximum of 6 hours after the previous dose. *The dose of IMP must be taken as soon as possible after the subject is awake*. After 24 hours, *the investigator may decrease the dose of IMP* to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia.
~~t) By NCA/PCA with morphine or hydromorphone in accordance with the standard of care at the site. Details of use will be recorded at times consistent with the memory of the NCA/PCA pump from first dose of IMP until 4 hours after the last administration of IMP. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails.~~	t) Footnote deleted and merged with footnote r. New footnote inserted *t) Pain intensity scores should be obtained before each each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.*
v) Between 30 minutes and 60 minutes after IMP~~, for which the subject may be woken if necessary~~.	v) Between 30 minutes and 60 minutes after IMP. *Subjects do not need to be woken for this assessment*.
w) In subjects aged ~~3 years~~ to less than 18 years old.	w) In subjects aged *2 years* to less than 18 years old.
[New footnote]	*z) Years for subjects aged 2 years and older, months for subjects aged 2 months (i.e., 60 days) to less than 2 years, and days for subjects aged less than 2 months (i.e., less than 60 days).*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.3.1: Inclusion criteria **Section 9.2.1: Inclusion criteria**	
5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after allocation/randomization to IMP.	5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after allocation/randomization to IMP. *Subjects must remain hospitalized until the End of Treatment Visit*.
Section 1.3.2: Exclusion criteria **Section 9.2.2: Exclusion criteria**	
... 10. Subject is not able to understand and comply with the protocol as appropriate for the age of the subject. ... 12. Subject is taking ~~forbidden~~ concomitant medication. ... 14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject is excluded if the: ... • Glomerular filtration rate <60 mL/min (calculated according to ~~a formula that is appropriate for the respective age group~~). ... [New criteria]	... 10. Subject is not able to understand and comply with the protocol as appropriate for the age of the subject *or subject is cognitively impaired in the investigator's judgment such that they cannot comply with the protocol*. ... 12. Subject is taking *prohibited* concomitant medication. ... 14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject is excluded if the: ... • Glomerular filtration rate <60 mL/min (calculated according to *Schwartz et al. 1984*). ... *18. Female subject is breast-feeding a child.*
Section 3: Abbreviations and definition of terms – Definition of terms	
Abbreviations IVRS/IWRS: ~~Integrated~~ voice/web response system **Definition of terms** Treatment completers: ~~Treatment completers are treated subjects who completed all doses of scheduled IMP administration according to the protocol~~. Trial completers: ~~Treated subjects~~ who have completed the ~~trial according to the protocol~~.	**Abbreviations** IVRS/IWRS: *Interactive* voice/web response system **Definition of terms** Treatment *period* completers: *Two sets of treatment period completers will be defined for subjects in accordance with the time points of the primary endpoint, i.e., 12 hours and 24 hours.* *Treatment period completers are defined for each of these sets as subjects who do not discontinue the treatment period before 12 hours and 24 hours, respectively.* Trial completers: *Trial completers are defined as treatment period completers* who have completed the *Follow-up Visit*. *For purposes of compliance with a US FDA request, completers beyond 24 hours and up to 72 hours will be tracked and data reported.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 4.2: Subject information and informed consent	
... As the inclusion of exclusively minors is foreseen for this trial, the subject has to be informed about the trial taking into consideration the age of the subject using an appropriate information sheet for the age of the subject and thorough explanation by qualified staff. The opinion of the minor has to be taken into account when deciding about participation in the trial.	... As the inclusion of exclusively minors is foreseen for this trial, the subject has to be informed about the trial taking into consideration the age of the subject using an appropriate information sheet for the age of the subject and thorough explanation by qualified staff. The opinion of the minor has to be taken into account when deciding about participation in the trial*, and an assent form signed as appropriate/applicable for the age of the subject*.
Section 6.2: Relevant non-clinical and clinical data	
Effects in humans Tapentadol has been given to adults as an oral solution, intravenous solution, immediate-release (IR) tablets or capsules, and as prolonged-release (PR) tablets (including a tamper resistant formulation [TRF]). To date, tapentadol has been administered to children aged ~~3 years~~ to less than 18 years in the pediatric clinical program. The oral solution has been given to these children as a single dose in ~~a~~ pharmacokinetic ~~trial~~. ... **Pharmacokinetics in children** A population pharmacokinetic model was developed by means of the non-linear mixed effect approach using the data available from 2 single-dose pharmacokinetic trials in children aged ~~6 years~~ to less than 18 years (KF5503/68 and KF5503/59). A 1 compartment model was found to describe the data adequately. The pharmacokinetic parameters of the allometrically scaled base model were as follows: CL/F = ~~189 L.h^{-1}~~, V/F = ~~783 L~~ (the CL/F and V/F are typical estimates for a subject with a body weight of ~~50 kg~~), first order absorption rate constant (Ka) = ~~2.14 h^{-1}~~, time delay between drug administration and beginning of absorption (TLAG) = 0.247 h. The modeled pharmacokinetic parameters in children aged ~~6 years~~ to less than 18 years old are in line with the corresponding modeled pharmacokinetic parameters in adults. The coefficients of weight on CL/F and V/F were estimated to be ~~0.495~~ and ~~0.726~~, respectively. The inter-individual variabilities on CL/F, V/F, and Ka were ~~20.1%~~, ~~10.2%~~, and ~~126.88%~~, respectively. ... **Safety in Phase II trials in children (tapentadol oral solution)** ~~To date, in~~ a single dose trial (KF5503/68) of ~~52~~ children ~~having undergone~~ dental, ear, nose, or throat surgery, there ~~have been~~ no deaths. There was 1 serious adverse event (post-operative bleeding after a tonsillectomy), and	**Effects in humans** Tapentadol has been given to adults as an oral solution, intravenous solution, immediate-release (IR) tablets or capsules, and as prolonged-release (PR) tablets (including a tamper resistant formulation [TRF]). To date, tapentadol has been administered to children aged *2 years* to less than 18 years in the pediatric clinical program. The oral solution has been given to these children as a single dose in *2* pharmacokinetic *trials (KF5503/68 and KF5503/59)*. ... **Pharmacokinetics in children** A population pharmacokinetic model was developed by means of the non-linear mixed effect approach using the data available from 2 single-dose pharmacokinetic trials in children aged *2 years* to less than 18 years (KF5503/68 and KF5503/59). A 1 compartment model was found to describe the data adequately. The pharmacokinetic parameters of the allometrically scaled base model were as follows: CL/F = *172 L.h^{-1}*, V/F = *677 L* (the CL/F and V/F are typical estimates for a subject with a body weight of *45 kg*), first order absorption rate constant (Ka) = *2.01 h^{-1}*, time delay between drug administration and beginning of absorption (TLAG) = 0.247 h. The modeled pharmacokinetic parameters in children aged *2 years* to less than 18 years old are in line with the corresponding modeled pharmacokinetic parameters in adults. The coefficients of weight on CL/F and V/F were estimated to be *0.635* and *0.853*, respectively. The inter-individual variabilities on CL/F, V/F, and Ka were *22.4%*, *17.3%*, and *145.3%*, respectively. ... **Safety in Phase II trials in children (tapentadol oral solution)** *In* a single dose trial (KF5503/68) of *66* children *undergoing* dental, ear, nose, or throat surgery, there *were* no deaths. There was 1 serious adverse event (post-

Changes to this protocol include:	
Formerly read:	**Now reads:**
6 subjects were discontinued due to an adverse event (vomiting, which was also considered a stopping criteria). ... **Safety experience from post-marketing data in adults** The total cumulative post-authorization patient exposure to tapentadol ~~IR and tapentadol PR~~ since the first launch in Jul 2008 up to ~~Apr 2013~~ was ~~95 068 714~~ patient treatment days with an estimated average daily dose of 280 mg. In the time period from first launch to ~~23 Apr 2013~~, ~~4118~~ spontaneous, medically confirmed individual *case safety reports (i.e., the physician confirmed the diagnosis)* were received, reporting tapentadol either as the suspect, co-suspect, or suspect-interacting drug. Among the ~~4118 cases~~, there were ~~73 cases~~ with a fatal outcome, ~~1265~~ serious nonfatal cases, and ~~2780~~ not serious cases. Age was reported in ~~1893 cases~~ and ranged from ~~1 year~~ to ~~96 years~~. The cases involved ~~1982 female~~ patients and ~~1247 male~~ patients (the sex was not reported or was reported as unknown in ~~889 cases~~). Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, headache, hallucination, and vomiting.	operative bleeding 6 days after a tonsillectomy), and 6 subjects were discontinued due to an adverse event (vomiting, which was also considered a stopping criteria). ... **Safety experience from post-marketing data in adults** The total cumulative post-authorization patient exposure to tapentadol *(IR and PR)* since the first launch in Jul 2008 up to *20 May 2014* was *142 923 321* patient treatment days with an estimated average daily dose *for tapentadol IR* of 280 mg. In the time period from first launch to *20 May 2014*, *5286* spontaneous, medically confirmed *cases* were received, reporting tapentadol either as the suspect, co-suspect, or suspect-interacting drug. Among the *5286 cases*, there were *85 cases* with a fatal outcome, *1607* serious nonfatal cases, and *3594* not serious cases. Age was reported in *2465 cases* and ranged from *<1 year* to *100 years*. The cases involved *2552 female* patients and *1557 male* patients (the sex was not reported or was reported as unknown in *1177 cases*). Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, headache, hallucination, and vomiting.
Section 8.2: Trial rationale	
Overall, there should be no difference in the intensity of pain measured between the 2 treatment groups. Hence, the opioid sparing effect (i.e., lower expected use of supplemental opioid analgesic in the tapentadol treatment group than in the placebo-treated group) can ~~thus~~ be considered a surrogate for more direct measures of analgesia, such as changes in pain intensity. The use of NCA/PCA will allow subjects on placebo to receive ~~standard of care~~.	Overall, there should be no difference in the intensity of pain measured between the 2 treatment groups. Hence, the opioid sparing effect (i.e., lower expected use of supplemental opioid analgesic in the tapentadol treatment group than in the placebo-treated group) can be considered a surrogate for more direct measures of analgesia, such as changes in pain intensity. The use of NCA/PCA will allow subjects on placebo to receive *analgesia*.
Section 8.4: Discussion of the trial design	
Choice of population and sites The age ranges selected for the trial conform to the requirements for development of medicines in children (see Section 8.3). The types of surgery allowed are restricted to those that are expected to produce pain severe enough to require opioid analgesic treatment.	**Choice of population and sites** The age ranges selected for the trial conform to the requirements for development of medicines in children (see Section 8.3). The types of surgery allowed are restricted to those that are expected to produce pain severe enough to require opioid analgesic treatment *via NCA/PCA*. *Examples of surgeries suitable for this trial include, but are not limited to, spinal fusions, cleft palate repair, Nuss procedures, scoliosis repair, nephrectomy, pyeloplasty, and orthopedic procedures such as club foot repair, leg lengthening, open reduction and internal fixation of long bone fractures. Subjects must remain hospitalized until the End of Treatment Visit.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Comparator and use of NCA/PCA ... Hence, due to the use of NCA/PCA as per usual routine, children ~~will~~ not be subjected to more pain than they would otherwise experience in the selected post-operative setting. ... A subject will be discontinued from the trial if ~~there is~~ pain not controlled by the NCA/PCA pump requiring treatments other than those defined in the protocol.	**Comparator and use of NCA/PCA** ... Hence, due to the use of NCA/PCA as per usual routine, children *should* not be subjected to more pain than they would otherwise experience in the selected post-operative setting. ... A subject will be discontinued from the trial if *their* pain *is* not controlled by the NCA/PCA pump, requiring treatments other than those defined in the protocol.
Dosing ... Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for tapentadol oral solution. The data from 2 dedicated single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R33133PAI2005]) were used for the population pharmacokinetic model and served as a basis for dose selection in the current trial for children aged ~~6 years~~ to less than 18 years old. ~~The doses for children 2 years to less than 6 years of age are still to be predicted, but will be based on further data accruing from these trials.~~ The doses for children aged from birth to 2 years will be predicted from additional pharmacokinetic sampling in children of the same age group. Simulations were performed to identify tapentadol doses that would produce total exposures (i.e., serum AUC for tapentadol) in pediatric subjects that are similar to those reported in adults. The approved adult therapeutic dose range that is generally associated with efficacy and good tolerability in adults, 50 mg to 100 mg, was used for comparison. These simulations showed that tapentadol doses of 1.25 mg/kg every 4 hours in subjects aged ~~6 years~~ to less than 18 years old are expected to produce exposures similar to those after administration of 50 mg to 100 mg every 4 hours, given as an immediate-release formulation in adults. The median steady state simulated AUCs after a 50 mg, 75 mg, and 100 mg dose in adults are 217 ng.h/mL, 325 ng.h/mL, and 433 ng.h/mL, respectively. In comparison, the median simulated steady state AUC in subjects aged ~~6 years~~ to 17 years old receiving 1.25 mg/kg is ~~318 ng.h/mL~~. Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged ~~6 years~~ to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the	**Dosing** ... Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for tapentadol oral solution. The data from 2 dedicated single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R33133PAI2005]) were used for the population pharmacokinetic model and served as a basis for dose selection in the current trial for children aged *2 years* to less than 18 years old. The doses for children aged from birth to *less than* 2 years will be predicted from additional pharmacokinetic sampling in children of the same age group. Simulations were performed to identify tapentadol doses that would produce total exposures (i.e., serum AUC for tapentadol) in pediatric subjects that are similar to those reported in adults. The approved adult therapeutic dose range that is generally associated with efficacy and good tolerability in adults, 50 mg to 100 mg, was used for comparison. These simulations showed that tapentadol doses of 1.25 mg/kg every 4 hours in subjects aged *2 years* to less than 18 years old are expected to produce exposures similar to those after administration of 50 mg to 100 mg every 4 hours, given as an immediate-release formulation in adults. The median steady state simulated AUCs after a 50 mg, 75 mg, and 100 mg dose in adults are 217 ng.h/mL, 325 ng.h/mL, and 433 ng.h/mL, respectively. In comparison, the median simulated steady state AUC in subjects aged *2 years* to 17 years old receiving 1.25 mg/kg is *306 ng.h/mL*. Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged *2 years* to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on *the investigator's judgment of* the effectiveness of the analgesia and the adverse event profile observed in each

Changes to this protocol include:	
Formerly read:	**Now reads:**
effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. The doses for subjects aged less than ~~6 years~~ old will be defined based on forthcoming pharmacokinetic data. Subjects less than ~~6 years~~ old will not be recruited into the trial until the dose has been defined for them.	child over the first 24 hour dosing period. The doses for subjects aged less than *2 years* old will be defined based on forthcoming pharmacokinetic data. Subjects less than *2 years* old will not be recruited into the trial until the dose has been defined for them.
Pain measurements To measure pain intensity, 3 pain intensity scales will be used to cover the different age-related abilities to report pain. These assessments are discussed in Section 12.4.	**Pain measurements** To measure pain intensity, 3 pain intensity scales will be used to cover the different age-related abilities to report pain. These assessments are discussed in Section 12.4. *In addition, the investigator/delegate or subject will record a pain intensity score prior to each NCA/PCA activation, whenever possible (as requested by the US FDA). Pain intensity data collected for this purpose, i.e., directly before each NCA/PCA activation, will be used only for the purpose of exploratory descriptive analysis.*
Blood sampling The total withdrawn blood volume in this trial will not exceed ~~approximately 15 mL (even when additional blood is drawn for a pharmacokinetic analysis when a serious adverse event occurs), i.e., well within~~ the maximum safe blood loss that is recommended in a pediatric population (e.g., EMEA ad hoc working party 2008).	**Blood sampling** The total withdrawn blood volume in this trial *is given in Section 11.7, and this* will not exceed the maximum safe blood loss that is recommended in a pediatric population (e.g., EMEA ad hoc working party 2008).
Section 8.5: Benefit/risk analysis	
Safety - background procedures All subjects will undergo a surgical procedure. The surgical procedure and anesthesia have inherent risks. However, these surgical procedures and the need for opioid treatment ~~would be~~ independent of participation in this trial.	Safety - background procedures All subjects will undergo a surgical procedure. The surgical procedure and anesthesia have inherent risks. However, these surgical procedures and the need for opioid treatment *are* independent of participation in this trial.
Safety - selection of sites The chosen investigative trial sites and the investigators will have experience in pediatric surgery and the trial sites will be properly prepared to conduct a clinical trial. The trial site staff will be trained in the use of the scales and instruments included in this trial to ensure that trial procedures and evaluations are carried out according to GCP, and in accordance with standard medical practice.	Safety - selection of sites The chosen investigative trial sites and the investigators will have experience in *the care of patients following* pediatric surgery and the trial sites will be properly prepared to conduct a clinical trial. The trial site staff will be trained in the use of the scales and instruments included in this trial to ensure that trial procedures and evaluations are carried out according to GCP, and in accordance with standard medical practice.
Section 9.3.1: Reasons for discontinuation of a subject	
The investigator must discontinue subjects from the trial for the compulsory reasons given in Table 1. If the reason is given as optional, then the investigator may decide to stop the participation of the subject in the trial if the benefit/risk ratio is not favorable for the continued participation of the subject.	The investigator must discontinue subjects from the trial for the compulsory reasons given in Table 1. If the reason is given as optional, then the investigator may decide to stop the participation of the subject in the trial if the benefit/risk ratio is not favorable for the continued participation of the subject. *The evaluation of optional reasons for discontinuation must be documented by the*

Changes to this protocol include:	
Formerly read:	**Now reads:**
... Table 1: Protocol deviation. The subject is taking ~~forbidden~~ medication (see Section 10.6.4). ... ~~A subject will be discontinued from IMP if they have not had a dose of IMP for 10 hours.~~ Further trial procedures should be performed as scheduled including Visit 3 (End of Treatment Visit) and Visit 4 (Follow-up Visit).	*investigator in the CRF.* ... Table 1: Protocol deviation. The subject is taking *prohibited* medication (see Section 10.6.4). ... Further trial procedures should be performed as scheduled including Visit 3 (End of Treatment Visit) and Visit 4 (Follow-up Visit).
Section 9.3.2: Procedure for the handling of prematurely discontinued subjects	
The investigator must inform the sponsor within 24 hours about any discontinuation of a subject ~~and must document any discontinuation of a subject~~. ... All efforts should be made to collect ~~more~~ data from subjects who are discontinued because of clinically relevant changes in liver parameters so that a valid causality assessment can be made.	The investigator must inform the sponsor within 24 hours about any discontinuation of a subject. ... All efforts should be made to collect data from subjects who are discontinued because of clinically relevant changes in liver parameters so that a valid causality assessment can be made.
Section 9.3.3: Premature termination or suspension of the trial	
... The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigator(s), the relevant IEC/IRB, the regulatory authorities, the sponsor/the sponsor's authorized delegate, ~~or~~ the DMC, as applicable).	... The party prematurely terminating or suspending the trial must promptly inform all other parties (i.e., the principal investigator(s), the relevant IEC/IRB, the regulatory authorities, the sponsor/the sponsor's authorized delegate, *and* the DMC, as applicable).
Section 9.3.3.1: Criteria to terminate or suspend the whole trial	
... A risk benefit committee organized by the operational lead will convene to decide on further action, which could include immediate stopping of the trial.	... A risk benefit committee organized *jointly* by the operational lead *and sponsor's steering committee* will convene to decide on further action, which could include immediate stopping of the trial.
Section 10: Treatments	
10.6 Allowed and ~~forbidden~~ prior/concomitant medications. 10.6.4 ~~Forbidden~~ prior and concomitant medication	10.6 Allowed and *prohibited* prior/concomitant medications. 10.6.4 *Prohibited* prior and concomitant medication
Section 10.2.1: Dose	
...	... *Volumes of 1 mL or less will be given using a 1 mL syringe with 0.05 mL graduations. Volumes of more than 1 mL will be given using a 5 mL syringe with 0.1 mL graduations.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.3: Method of assigning subjects to treatment groups (allocation/randomization)	
... Randomization numbers will be allocated in ascending order ~~according to age group, starting with the oldest age group and progressing to the next younger age group~~.	... Randomization numbers will be allocated in ascending order *within each age group, and by ascending age group*.
Section 10.4.1: Methods of blinding	
Randomization and blinding will be done in accordance with the ~~sponsor's~~ standard operating procedures (SOPs).	Randomization and blinding will be done in accordance with the *operational lead's* standard operating procedures (SOPs).
Section 10.4.2: Methods of unblinding	
The investigator, the responsible department of the ~~sponsor~~, and the responsible drug safety department and contract research organization will receive appropriate methods for unblinding of single cases, i.e., IVRS/IWRS ~~access to unblinding functionality~~. Personnel in the ~~sponsor's~~ departments of clinical trials supply will be unblinded during the trial according to the ~~sponsor's~~ SOPs for randomization and unblinding during the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after database lock at the end of the trial. Unblinding will be initiated by the ~~sponsor's~~ department of biostatistics according to the ~~sponsor's~~ SOPs for randomization and unblinding.	The investigator, the responsible department of the *operational lead*, and the responsible drug safety department and contract research organization will receive appropriate methods for unblinding of single cases, i.e., *via the* IVRS/IWRS. Personnel in the *operational lead's* departments of clinical trials supply will be unblinded during the trial according to the *operational lead's* SOPs for randomization and unblinding during the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after database lock at the end of the trial. Unblinding will be initiated by the *operational lead's* department of biostatistics according to the *operational lead's* SOPs for randomization and unblinding.
Section 10.5.1: Supplemental opioid analgesic medication	
... After the first dose of IMP (see ~~table below~~), NCA/PCA will be 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.	... After the first dose of IMP (see *Table 2*), NCA/PCA will be 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.
Section 10.6.2: Concomitant medications	
If, in the interests of the subject's safety, the administration of ~~forbidden~~ concomitant medications is required, the sponsor should be informed in advance (or promptly after the instance).	If, in the interests of the subject's safety, the administration of *prohibited* concomitant medications is required, the sponsor should be informed in advance (or promptly after the instance).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.1: Course of the trial	
The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may be enrolled in the trial either pre- or post-operatively; a Treatment and Evaluation Period (up to ~~48 hours~~); and a Follow-Up Period (10 days to 14 days after the first dose of IMP).	The trial consists of an Enrollment Period starting up to 28 days before allocation/randomization to IMP and lasting up to the time of allocation/randomization to IMP, whereby subjects may 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).
Section 11.1.1: Enrollment Period (Visit 1)	
The following evaluations will be performed during this period: ... • Record ~~demographic data:~~ date of signing the informed consent/assent form, sex, ~~age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months to less than 2 years, and days for subjects aged less than 2 months – the day of birth is counted as day 1),~~ race/ethnicity, height~~, and weight~~. ~~The BMI will be calculated automatically.~~ The data may be extracted from the hospital charts if already available according to the standard of care. ~~The weight should be measured after surgery if the surgery notably changes the weight of the child.~~ ... • Complete the C-SSRS "children's baseline" questionnaire if the subject is aged 6 years or older. ~~Any~~ refusal to ~~complete~~ the questionnaire must be recorded with the reason. ~~This~~ must be performed after surgery. ... • Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) ~~within 2 hours~~ before allocation/randomization to IMP. • Record oxygen saturation ~~within 2 hours~~ before allocation/randomization to IMP. ... [New]	The following evaluations will be performed during this period: ... • Record date of signing the informed consent/assent form, sex, race/ethnicity, *and* height. The data may be extracted from the hospital charts if already available according to the standard of care. • *Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight). The BMI will be calculated automatically.* ... • Complete the C-SSRS "children's baseline" questionnaire if the subject is aged 6 years or older. *The C-SSRS will be explained and shown to the parents/legal guardian at the time of the informed consent procedure*. *The administration of the C-SSRS* must be performed after surgery. *A* refusal to *answer the questions in* the questionnaire *that are appropriate for the subject* must be recorded with the reason. *Referrals to mental health professionals will be made as determined by the investigator. Record the initials of the interviewer.* ... • Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) *after surgery directly* before allocation/randomization to IMP. • Record oxygen saturation *after surgery directly* before allocation/randomization to IMP. ... • *Record age at time of allocation/randomization (years for subjects aged 2 years and older, months for subjects aged 2 months (i.e., 60 days) to less than 2 years, and days for subjects aged less than 2 months (i.e., less than 60 days) – the day of birth is counted as day 1).*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.1.2.1: Visit 2	
Before first dose of investigational medicinal product • Record the following details about opioid analgesic medication ... − The times of starting and stopping the background infusion. • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject ~~after surgery (starting up to 24 hours before first IMP dose)~~. ... • Record the following directly before (i.e., within 10 minutes) administration of IMP: − Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate). ... Record values ~~under~~ 92% for at least 60 seconds (excluding technical failures or artifacts).	**Before first dose of investigational medicinal product** • Record the following details about opioid analgesic medication ... − The times of starting and stopping the background infusion. *− The lockout time.* • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of *opioid and* non-opioid analgesic medication given to the subject *for the time period indicated in the schedule of events for analgesic medication (Section 1.2).* ... • Record the following directly before (i.e., within 10 minutes) administration of IMP: − Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate). *− Sedation score (see Section 12.3.10).* ... Record values *below* 92% for at least 60 seconds (excluding technical failures or artifacts).
Administration of first dose of investigational medicinal product (Day 1) Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, or after ~~a maximum of 48~~ hours.	**Administration of first dose of investigational medicinal product (Day 1)** *The subject will only receive IMP if the SpO_2 does not drop below 92% for a period of ≥60 seconds in the 10 minutes before IMP administration.* Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, or after *72* hours *after first IMP administration*.
After the first dose of investigational medicinal product ... • Administer supplemental opioid analgesic medication as required (by NCA/PCA, see Section 10.5.1). Record the following at times consistent with the memory of the NCA/PCA pump ~~from first dose of IMP until 4 hours after the last administration of IMP~~: ... − The doses of each administration. …	**After the first dose of investigational medicinal product** ... • Administer supplemental opioid analgesic medication as required (by NCA/PCA, see Section 10.5.1). Record the following at times consistent with the memory of the NCA/PCA pump *for the time period indicated in the schedule of events (Section 1.2)*: ... − The doses of each administration. *− The lockout time.* … *• Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.* • Record pain intensity within 30 minutes to 60 minutes

Changes to this protocol include:	
Formerly read:	**Now reads:**
• Record pain intensity within 30 minutes to 60 minutes after the first dose of IMP only (see Section 12.2.5)~~, for which the subject may be woken if necessary~~. … • Record the palatability and acceptability of the oral solution after the first dose of IMP in subjects aged ~~3 years~~ to less than 18 years old. ... • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject ~~until 4 hours after the last administration of IMP~~.	after the first dose of IMP only (see Section 12.2.5). *Subjects do not need to be woken for this assessment*. … • Record the palatability and acceptability of the oral solution after the first dose of IMP in subjects aged *2 years* to less than 18 years old. ... • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events (Section 1.2). *The same details of any additional opioid medication used inadvertently must be collected.*
Before subsequent doses of investigational medicinal product ... • Record the following directly before (i.e., within 10 minutes) administration of IMP: ... • Record the following details about the use of supplemental opioid analgesic medication (by NCA/PCA) at times consistent with the memory of the NCA/PCA pump ~~from first dose of IMP until 4 hours after the last administration of IMP~~: … − The doses of each administration. … • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject ~~until 4 hours after the last administration of IMP~~.	**Before subsequent doses of investigational medicinal product** *The subject will only receive IMP if the SpO_2 does not drop below 92% for a period of ≥60 seconds in the 10 minutes before IMP administration.* ... • Record the following directly before (i.e., within 10 minutes) administration of IMP: − *Sedation score (see Section 12.3.10).* ... • Record the following details about the use of supplemental opioid analgesic medication (by NCA/PCA) at times consistent with the memory of the NCA/PCA pump *for the time period indicated in the schedule of events (Section 1.2)*: … − The doses of each administration. − *The lockout time.* … • *Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.* … • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject for the time period indicated in the schedule of events (Section 1.2). *The same details of any additional opioid medication used inadvertently must be collected.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.1.2.3: Visit 3 (End of Treatment Visit)	
... • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject ~~until 4 hours after the last administration of IMP~~. ... • Complete the C-SSRS questionnaire "children's since last visit" if the subject is aged 6 years or older. ~~Any~~ refusal to ~~complete~~ the questionnaire must be recorded with the reason. ... • Record pain intensity (see Section 12.2.5). • Record the palatability and acceptability of the oral solution in subjects aged ~~3 years~~ to less than 18 years old.	... • Record the trade name, date, time, dose, dose unit, formulation, and route of administration of non-opioid analgesic medication given to the subject *for the time period indicated in the schedule of events (Section 1.2). The same details of any additional opioid medication used inadvertently must be collected.* ... • Complete the C-SSRS questionnaire "children's since last visit" if the subject is aged 6 years or older. *A* refusal to *answer the questions in* the questionnaire *that are appropriate for the subject* must be recorded with the reason*. Record the initials of the interviewer.* ... • Record pain intensity (see Section 12.2.5). *Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.* • Record the palatability and acceptability of the oral solution in subjects aged *2 years* to less than 18 years old.
Section 11.7: Overview of blood sampling in this trial	
... ~~The approximate amount of blood drawn for this trial is given in Table 3.~~ Repeat or unscheduled samples may be taken for safety reasons. For details of steps taken to reduce the risk to the subjects regarding blood sampling, please see Section 8.5. Table 3: Approximate volume of blood to be collected from each subject The total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even ~~when~~ additional blood is drawn for a pharmacokinetic analysis ~~when~~ a serious adverse event occurs) (Table 3)~~, therefore~~ subjects who participate in the trial will not exceed the recommended limits for blood drawn (Section 8.4).	... Repeat or unscheduled samples may be taken for safety reasons. For details of steps taken to reduce the risk to the subjects regarding blood sampling, please see Section 8.5. *For subjects aged 2 years and older, the approximate amount of blood drawn for this trial is given in Table 3.* Table 3: Approximate volume of blood to be collected from each subject *aged 2 years and older* *For subjects aged 2 years and older,* the total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even *if* additional blood is drawn for a pharmacokinetic analysis *if* a serious adverse event occurs) (Table 3). *For subjects aged less than 2 years old, blood sampling for clinical chemistry and hematology should be performed such that blood volumes taken do not exceed 0.8 mL/kg body weight for each sampling time point, and 2.4 mL/kg in total* (*EMEA ad hoc working party 2008*). *The volume of blood drawn from* subjects who participate in the trial will not exceed the recommended limits (Section 8.4).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.1.2: Prior and concomitant medications	
... Section 12.1.2.1 Opioid analgesic medication given by NCA/PCA and background infusion ~~before first dose of investigational medicinal product~~	... Section 12.1.2.1: Opioid analgesic medication given by NCA/PCA and background infusion
Section 12.1.2.1: Opioid analgesic medication given by NCA/PCA and background infusion	
The following details about opioid analgesic medication given by NCA/PCA and by background infusion (if any) after surgery will be recorded. The recording is ~~for a maximum of 24 hours before the first IMP dose~~: • The trade names of the opioid analgesic medications used. ... • The times of starting and stopping the background infusion.	The following details about opioid analgesic medication given by NCA/PCA and by background infusion (if any) after surgery will be recorded. The recording is *from up to 24 hours before first dose of IMP until the End of Treatment Visit*: • The trade names of the opioid analgesic medications used. ... • The times of starting and stopping the background infusion. • *The lockout time.* *See Section 12.1.3 for medication used outside of this timeframe.*
Section 12.1.2.2: Detailed information for other analgesic (opioid and non-opioid) medication [New section]	
...	*The trade name, date, time, dose, dose unit, formulation, and route of administration of analgesic medication will be recorded, irrespective of the indication. The detailed recording of these medications is limited to after surgery (starting up to 24 hours before first IMP dose) until the End of Treatment Visit, as indicated in the schedule of events (see Section 1.2).* *See Section 12.1.3 for medication used outside of this timeframe.*
Section 12.1.3: Prior and concomitant therapies	
All therapies used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded.	All therapies*, excluding anesthetics and medication used during the surgery,* used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded.
Section 12.1.6: Other data	
The times of starting and stopping the continuous monitoring of pulse oximetry, respiration rate, and heart rate will be recorded. If the IMP is given via a nasogastric tube, this will be documented.	The times of starting and stopping the continuous monitoring of pulse oximetry, respiration rate, and heart rate will be recorded. If the IMP is given via a nasogastric tube, this will be documented. *Pain intensity scores (see Section 12.2.5 for a description of the pain intensity scales) will be collected before each NCA/PCA activation, whenever possible.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.2.1: Amount of supplemental opioid used	
The details of the supplemental opioid analgesic medication used will be recorded at times consistent with the memory of the NCA/PCA pump from the first dose of IMP ~~until 4 hours after the last administration of IMP~~ as indicated in the schedule of events (see Section 1.2). ~~The following details will be recorded:~~ ~~• The trade names of the supplemental opioid analgesic medications used.~~ ~~• The doses of each administration.~~ ~~• The times of each administration.~~ Details of intravenous morphine or hydromorphone used if the NCA/PCA line fails will also be recorded.	The details of the supplemental opioid analgesic medication used *(see Section 12.1.2.1)* will be recorded at times consistent with the memory of the NCA/PCA pump from the first dose of IMP, as indicated in the schedule of events (see Section 1.2). Details of intravenous morphine or hydromorphone used if the NCA/PCA line fails will also be recorded.
Section 12.2.2: Amount of non-opioid analgesic medication used	
~~The trade name, date, time, dose, dose unit, formulation, and route~~ of administration of non-opioid analgesic medication will be recorded, irrespective of the indication. ~~Recording is limited to after surgery (starting up to 24 hours before first IMP dose) until 4 hours after the last administration of IMP, as indicated in the schedule of events (see Section 1.2).~~	*Detail* of *the* administration of non-opioid analgesic medication will be recorded *as given in Section 12.1.2.2,* irrespective of the indication.
Section 12.2.3.2: Clinical Global Impression of Change	
The CGIC (Schneider et al. 1997) was chosen as a complementary assessment of analgesic efficacy.	The CGIC (Schneider et al. 1997) was chosen as a complementary assessment of analgesic efficacy. *Inter-rater reliability will be assessed for the CGIC as part of site training.*
Section 12.2.4: Palatability and acceptability of IMP	
Responses for palatability and acceptability will be evaluated in subjects aged ~~3 years~~ to less than 18 years old on 5-point hedonic scales in combination with a verbal rating and documented (Guinard 2001), unless the subject is administered the IMP by a nasogastric tube.	Responses for palatability and acceptability will be evaluated in subjects aged *2 years* to less than 18 years old on 5-point hedonic scales in combination with a verbal rating and documented (Guinard 2001), unless the subject is administered the IMP by a nasogastric tube.
Section 12.2.5.1: Face, Legs, Activity, Cry, and Consolability scale	
... The investigator will record the results of these measurements in the subject's ~~medical file~~ before recording the data.	... The investigator will record the results of these measurements in the subject's *questionnaire* before recording the data *in the CRF. The total score will not be captured by the CRF but will be calculated during the analysis of the trial. Inter-rater reliability will be evaluated for the FLACC as part of site training.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.3.2: Safety laboratory	
White blood cell (WBC) count with differential count ~~if abnormal~~ Lipase **Clinical chemistry and hematology – central laboratory** ... The creatinine clearance (CL_{CR}) will be calculated ~~using a central laboratory standard age appropriate formula~~.	[table of parameters moved to here] White blood cell (WBC) count with differential count Lipase *(not required for the local laboratory assessment)* **Clinical chemistry and hematology – central laboratory** ... The creatinine clearance (CL_{CR}) will be calculated *according to Schwartz et al. 1984*. *If the red or white blood cell analyses are clinically relevantly abnormal, the red or white cell morphologies must be reported, respectively.*
Section 12.3.4: Twelve-lead electrocardiogram	
Twelve-lead ECGs will be recorded after surgery prior to allocation/randomization to IMP and at End of Treatment. The measured ECG intervals will be RR, PR, QRS, and QT; the corrected [Fridericia] QTcF will be calculated. ~~Cardiologists at a central ECG laboratory will read all 12-lead ECGs.~~ The investigator will review the 12-lead ECG for clinically relevant abnormalities prior to dosing subjects. ~~Specific 12-lead ECG procedures will be provided in a separate manual.~~ The investigator will document all abnormal 12-lead ECG results, with a judgment whether the abnormality is clinically relevant.	Twelve-lead ECGs will be recorded after surgery prior to allocation/randomization to IMP and at End of Treatment. The measured ECG intervals will be RR, PR, QRS, and QT; the corrected [Fridericia] QTcF will be calculated. The investigator will review the 12-lead ECG for clinically relevant abnormalities prior to dosing subjects. The investigator will document all abnormal 12-lead ECG results, with a judgment whether the abnormality is clinically relevant.
Section 12.3.5: Vital signs (respiratory rate, systolic and diastolic blood pressure, and heart rate) and oxygen saturation	
Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) and oxygen saturation (by pulse oximetry) will be measured as per standard of care and recorded at the times specified in the schedule of events (see Section 1.2) ~~and recorded~~.	Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) and oxygen saturation (by pulse oximetry) will be measured as per standard of care and recorded at the times specified in the schedule of events (see Section 1.2).
Section 12.3.7: Continuous monitoring of oxygen saturation	
If the saturation falls below 92% for ~~more than~~ 60 seconds (excluding technical failures or artifacts), the lowest value, the length of time the saturation is below 92%, and vital signs are to be recorded.	If the *oxygen* saturation falls below 92% for *at least* 60 seconds (excluding technical failures or artifacts), the lowest value, the length of time the *oxygen* saturation is below 92%, and vital signs are to be recorded.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.3.9: Columbia–suicide severity rating scale	
... ~~Any~~ refusal to ~~complete~~ the questionnaire must be recorded with the reason. ... The C-SSRS will be administered by a clinician who has been certified to administer the C-SSRS.	... *A* refusal to *answer the questions in* the questionnaire *that are appropriate for the subject* must be recorded with the reason. ... The C-SSRS will be administered by a clinician who has been certified to administer the C-SSRS. *The C-SSRS will be explained and shown to the parents/legal guardians prior to use.*
Section 12.3.10: University of Michigan Sedation Scale	
[new section]	*The University of Michigan Sedation Scale (Section 19.11) is a validated (Malviya et al. 2002) observational pediatric 5-point sedation scale. It will be used to assist in accurately assessing the depth of sedation before the administration of IMP. The investigator will record the sedation score at the times specified in the schedule of events (see Section 1.2).*
Section 13.4: Source data	
In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents. When this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF are: race/ethnic group.	In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents. When this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF are: race/ethnic group, and the result of the calculation of creatinine clearance (CL_{CR}) according to Schwartz et al. 1984.
Section 14: Statistical methods and sample size determination	
There are different requirements for the EU PDCO and US FDA including the age range of the patient population (EU PDCO: 2 years to <18 years of age, US FDA: birth to <17 years of age) and the timing of the primary efficacy endpoint (EU PDCO: 24 hours, US FDA: 12 hours) that impact the statistical methods and are reflected in the following sections.	There are different requirements for the EU PDCO and US FDA including the age range of the patient population (EU PDCO: 2 years to <18 years of age, US FDA: birth to <17 years of age) and the timing of the primary efficacy endpoint (EU PDCO: 24 hours, US FDA: 12 hours) that impact the statistical methods and are reflected in the following sections. *As applicable and appropriate for the individual endpoint, the endpoints will be analyzed in the age ranges for the EU PDCO and for the US FDA.*
Section 14.1: Sample size rationale	
... ~~To meet US FDA requirements, enrollment will continue, if necessary, until a minimum of 100 subjects have received at least 2 doses of tapentadol and 25 subjects have received tapentadol for at least 48 hours. Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the~~	...

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~targeted sample size (i.e., approximately 168 subjects).~~ ... The trial enrollment will then complete when the following ~~4~~ criteria are met: ... • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses. ~~• 25 subjects in the age range birth to less than 17 years of age (US FDA) have received tapentadol for at least 48 hours.~~ Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial. ... The sample size calculation was performed using the ~~Procedure MTT0-1 for the two group t-test, assuming equal group means and variance, and unequal group sizes using the~~ sample size program nQuery v7.0 (Dixon and Massey 1983, O'Brien and Muller 1993).	... The trial enrollment will then complete when the following *3* criteria are met: ... • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses *(US FDA). Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size.* Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial. *An additional objective of the study is to meet a US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age who have been exposed to tapentadol for at least 48 hours. As medically appropriate, every effort will be made to enroll subjects in this trial to meet this objective.* ... The sample size calculation was performed using the sample size program nQuery v7.0 (Dixon and Massey 1983, O'Brien and Muller 1993) *for unequal group sizes and the above assumptions regarding the effect size and the allocation ratio of 2:1 (tapentadol:placebo).*
Section 14.2: Analysis of the trial – statistical analysis	
The statistical analysis of this trial will be planned, performed, and reported by ~~sponsor~~ personnel or by authorized ~~sponsor~~ delegates, in accordance with ~~sponsor~~ SOPs. The statistical analysis of this trial will be performed as summarized in this protocol and given in detail in the statistical analysis plan. The statistical analysis plan will be ~~prepared before the database is released (locked and unblinded)~~.	The statistical analysis of this trial will be planned, performed, and reported by *operational lead* personnel or by authorized *operational lead* delegates, in accordance with *operational lead's* SOPs. The statistical analysis of this trial will be performed as summarized in this protocol and given in detail in the statistical analysis plan. The statistical analysis plan will be *finalized before the first subject in*.
Section 14.2.3: Analysis of subject characteristics data	
...	... *Pain intensity scores collected before each NCA/PCA activation will be analyzed descriptively by treatment group.*
Section 14.2.5.1: Primary efficacy endpoint	
... For subjects who withdraw from the trial prior to the 12-hour or 24-hour time point, cumulative supplemental opioid analgesia over the respective time period will be based on the observed supplemental opioid use up to the	... For subjects who withdraw from the trial prior to the 12-hour or 24-hour time point *due to any other reason than no further need of opioid analgesic medication*, cumulative supplemental opioid analgesia over the

Changes to this protocol include:	
Formerly read:	**Now reads:**
time of the subject's discontinuation. If a subject used a total of X mg/kg of supplemental opioid through Hour T (≤24 hours), cumulative use over 24 hours will be estimated as (X/T)*24 mg/kg. If T is <12 hours, cumulative use over 12 hours will be estimated as (X/T)*12. This extrapolation assumes a constant use (in mg/kg per hour) of supplemental opioid over 24 hours. Other imputation methods will be used for sensitivity analyses. These will be described in detail in the statistical analysis plan. ... A sensitivity analysis will be performed using the respective Per Protocol Set and analyzed using the same ANOVA model.	respective time period will be based on the observed supplemental opioid use up to the time of the subject's discontinuation. If a subject used a total of X mg/kg of supplemental opioid through Hour T (≤24 hours), cumulative use over 24 hours will be estimated as (X/T)*24 mg/kg. If T is <12 hours, cumulative use over 12 hours will be estimated as (X/T)*12. This extrapolation assumes a constant use (in mg/kg per hour) of supplemental opioid over 24 hours. *For subjects who withdraw from the trial due to no further need of opioid analgesic medication, the cumulative use of supplemental opioid will equal the total amount of supplemental opioid used up to the time of withdrawal*. Other imputation methods will be used for sensitivity analyses. These will be described in detail in the statistical analysis plan. ... A sensitivity analysis will be performed using the respective Per Protocol Set and analyzed using the same ANOVA model. *The primary endpoint will also be evaluated using Bayesian statistics as a supportive analysis (EU PDCO). The methodology will be described in the statistical analysis plan.*
Section 14.2.5.2: Secondary endpoints *and subgroup analyses*	
... The amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours or 24 hours after first IMP intake will be a secondary efficacy endpoint for the EU PDCO or US FDA, respectively. ... ~~The analysis will also be repeated for the total amount of supplemental opioid analgesic medication received during treatment with IMP within 72 hours after the first dose of IMP~~. ... The total amounts of non-opioid analgesic medications used (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake will be grouped	... The amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours or 24 hours after first IMP intake will be a secondary efficacy endpoint for the EU PDCO or US FDA, respectively. ... *In addition, the total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours, will be summarized descriptively. The intervals will be >24 to 36 hours, >36 to 48 hours, >48 to 60 hours, >60 to 72 hours, >72 to 84 hours, and >84 to 96 hours. For each interval, only subjects who have their End of Treatment Visit after the start of the interval will be included. If a subject has their End of Treatment Visit during a given interval, the missing data for the remainder of the given interval will be imputed using a similar methodology as for the primary efficacy endpoint, but using only data from within the given interval. The subject will then not be included in the subsequent intervals.* ... The total amounts of non-opioid analgesic medications used (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake will be grouped

Changes to this protocol include:	
Formerly read:	**Now reads:**
according ~~to ingredient~~ and route of administration, and descriptively summarized by treatment group and presented in tables. ... Pain intensity scores ~~and change~~ from baseline values will be summarized descriptively over time by treatment group and age categories (respective age-defined pain scale), as well as being listed. Figures will also be produced, where required.	according *the Anatomical Therapeutic Chemical Classification System (World Health Organization Drug Dictionary coding)* and route of administration, and descriptively summarized by treatment group and presented in tables. ... Pain intensity scores *recorded relative to IMP intake, and at the End of Treatment Visit, with changes* from baseline values, will be summarized descriptively over time by treatment group and age categories (respective age-defined pain scale), as well as being listed. Figures will also be produced, where required. ... ***Subgroup analyses*** *Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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 method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.*
Section 14.2.6.7: Analysis of sedation scores	
[new section]	Descriptive statistics of sedation scores will be provided at each scheduled time point as described in Section 1.2.
Section 14.3: Ad hoc meta-analyses	
[section deleted]	
Section 16.5: Publication policy	
The results of this trial will be publically disclosed in accordance with applicable regulatory guidance ~~(e.g., on ClinicalTrials.gov)~~.	The results of this trial will be publically disclosed in accordance with *the sponsor's disclosure policy (e.g., on ClinicalTrials.gov) and operational lead's disclosure policy (e.g., according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing) and* applicable regulatory guidance. *The operational lead will post clinical trial information in a lay person understandable form in a freely accessible operational lead's internet portal.*
Section 17: References	
[New citations]	*Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). Br J Anaesth 2002; 88(2): 241–5.* *Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 1984; 104(6): 849–54.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 19.2: Face, Legs, Activity, Cry, Consolability scale	
[Scale updated with latest version] ~~Instructions for use:~~ ~~1. Rate patient in each of the five measurement categories.~~ ~~2. Add the scores together.~~ ~~3. Document the total pain score.~~	
Section 19.3: Faces pain scale - Revised	
	[scale has been updated (attribution was moved from bottom to top of page)]
Section 19.6: Palatability and acceptability questionnaire	
a ~~little~~ bit bad/a ~~little~~ bit good a ~~little~~ bit difficult/a ~~little~~ bit easy	a bit bad/a bit good a bit difficult/a bit easy [reference given]
Section 19.10.3: Procedure	
• Fill S-Monovette® with ~~1 mL~~ of blood.	• Fill S-Monovette® with *0.5 mL* of blood.
Section 19.10.5: Contact	
Contact person Dr [redacted] E-mail address Operational lead [redacted]@grunenthal.com Bioanalytical laboratory [redacted]@grunenthal.com Phone Operational lead +49 (0) 241-569-[redacted] Bioanalytical laboratory +49 (0) 241-569-[redacted]	Contact person Dr [redacted] *Deputy:* [redacted] E-mail address Operational lead [redacted]@grunenthal.com Bioanalytical laboratory [redacted]@grunenthal.com [redacted]*@grunenthal.com* Phone Operational lead +49 (0) 241-569-[redacted] Bioanalytical laboratory +49 (0) 241-569-[redacted] *+49 (0) 241-569*[redacted]
Section 19.11: University of Michigan Sedation Scale	
	[scale has been added]

18.3 Protocol Amendment 03

Amendment rationale

This amendment has been enacted to reflect a change in the sponsor from Janssen Research & Development, LLC to Grünenthal GmbH. As a consequence, the functions of the sponsor and the operational lead were merged.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Title page:	
Tapentadol (code numbers CG5503 and R331333, respectively) is being developed under a Licensing agreement between Ortho-McNeil Pharmaceutical Inc., Janssen Research & Development, L.L.C., and Grünenthal GmbH that was executed in February 2003.	Tapentadol (code numbers CG5503 and R331333, respectively) is being developed under a Licensing agreement between Ortho-McNeil Pharmaceutical Inc., Janssen Research & Development, L.L.C., and Grünenthal GmbH that was executed in February 2003, *the rights to which were subsequently acquired by Depomed, Inc. in April 2015*.
Trial number~~s~~: KF5503/65 ~~(Grünenthal)~~ R331333PAI3037 ~~(Janssen)~~	Trial number: KF5503/65 R331333PAI3037
IND number: 108134 ~~(Janssen Research & Development)~~.	IND number: 108134
Sponsor: ~~Janssen Research & Development LLC, Titusville, United States~~.	Sponsor: *Grünenthal GmbH, 52099 Aachen, Germany.*
~~Operational lead~~ ~~Grünenthal GmbH, 52099 Aachen, Germany.~~	[deleted]
Sponsor's medically qualified person: ~~Dr~~ [redacted] ~~, Clinical Leader,~~ ~~Janssen Research & Development, LLC~~ ~~Phone: +1 609-730-~~ [redacted] [redacted] ~~@ITS.JNJ.com~~ [a]	Sponsor's medically qualified person: *Dr* [redacted] *, Head Global Clinical Development Strategy,* *Grünenthal GmbH* *Phone: +49 241-569-* [redacted] [redacted] *@grunenthal.com* [a]
Sponsor's signatory: ~~Dr~~ [redacted] ~~, Clinical Leader~~ ~~Janssen Research & Development, LLC~~	Sponsor's signatory: *Dr* [redacted] *, Head Global Clinical Development Strategy,* *Grünenthal GmbH*
~~Operational lead's medically qualified person:~~ ~~Dr~~ [redacted] ~~, Head Global Clinical Development Strategy,~~ ~~Grünenthal GmbH~~ ~~Phone: +49 241-569-~~ [redacted] [redacted] ~~@grunenthal.com~~	[deleted]
~~Operational lead's signatory:~~ ~~Dr~~ [redacted] ~~, Head Global Clinical Development Strategy,~~ ~~Grünenthal GmbH~~	[deleted]
[New section]	*Collaborator: Depomed, Newark, California*
[New section]	*Collaborator's signatory:* [redacted] *, Chief Medical Officer & Senior Vice President,* [redacted] *, Senior Director, Clinical Operations, Depomed, Inc, Newark, California*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Statistical methods:	
... Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) used by the ~~operational lead~~.	... Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) used by the *sponsor*.
Section 3: Abbreviations and definition of terms	
By definition, ~~the~~ Enrollment Period ~~as used by the operational lead company (Grünenthal GmbH)~~ is synonymous with ~~the~~ Screening Period ~~as used by the sponsor company (Janssen Research & Development)~~, and allocation ~~as used by the operational lead company~~ is synonymous with randomization ~~as used by the sponsor company~~.	By definition, Enrollment Period is synonymous with Screening Period, and allocation is synonymous with randomization.
Section 5.3: The sponsor and sponsor's personnel	
~~Janssen Research & Development~~ accepts the responsibility to be the sponsor of this clinical trial. ~~Grünenthal GmbH, 52099 Aachen, Germany is the sponsor's designee and accepts the responsibility of the operational lead for the trial.~~ ~~The sponsor can delegate tasks to the operational lead. The extent of the delegation will be documented.~~ The sponsor~~/operational lead~~ will designate appropriately qualified personnel to give advice on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed. A list of key sponsor~~/operational lead~~ personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained.	*Grünenthal GmbH, 52099 Aachen*, accepts the responsibility to be the sponsor of this clinical trial. The sponsor will designate appropriately qualified personnel to give advice on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed. A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained.
Section 5.4: Data monitoring committee	
... The DMC members will neither be employees of the sponsor~~/operational lead~~ nor be directly involved in the ongoing pediatric trials with tapentadol. Further details describing the data to be assessed and operational aspects of the DMC will be given in a charter which will be issued before the first subject is enrolled in this trial. Based on the reviewed data, the DMC may recommend the implementation of additional measures or dose changes. The final decision on how to further proceed with the trial will be made by the sponsor~~/operational lead~~ on the basis of the DMC recommendation.	... The DMC members will neither be employees of the sponsor *or collaborator* nor be directly involved in the ongoing pediatric trials with tapentadol. Further details describing the data to be assessed and operational aspects of the DMC will be given in a charter which will be issued before the first subject is enrolled in this trial. Based on the reviewed data, the DMC may recommend the implementation of additional measures or dose changes. The final decision on how to further proceed with the trial will be made by the sponsor *or collaborator* on the basis of the DMC recommendation.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 9.3.3.1: Criteria to terminate or suspend the whole trial	
... A risk benefit committee organized ~~jointly by the operational lead and sponsor's steering committee~~ will convene to decide on further action, which could include immediate stopping of the trial. The DMC may recommend stopping the trial, but the final decision will rest ~~jointly~~ with the sponsor and ~~operational lead~~. The trial may be restarted following a thorough evaluation by the sponsor and ~~operational lead~~.	... A risk benefit committee organized *by the sponsor* will convene to decide on further action, which could include immediate stopping of the trial. The DMC may recommend stopping the trial, but the final decision will rest with the sponsor and *collaborator*. The trial may be restarted following a thorough evaluation by the sponsor and *collaborator*.
Section 10.1.1: Identity and composition – tapentadol oral solution (test) **Section 10.1.2: Identity and composition – placebo (comparator)**	
... Manufacturer: Janssen Pharmaceutica NV, Beerse, Belgium.	... Manufacturer: Grünenthal GmbH, Aachen, Germany.
Section 10.4.1: Methods of blinding	
... Randomization and blinding will be done in accordance with the ~~operational lead's~~ standard operating procedures (SOPs).	... Randomization and blinding will be done in accordance with the *sponsor's* standard operating procedures (SOPs).
Section 10.4.2: Methods of unblinding	
... The investigator, the responsible department of the ~~operational lead~~, ~~and~~ the responsible drug safety department and contract research organization will receive appropriate methods for unblinding of single cases, i.e., via the IVRS/IWRS. Personnel in the ~~operational lead's~~ departments of clinical trials supply will be unblinded during the trial according to the ~~operational lead's~~ SOPs for randomization and unblinding during the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after database lock at the end of the trial. Unblinding will be initiated by the ~~operational lead's~~ department of biostatistics according to the ~~operational lead's~~ SOPs for randomization and unblinding.	... The investigator, the responsible department of the *sponsor*, the responsible drug safety department, and contract research organization will receive appropriate methods for unblinding of single cases, i.e., via the IVRS/IWRS. Personnel in the *sponsor's* departments of clinical trials supply will be unblinded during the trial according to the *sponsor's* SOPs for randomization and unblinding during the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after database lock at the end of the trial. Unblinding will be initiated by the *sponsor's* department of biostatistics according to the *sponsor's* SOPs for randomization and unblinding.
Section 10.5.1: Supplemental opioid analgesic medication	
... The supplemental opioid analgesic medication must be purchased by the trial site unless otherwise agreed upon with the sponsor~~/operational lead~~.	... The supplemental opioid analgesic medication must be purchased by the trial site unless otherwise agreed upon with the sponsor.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.7: Documentation of drug accountability	
... Before the unused and residual IMPs and other medications supplied to the investigator are returned or destroyed, the investigator must allow the ~~operational lead's~~ representative to perform drug reconciliation.	... Before the unused and residual IMPs and other medications supplied to the investigator are returned or destroyed, the investigator must allow the *sponsor's* representative to perform drug reconciliation.
Section 12.3.2.1: Serum concentrations of tapentadol	
... Serum samples will be analyzed to determine concentrations of tapentadol and, optionally, tapentadol-O-glucuronide using a validated liquid chromatography-tandem mass spectrometry bioanalytical assay under the supervision of the department of pharmacokinetics at the ~~operational lead~~.	... Serum samples will be analyzed to determine concentrations of tapentadol and, optionally, tapentadol-O-glucuronide using a validated liquid chromatography-tandem mass spectrometry bioanalytical assay under the supervision of the department of pharmacokinetics at the *sponsor*.
Section 13.3: Data management: Coding	
Medication names will be coded using the World Health Organization-Drug Dictionary. Medical history terms and adverse events will be coded using MedDRA. As required by the ~~operational lead's~~ SOPs, the version most recently implemented by the ~~operational lead~~ will be used at the time of database lock. Coding will be reviewed by the ~~operational lead's~~ personnel according to standard procedures.	Medication names will be coded using the World Health Organization-Drug Dictionary. Medical history terms and adverse events will be coded using MedDRA. As required by the *sponsor's* SOPs, the version most recently implemented by the *sponsor* will be used at the time of database lock. Coding will be reviewed by the *sponsor's* personnel according to standard procedures.
Section 13.4: Source data	
... During trial conduct, vendors are responsible for data security with oversight from the ~~operational lead~~. All data captured from all subjects will be sent to the sponsor~~/operational lead~~ in human readable form on a read-only compact disc for filing/archiving according to sponsor~~/operational lead~~ SOPs.	... During trial conduct, vendors are responsible for data security with oversight from the *sponsor*. All data captured from all subjects will be sent to the sponsor in human readable form on a read-only compact disc for filing/archiving according to sponsor SOPs.
Section 13.5: Investigator's site file and the trial master file	
... The investigator will keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the clinic/hospital policy, but at least until informed by the sponsor~~/operational lead~~ that the trial-related records are no longer required.	... The investigator will keep the investigator's site file, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the clinic/hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.
Section 14.2: Analysis of the trial – statistical analysis	
The statistical analysis of this trial will be planned, performed, and reported by ~~operational lead~~ personnel or by authorized ~~operational lead~~ delegates, in accordance with ~~operational lead's~~ SOPs.	The statistical analysis of this trial will be planned, performed, and reported by *sponsor* personnel or by authorized *sponsor* delegates, in accordance with *sponsor* SOPs.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2.6.1: Analysis of adverse events	
The original terms used in the CRFs by investigators to identify adverse events will be coded using the most recent version of MedDRA used by the ~~operational lead~~.	The original terms used in the CRFs by investigators to identify adverse events will be coded using the most recent version of MedDRA used by the *sponsor*.
Section 15.1: Quality system	
The sponsor~~/operational lead~~ is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.	The *sponsor* is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.
Section 15.2: Data quality assurance	
The accuracy and reliability of the trial data will be assured by careful clinical research organization/investigator selection and oversight by the performance of a combination of trial site visits, training, monitoring visits, remote verification by the sponsor~~/operational lead~~ of appropriate use of electronic tools by the site, data cleaning, and audits.	The accuracy and reliability of the trial data will be assured by careful clinical research organization/investigator selection and oversight by the performance of a combination of trial site visits, training, monitoring visits, remote verification by the sponsor of appropriate use of electronic tools by the site, data cleaning, and audits.
Section 15.2.2: Trial site monitoring	
Trial site monitoring as defined in GCP will be performed by sponsor~~/operational lead~~ personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial.	Trial site monitoring as defined in GCP will be performed by sponsor personnel or by authorized sponsor delegates at pre-defined intervals depending on the progress of the trial.
Section 15.2.3: Audits	
Audits as defined by GCP will be performed for this trial. The investigator will permit sponsor~~/operational lead~~ personnel or authorized delegates to audit the trial facilities and documentation at agreed times.	Audits as defined by GCP will be performed for this trial. The investigator will permit sponsor personnel or authorized delegates to audit the trial facilities and documentation at agreed times.
Section 15.3: Inspections	
The investigator, the sponsor, ~~the operational lead,~~ or personnel at other establishments, are obliged to cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, ~~at the operational lead,~~ or at other establishments. The investigator or personnel at other establishments should notify the sponsor~~/operational lead~~ as soon as possible about any upcoming regulatory authority inspection.	The investigator, the sponsor, or personnel at other establishments, are obliged to cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments. The investigator or personnel at other establishments should notify the sponsor as soon as possible about any upcoming regulatory authority inspection.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 16.1: Insurance	
If insurance for subjects is required by applicable regulatory requirements in the participating countries, the sponsor~~/operation lead~~ will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance. ... If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor~~/operational lead~~ will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor~~/operational lead~~ will inform the investigators who will then inform their subjects/parents/legal guardians about relevant changes, if required.	If insurance for subjects is required by applicable regulatory requirements in the participating countries, the sponsor will arrange suitable insurance for the subjects included in this trial and provide the investigator with the relevant terms and conditions of this insurance. ... If changes to the trial are implemented after the initial insurance was arranged, e.g., due to protocol amendments, the sponsor will notify the insurance company of these changes in accordance with the insurance conditions. If changes to insurance arise, the sponsor will inform the investigators who will then inform their subjects/parents/legal guardians about relevant changes, if required.
Section 16.2: Legal regulations	
... Before initiating the trial, if required by the applicable regulatory requirements, the sponsor~~/operation lead~~ or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.	... Before initiating the trial, if required by the applicable regulatory requirements, the sponsor or its authorized legal representative and/or the investigator will submit any required documents to the appropriate authorities for review, acceptance, and/or permission to begin the trial.
Section 16.3: Contracts	
Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial site(s) and the sponsor~~/operational lead~~ or its local offices or contract research organization or its affiliates authorized by the sponsor~~/operational lead~~, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation, e.g., the "Investigator Confirmation Sheet", may serve as the basis of such contracts. In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator's participation in the trial will be specified in a contract between the investigator and sponsor~~/operational lead~~, if applicable.	Specific contracts between the relevant parties, i.e., between the investigator/other parties at the trial site(s) and the sponsor or its local offices or contract research organization or its affiliates authorized by the sponsor, will be used to set out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. This protocol and other documentation, e.g., the "Investigator Confirmation Sheet", may serve as the basis of such contracts. In addition, responsibility for insurance or indemnity to cover any liability of the investigator that may arise directly or indirectly from the investigator's participation in the trial will be specified in a contract between the investigator and sponsor, if applicable.
Section 16.4: Subject data and data protection	
... The investigator is required to ensure that any documents or data given to the sponsor~~/operational lead~~ or its representatives do not contain information that would affect the anonymity of the subjects.	... The investigator is required to ensure that any documents or data given to the sponsor or its representatives do not contain information that would affect the anonymity of the subjects.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 16.5: Publication policy	
The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy (e.g., on ClinicalTrials.gov) ~~and operational lead's disclosure policy (e.g.~~, according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing~~)~~ and applicable regulatory guidance. The ~~operational lead~~ will post clinical trial information in a lay person understandable form in a freely accessible ~~operational lead's~~ internet portal. The results of this trial may also be published as a full publication (e.g., journal publication) or publically disclosed as a poster or presentation at a congress. The sponsor ~~and operational lead~~ reserve the right to review any proposed presentation of the results of this trial before they are submitted for publication or public disclosure. Neither party (e.g., the sponsor, ~~operational lead, or~~ the coordinating investigator) has the right to prohibit publication or public disclosure unless it can be shown to affect possible patent rights.	The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy (e.g., on ClinicalTrials.gov), according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing, and applicable regulatory guidance. The *sponsor* will post clinical trial information in a lay person understandable form in a freely accessible *sponsor* internet portal. The results of this trial may also be published as a full publication (e.g., journal publication) or publically disclosed as a poster or presentation at a congress. The sponsor reserves the right to review any proposed presentation of the results of this trial before they are submitted for publication or public disclosure. Neither party (e.g., the sponsor, the coordinating investigator) has the right to prohibit publication or public disclosure unless it can be shown to affect possible patent rights.
Section 16.6: Final report	
A final report integrating clinical and statistical results will be prepared by the sponsor~~/operational lead~~. The coordinating investigator will approve the final report on behalf of the participating investigators. The sponsor~~/operational lead~~ will provide the competent authority and relevant IEC/IRB with a summary of the final report in accordance with applicable regulatory requirements.	A final report integrating clinical and statistical results will be prepared by the sponsor. The coordinating investigator will approve the final report on behalf of the participating investigators. The sponsor will provide the competent authority and relevant IEC/IRB with a summary of the final report in accordance with applicable regulatory requirements.
Section 16.7: Approval	
16.7.1 Sponsor ~~and operational lead~~ This protocol has been approved in accordance with sponsor ~~and operational lead~~ SOPs.	16.7.1 Sponsor This protocol has been approved in accordance with sponsor SOPs.
Section 19.10.2: Devices	
... Other devices may be used if equivalent after approval by the ~~operational lead~~.	... Other devices may be used if equivalent after approval by the *sponsor*.
Section 19.10.4: Shipment	
... • Send the samples by premium courier door-to-door delivery to the bioanalytical laboratory (address given in Section 19.10.5). Choice of courier has to be approved by the ~~operational lead~~.	... • Send the samples by premium courier door-to-door delivery to the bioanalytical laboratory (address given in Section 19.10.5). Choice of courier has to be approved by the *sponsor*.
Section 19.10.5: Contact	
~~Operational lead~~ ... Bioanalytical laboratory	*Sponsor* ... Bioanalytical laboratory

18.4 Protocol Amendment 04

Amendment rationale

This amendment has been enacted to:

- Clarify the definition for stopping IMP.
- Allow dosing with morphine or hydromorphone for technical reasons if an NCA/PCA dose cannot be given.
- Allow a clinician bolus or intravenous bolus of morphine or hydromorphone if the subject had unbearable pain in exceptional cases. This has been enacted to ensure that the subjects are not exposed to more pain than would normally be the case.
- Add peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia to the prohibited medication from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP.
- Exclude continuous positive airway pressure or mechanical ventilation from time of allocation/randomization to IMP until 4 hours after the last administration of IMP.
- Modify 2 exclusion criteria to:
  - 8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9).
  - 16. 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/randomization to IMP.
- Add an exclusion criteria of: Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP.
- Allow the use of non-sponsor supplied dosing syringes. This has been enacted for logistical reasons and does not affect the outcome parameters.
- Specify that the administration of IMP must not be repeated if the subject vomits or regurgitates a complete dose. If only part of the dose is vomited or regurgitated, the remainder of the dose may be administered at the investigator's discretion.
- Allow the pregnancy test to be done on either a urine sample or a serum sample.
- Restrict CGIC and PGIC data to a descriptive analysis in the final report.
- Only list physical examination findings in the final report.

In addition, a number of clarifications have been made, and discrepancies and inconsistencies have been corrected.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Title page:	
Tapentadol (code numbers CG5503 and R331333, respectively) is being developed under a Licensing agreement between Ortho-McNeil Pharmaceutical Inc., Janssen Research & Development, L.L.C., and Grünenthal GmbH that was executed in February 2003, the rights to which were subsequently acquired by Depomed, Inc. in April 2015.	Tapentadol (code numbers CG5503 and R331333, respectively) is being developed under a Licensing agreement between Ortho-McNeil Pharmaceutical Inc., Janssen Research & Development, L.L.C., and Grünenthal GmbH that was executed in February 2003, the *United States* rights to which were subsequently acquired by Depomed, Inc. in April 2015. *Subsequent to investigational new drug (IND) and new drug application (NDA) acquisition, Depomed Inc. has further transferred sponsor regulatory obligations for this trial to Grünenthal.*
Trial design: This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol ~~(Nucynta/Palexia)~~.	Trial design: This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol *oral solution*.
Sponsor's medically qualified person: Dr [redacted], ~~Head Global Clinical Development Strategy~~, Grünenthal GmbH	Sponsor's medically qualified person: Dr [redacted], *Senior International Clinical Lead*, Grünenthal GmbH
Sponsor's signatory: Dr [redacted], ~~Head Global Clinical Development Strategy~~, Grünenthal GmbH	Sponsor's signatory: Dr [redacted], *Senior International Clinical Lead*, Grünenthal GmbH
Collaborator's ~~signatory~~:	Collaborator's *signatories*:
Section 1: Protocol synopsis: Trial design **Section 8: Trial design** **Section 8.4: Discussion of the trial design**	
This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol ~~(Nucynta/Palexia)~~.	This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol *oral solution*.
Section 1: Protocol synopsis: Trial population **Section 9.1: Subject enrollment procedure**	
... The trial enrollment will be initiated in a staggered approach, starting with enrollment of an older age group until pharmacokinetic data are available in younger age groups.	... The trial enrollment will be initiated in a staggered approach, starting with enrollment of an older age group until pharmacokinetic data are available in younger age groups *from other trials in the pediatric clinical development program of tapentadol*.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Trial treatments **Section 10.2.2: Total dosing time and dosing interval** **Section 11.1.2.1: Visit 2: Administration of first dose of investigational medicinal product (Day 1)**	
... Dosing with IMP will be stopped ~~when~~ opioid analgesic medication is no longer needed~~, or~~ 72 hours ~~after first IMP administration~~.	... Dosing with IMP will be stopped *if:* • *A switch to exclusively oral opioid analgesic medication is indicated according to the local standard of care.* • Opioid analgesic medication is no longer needed. • *IMP has been administered for* 72 hours.
Section 1: Protocol synopsis: Concomitant medications/therapies **Section 10.6.3: Allowed prior and concomitant medication**	
... If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously.	... If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously. *In exceptional cases, if a subject has unbearable pain despite using NCA/PCA, an additional bolus (defined as a clinician bolus) of morphine or hydromorphone may be administered. The clinician bolus can be given either using the NCA/PCA pump system or by an intravenous bolus injection.* *The opioid given as a clinician bolus or if the NCA/PCA intravenous line fails must be the same as that used in the NCA/PCA pump system.*
Section 1: Protocol synopsis: Concomitant medications/therapies **Section 10.6.4: Prohibited prior and concomitant medication*/therapy***	
Prohibited medication from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP • Long-acting opioids. • Medication used for sedation (as noted above, benzodiazepines may be used to treat muscle spasms or anxiety).	Prohibited medication from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP • Long-acting opioids. • Medication used for sedation (as noted above, benzodiazepines may be used to treat muscle spasms or anxiety). • *Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia.*
Prohibited medication from time of allocation/randomization to IMP until 4 hours after the last administration of IMP • Opioids (other than morphine, hydromorphone, or IMP).	Prohibited medication*/therapy* from time of allocation/randomization to IMP until 4 hours after the last administration of IMP • Opioids (other than *protocol defined* morphine, hydromorphone, or IMP). • *Continuous positive airway pressure or mechanical ventilation.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Key data collected	
Efficacy • Trade name, dose, and time of each administration of intravenous morphine or hydromorphone given if the NCA/PCA line fails. ... Safety ... • Pregnancy test ~~(urine)~~ for female subjects aged 12 years or older, or post-menarchal, or sexually active.	Efficacy • Trade name, dose, and time of each administration of intravenous morphine or hydromorphone given if the NCA/PCA line fails*, or a clinician bolus is given*. ... Safety ... • Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.
Section 1: Protocol synopsis: Statistical methods	
... ~~Changes in~~ physical examination findings ~~compared to Visit 1 will be summarized by body system and results~~ will be listed.	... *The* physical examination findings will be listed *per time point*.
Section 1.2: Schedule of events	
... Perform a ~~urine~~ pregnancy test ... [Footnotes] j) In subjects aged 6 years or older. The administration of the C-SSRS "children's baseline" must be performed after surgery. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. The initials of the interviewer are to be recorded. q) For female subjects if aged 12 years or older, or post-menarchal, or sexually active~~, a urine sample will be provided by the subject within~~ 48 hours prior to allocation/randomization to IMP. r) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.1). NCA/PCA is with morphine or hydromorphone in accordance with the standard of care at the site. Detailed information on use will be recorded at times consistent with the memory of the NCA/PCA pump. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails.	... Perform a pregnancy test ... [Footnotes] j) In subjects aged 6 years or older. The administration of the C-SSRS "children's baseline" must be performed after surgery. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. The initials of the interviewer are to be recorded. *The C-SSRS will only be used at a trial site if its use has not been rejected by the responsible ethics committee.* q) For female subjects if aged 12 years or older, or post-menarchal, or sexually active*. Within* 48 hours prior to allocation/randomization to IMP. r) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.1). NCA/PCA is with morphine or hydromorphone in accordance with the standard of care at the site. Detailed information on use will be recorded at times consistent with the memory of the NCA/PCA pump. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails*, or a clinician bolus is given*.

Changes to this protocol include:	
Formerly read:	**Now reads:**
t) Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.	t) Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. *Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.*
Section 1.3.1: Inclusion criteria **Section 9.2.1: Inclusion criteria**	
4. A female subject must have a negative ~~urine~~ pregnancy test if aged 12 years or older, or is post-menarchal, or is sexually active. 5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after ~~allocation/randomization to~~ IMP. Subjects must remain hospitalized until the End of Treatment Visit.	4. A female subject must have a negative pregnancy test if aged 12 years or older, or is post-menarchal, or is sexually active. 5. Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after *first dose of* IMP. Subjects must remain hospitalized until the End of Treatment Visit.
Section 1.3.2: Exclusion criteria **Section 9.2.2: Exclusion criteria**	
8. Subject is obese~~,~~ e.g., BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). 16. Peri- or post-operative analgesia supplied by a continuous regional technique (~~i.e.~~, nerve block) or subject controlled epidural analgesia that was terminated less than 6 hours before allocation/randomization to IMP. [New exclusion criterion]	8. Subject is obese *in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables;* e.g., *a* BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). 16. 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/randomization to IMP. *Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP. [Rationale] Safety*
Section 3: Abbreviations and definition of terms: Definition of terms	
... [New] ... Enrolled subjects: Informed consent given according to local regulations, and subject given a subject identification number by the IVRS/IWRS.	... *Clinician bolus: An additional bolus of morphine or hydromorphone given either using the NCA/PCA pump system or by an intravenous bolus injection. The clinician bolus can only be given in exceptional cases if a subject suffers unbearable pain despite using NCA/PCA.* ... Enrolled subjects: Informed consent*/assent* given according to local regulations, and subject given a

Changes to this protocol include:	
Formerly read:	**Now reads:**
... Treated subjects: ~~Allocated s~~subjects with at least 1 administration of IMP.	subject identification number by the IVRS/IWRS. ... Treated subjects: *S*ubjects with at least 1 administration of IMP.
Section 8.4: Discussion of the trial design	
Comparator and use of NCA/PCA ... A subject will be discontinued from the trial if their pain is not controlled by the NCA/PCA ~~pump~~, requiring treatments other than those defined in the protocol.	Comparator and use of NCA/PCA ... A subject will be discontinued from the trial if their pain is not controlled by the *IMP plus* NCA/PCA, requiring treatments other than those defined in the protocol.
Section 9.3.1: Reasons for discontinuation of a subject: Table 1	
Protocol deviation ... • The subject is taking prohibited medication (see Section 10.6.4).	Protocol deviation ... • The subject is taking prohibited medication*/therapy* (see Section 10.6.4).
Section 10.1.3: Preparation	
... The IMP will be supplied as a liquid in 100 mL bottles intended for multiple use per subject. A dosing syringe for oral use ~~will be provided with the IMP and~~ must be used for IMP administration.	... The IMP will be supplied as a liquid in 100 mL bottles intended for multiple use per subject. A dosing syringe for oral use *(either a syringe supplied by the sponsor or a suitable sponsor-approved alternative, as defined in Section 10.2.1 and in the Investigational Product Preparation Instructions supplied by the sponsor)* must be used for IMP administration.
Section 10.2.1: Dose	
... [New text]	... *Dosing charts will be provided by the sponsor.*
Section 10.2.3: Administration	
... [New text]	... *The administration must not be repeated if the subject vomits or regurgitates a complete dose. If only part of the dose is swallowed before vomiting or regurgitation, the remainder of the dose may be administered at the investigator's discretion. Vomiting and/or regurgitation must be recorded as an adverse event.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.5.1: Supplemental opioid analgesic medication	
... [New text]	... *If the NCA/PCA intravenous line fails for any reason, it should be restarted/repaired immediately. During the interim, morphine or hydromorphone may be administered intravenously.* *In exceptional cases, if a subject has unbearable pain despite using NCA/PCA, an additional bolus (defined as a clinician bolus) of morphine or hydromorphone may be administered. The clinician bolus can be given either using the NCA/PCA pump system or by an intravenous bolus injection.*
Section 10.7: Documentation of drug accountability	
... The bottles of oral solution (tapentadol or placebo) will be weighed to determine the amount used. The instructions for weighing will be given separately. The weighing scales used must be appropriately calibrated and verified.	... The bottles of oral solution (tapentadol or placebo) will be weighed to determine the amount used. The instructions for weighing will be given separately. The weighing scales used must be appropriately calibrated and verified. *Instructions for drug accountability will be given in the drug accountability log.*
Section 11.1.1: Enrollment Period (Visit 1)	
... • Complete the C-SSRS "children's baseline" questionnaire if the subject is aged 6 years or older. The C-SSRS will be explained and ~~shown to the parents/legal guardian~~ at the time of the informed consent procedure ... • ~~Take a urine sample and perform~~ a ~~urine~~ pregnancy test in female subjects if aged 12 years or older, or post-menarchal, or sexually active, within 48 hours prior to allocation/randomization to IMP.	... • Complete the C-SSRS "children's baseline" questionnaire if the subject is aged 6 years or older. The C-SSRS will be explained and *demonstrated* at the time of the informed consent procedure. ... • *Perform* a pregnancy test in female subjects if aged 12 years or older, or post-menarchal, or sexually active, within 48 hours prior to allocation/randomization to IMP.
Section 11.1.2.1: Visit 2	
Administration of first dose of investigational medicinal product (Day 1) ... The first dose of IMP is given when IMP is available on the ward and the investigator determines it is medically appropriate for the subject to receive the IMP. At the time of the first IMP administration, the background opioid infusion (if any) will be discontinued. The IMP will be administered as an oral solution as described in Section 10.2. ~~Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, or after 72 hours after first IMP administration.~~	Administration of first dose of investigational medicinal product (Day 1) ... The first dose of IMP is given when IMP is available on the ward and the investigator determines it is medically appropriate for the subject to receive the IMP. *The time between allocation to IMP and first administration should be kept as short as possible.* At the time of the first IMP administration, the background opioid infusion (if any) will be discontinued. The IMP will be administered as an oral solution as described in Section 10.2.
After the first dose of investigational medicinal product ... • Administer supplemental opioid analgesic medication	After the first dose of investigational medicinal product ... • Administer supplemental opioid analgesic medication

Changes to this protocol include:	
Formerly read:	**Now reads:**
as required (by NCA/PCA, see Section 10.5.1). Record the following at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2): ... − The trade name of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails. • Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.	as required (by NCA/PCA, see Section 10.5.1). Record the following at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2): ... − The trade name of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails*, or a clinician bolus is given.* • Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. *Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.*
Before subsequent doses of investigational medicinal product ... • Record the following details about the use of supplemental opioid analgesic medication (by NCA/PCA) at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2): ... − The trade name of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails. • Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.	Before subsequent doses of investigational medicinal product ... • Record the following details about the use of supplemental opioid analgesic medication (by NCA/PCA) at times consistent with the memory of the NCA/PCA pump for the time period indicated in the schedule of events (Section 1.2): ... − The trade name of intravenous morphine or hydromorphone, dose, and time of dosing if the NCA/PCA fails*, or a clinician bolus is given.* • Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. *Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.*
Section 11.1.2.3: Visit 3 (End of Treatment Visit)	
... • Record pain intensity (see Section 12.2.5). Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment.	... • Record pain intensity (see Section 12.2.5). Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. *Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.*
Section 12.2.1: Amount of supplemental opioid used	
Details of intravenous morphine or hydromorphone used if the NCA/PCA line fails will also be recorded.	Details of intravenous morphine or hydromorphone used if the NCA/PCA line fails*, or a clinician bolus is given* will also be recorded.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.3: Collection of safety data	
• Pregnancy test ~~(urine)~~ for female subjects aged 12 years or older, or post-menarchal, or sexually active.	• Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.
Section 12.3.2: Safety laboratory	
The ~~creatinine clearance (CL_{CR})~~ will be ~~calculated~~ according to Schwartz et al. 1984.	The *glomerular filtration* rate will be *estimated* according to Schwartz et al. 1984.
Section 12.3.3: Pregnancy test	
For female subjects if aged 12 years or older, or post-menarchal, or sexually active, a ~~dipstick~~ test will be performed ~~on a urine sample provided~~ within 48 hours prior to allocation/randomization to IMP.	For female subjects if aged 12 years or older, or post-menarchal, or sexually active, a *pregnancy* test will be performed within 48 hours prior to allocation/randomization to IMP. *This may be done on a serum sample according to local routine, or using a urine dipstick test (either supplied by the sponsor or a local test capable of detecting human chorionic gonadotropin levels of 25 mIU/mL or greater and a sensitivity/specificity of >99%).*
Section 12.3.7: Continuous monitoring of oxygen saturation	
Oxygen saturation will be monitored continuously using pulse oximetry from after surgery until 4 hours after the last administration of IMP.	Oxygen saturation will be monitored continuously using pulse oximetry from *before allocation/randomization to IMP (*but after surgery*)* until 4 hours after the last administration of IMP.
Section 12.3.9: Columbia–suicide severity rating scale	
… The C-SSRS will be explained and shown to the parents/legal guardians prior to use.	… The C-SSRS will be explained and shown to the parents/legal guardians prior to use. *The C-SSRS will only be used at a trial site if its use has not been rejected by the responsible ethics committee.*
Section 13.4: Source data	
Data expected to be only recorded in the CRF are: race/ethnic group, and the result of the ~~calculation~~ of ~~creatinine clearance (CLCR)~~ according to Schwartz et al. 1984.	Data expected to be only recorded in the CRF are: race/ethnic group, and the result of the *estimation* of *the glomerular filtration rate* according to Schwartz et al. 1984.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2.5.2: Secondary endpoints and subgroup analyses	
... The CGIC and PGIC, both using a 7-point rating scale at the End of Treatment Visit (Visit 3), will be ~~tabulated by treatment group and analyzed using the Cochran-Mantel-Haenszel (CMH) test, controlling for baseline age group and supplemental opioid analgesic used~~. ... The time to first and time to second NCA/PCA after the first dose of IMP will be summarized descriptively and displayed by treatment group and by treatment group and age categories. Figures will also be produced, where required.	... The CGIC and PGIC, both using a 7-point rating scale at the End of Treatment Visit (Visit 3), will be *described descriptively*. ... The time to first and time to second NCA/PCA after the first dose of IMP will be summarized descriptively and displayed by treatment group and by treatment group and age categories. Figures will also be produced, where required. *Any supplemental opioid analgesic medication given intravenously if the NCA/PCA pump fails and any clinician bolus will be included in this analysis.*
Section 14.2.6.5: Analysis of physical examination data	
~~Changes in~~ physical examination findings ~~compared to Visit 1~~ will be ~~summarized by body system. Results will also be listed~~.	*The* physical examination findings will be *listed per time point as described in Section 1.2*.

18.5 Protocol Amendment 05

Amendment rationale

This amendment has been enacted to:

- Define the dosing for subjects aged 6 months to <2 years old.
- Provide restrictions for the medication that can be taken by mothers of a newborn or breastfeeding mother.
- Allow the safety laboratory blood sample analysis to be performed at a local laboratory for subjects <2 years old to limit the amount of blood taken.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Trial treatments: Investigational medicinal products: Table of dosing regimen **Section 10.2.1: Dose: Table 2: Determination of tapentadol dose and oral solution concentration**	
~~2 years~~ to <18 years old	*6 months* to <18 years old
Birth to <~~2 years~~ old	Birth to <*6 months* old
a) The doses for subjects aged less than ~~2 years~~ old (as determined at the time of allocation to IMP) will be defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.	a) The doses for subjects aged less than *6 months* old (as determined at the time of allocation to IMP) will be defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.
Section 1: Protocol synopsis: Concomitant medications/therapies: **Section 10.6.4: Prohibited prior and concomitant medications/therapy**	
Prohibited medication from 6 hours ~~prior to time of~~ allocation/randomization to IMP until 4 hours after the last administration of IMP … [New text]	Prohibited medication from 6 hours before allocation/randomization to IMP until 4 hours after the last administration of IMP … *Restrictions for the mother of a newborn or breastfeeding mother* *• For monoamine oxidase inhibitors, neuroleptics, anticonvulsants, antiparkinsonian drugs, methadone, and all serotonergic drugs including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, and triptans:* *− Prepartum intake by a mother of a newborn subject is prohibited in the 14 days prior to the subject's allocation/randomization to IMP.* *− The intake of these medications by the breastfeeding mother of a subject is prohibited from 14 days prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.* *• For opioid medication (including tapentadol formulations) and medication used for sedation:* *− The intake of opioid medication (including tapentadol formulations) and medication used for sedation by the breastfeeding mother of a subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP until the end of treatment with the IMP.* *− The intake of opioid medication (including tapentadol formulations) and medication used for sedation taken prepartum by the mother of a newborn subject is prohibited from 48 hours prior to the subject's allocation/randomization to IMP.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Statistical methods:	
… Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings will be provided for summarizing safety laboratory parameters, 12-lead ECG, vital signs, and oxygen saturation across treatment group.	… Descriptive statistics, changes from baseline, frequency tabulations of abnormalities and subject listings will be 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.
Section 1.2: Schedule of events: footnote	
h) Record all medications, including opioid and non-opioid analgesics but excluding anesthetics and medication used during the surgery (Section 12.1.2).	h) Record all medications, including opioid and non-opioid analgesics but excluding anesthetics and medication used during the surgery (Section 12.1.2). *This includes the recording of prohibited medication used by breastfeeding mothers and prohibited prior medication used by mothers of a newborn subject.*
Section 1.3.2: Exclusion criteria **Section 9.2.2: Exclusion criteria**	
[New text]	*20. The mother of a newborn subject or the breastfeeding mother of a subject was administered a prohibited medication (see Restrictions for the mother of a newborn or breastfeeding mother).* *Standardization of trial population.*
Section 6.2: Relevant non-clinical and clinical data: Pharmacokinetics in children	
A population pharmacokinetic model was developed	A population pharmacokinetic model was developed ... *The addition of data from children aged 1 month to less than 2 years (KF5503/72) resulted in minor changes in the model and was best described by incorporation of an E_{max} type maturation function. The pharmacometric parameters changed to: CL/F = 160 L.h^{-1}, V/F = 546 L (the CL/F and V/F are typical estimates for a subject with a body weight of 34 kg), Ka = 2.21 h^{-1}, T_{LAG} = 0.267 h, with the coefficients of weight on CL/F and V/F being estimated as 0.551 and 0.829, respectively. The maturation function, which describes the age at which half the maximum CL/F within the data set is reached, was estimated as 46 weeks. The inter-individual variabilities on CL/F and V/F remained the same with only the variability on Ka increasing to 148%.*
Section 8.4: Discussion of the trial design: Dosing	
Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for tapentadol oral solution. The data from 2 dedicated single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R33133PAI2005]) were used for the population pharmacokinetic model and served as a basis for dose selection in the current trial for children aged 2 years to less than 18 years old. The doses for children aged from birth to less than 2 years ~~will be~~	Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for tapentadol oral solution. The data from 2 dedicated single-dose pharmacokinetic trials (KF5503/68 and KF5503/59 [R33133PAI2005]) were used for the population pharmacokinetic model and served as a basis for dose selection in the current trial for children aged 2 years to less than 18 years old. The doses for children aged from birth to less than 2 years *are*

Changes to this protocol include:	
Formerly read:	**Now reads:**
predicted from additional pharmacokinetic sampling in children of the same age group. … [New paragraph] Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged ~~2 years~~ to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the investigator's judgment of the effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. The doses for subjects aged less than ~~2 years old~~ will be defined based on forthcoming pharmacokinetic data. ~~S~~subjects ~~less than 2 years old~~ will not be recruited into the trial until the dose has been defined for them.	predicted from additional pharmacokinetic sampling in children of the same age group. … *The population pharmacokinetic model used for the pediatric dose simulations was updated with exposure data obtained from children aged 1 month to less than 2 years (KF5503/72), the simulations were then redone to determine the appropriate dose for the age group 6 months to less than 2 years. The simulations specified that the dose of 1.25 mg/kg would give similar exposures as that observed in the age group 2 years to less than 18 years.* Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged *6 months* to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the investigator's judgment of the effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. The doses for *younger* subjects aged less than *6 months* will be defined based on forthcoming pharmacokinetic data. *Younger s*ubjects will not be recruited into the trial until the dose has been defined for them.
Section 9.1: Subject enrollment procedure	
… The trial enrollment will be initiated in a staggered approach~~, starting with e~~nrollment ~~of~~ an older age group until pharmacokinetic data are available in younger age groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years ~~will~~ be recruited. Subjects from birth to less than ~~2 years~~ of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups. Allocation/randomization to IMP will be stratified by 7 age groups and by use of morphine or hydromorphone as supplemental opioid analgesia (Section 10.3).	… The trial enrollment will be initiated in a staggered approach. *E*nrollment *starts with* an older age group until pharmacokinetic data are available in younger age groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years *are to* be recruited. *The recruitment of subjects aged 6 months to less than 2 years is allowed following Amendment 05, based on pharmacokinetic and safety data gathered from a separate trial in the same age group.* Subjects from birth to less than *6 months* of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups. Allocation/randomization to IMP will be stratified by 7 age groups and by use of morphine or hydromorphone as supplemental opioid analgesia (Section 10.3).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 9.3.1: Reasons for discontinuation of a subject: Table 1: Reasons for compulsory and optional discontinuation of subjects from trial participation (discontinuation criteria)	
Protocol deviation: ... The subject ~~is taking~~ prohibited medication/therapy (see Section 10.6.4).	Protocol deviation: ... The subject *or mother of a newborn or breastfeeding mother has taken* prohibited medication/therapy (see Section 10.6.4).
Section 11.1.1: Enrollment Period (Visit 1)	
The following ~~evaluations~~ will be performed during this period: … • Record prior medication and therapies, as appropriate (excluding anesthetics and medication used during the surgery). ... • Take blood for both local and central safety laboratory (clinical chemistry and hematology) investigations when the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.	The following *procedures* will be performed during this period: … • Record prior medication and therapies, as appropriate (excluding anesthetics and medication used during the surgery). *This includes the recording of prohibited medication used by breastfeeding mothers and prohibited prior medication used by mothers of a newborn subject.* ... • Take blood for both local and central *(children aged 2 years or older) or local (children younger than 2 years old)* safety laboratory (clinical chemistry and hematology) investigations when the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.
Section 11.1.2.1: Visit 2	
Before first dose of investigational medicinal product … • Record intake of other concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed), excluding anesthetics and medication used during the surgery. … After the first dose of investigational medicinal product … • Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). … Before subsequent doses of investigational medicinal product … • Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant	Before first dose of investigational medicinal product … • Record intake of other concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed), excluding anesthetics and medication used during the surgery. *This includes the recording of prohibited medication used by breastfeeding mothers.* … After the first dose of investigational medicinal product … • Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). *This includes the recording of prohibited medication used by breastfeeding mothers.* … Before subsequent doses of investigational medicinal product …

Changes to this protocol include:	
Formerly read:	**Now reads:**
medication and therapies is to be recorded when they are started, stopped, or the dose changed).	• Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). *This includes the recording of prohibited medication used by breastfeeding mothers.*
Section 11.1.2.3: Visit 3 (End of Treatment Visit)	
The following ~~evaluations~~ will be performed during this period: … • Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). ... • Take blood for safety laboratory (to be sent to the central laboratory).	The following *procedures* will be performed during this period: … • Record intake of concomitant medication and use of therapies as appropriate (the use of concomitant medication and therapies is to be recorded when they are started, stopped, or the dose changed). *This includes the recording of prohibited medication used by breastfeeding mothers.* ... • Take blood for safety laboratory (to be sent to the central laboratory *for children aged 2 years or older or local laboratory for children younger than 2 years old*).
Section 11.7: Overview of blood sampling in this trial	
~~For subjects aged 2 years and older, t~~he approximate amount of blood drawn for this trial is given in Table 3.	*T*he approximate amount of blood drawn for this trial is given in Table 3. *Local laboratories can use microsampling, especially for subjects aged <2 years old, so these blood volumes may be lower.*
Table 3: Approximate volume of blood to be collected from each subject ~~aged 2 years and older~~	Table 3: Approximate volume of blood to be collected from each subject
Number of samples Clinical chemistry: 2 for central, 1 for local Hematology: 2 for central, 1 for local	Number of samples *2 years to <18 years* *<2 years* Clinical chemistry: 2 for central, 1 for local *2 for local* Hematology: 2 for central, 1 for local *2 for local*
Approximate total blood volume per test Clinical chemistry: 6 mL Hematology: 6 mL Total: 12 mL	Approximate total blood volume per test *2 years to <18 years* *<2 years* Clinical chemistry: 6 mL *4 mL* Hematology: 6 mL *4 mL* Total: 12 mL *8 mL*
Section 12.1.2: Prior and concomitant medications	
… Trade names should be given in preference to generic names when recording medication. The generic name may be used if the trade name is not available.	… Trade names should be given in preference to generic names when recording medication. The generic name may be used if the trade name is not available. *Prohibited medication used by the mother of a newborn or breastfeeding mother will be recorded.*
Section 12.3.1: Adverse events: Special procedures for serious adverse events	
If possible, after all serious adverse events, a blood sample for the quantitation of systemic exposure of	If possible, after all serious adverse events, a blood sample for the *central laboratory* quantitation of

Changes to this protocol include:	
Formerly read:	**Now reads:**
tapentadol and tapentadol-O-glucuronide should be drawn in close temporal relationship to the serious adverse event.	systemic exposure of tapentadol and tapentadol-O-glucuronide should be drawn in close temporal relationship to the serious adverse event.
Section 12.3.2: Safety laboratory	
… Clinical chemistry and hematology – central laboratory … Clinical chemistry and hematology – local laboratory Blood samples for clinical chemistry and hematology for the local laboratory will be taken at the same time as the blood sample for the central laboratory before allocation/randomization to IMP. The results of blood analyzed in a local laboratory for clinical chemistry and hematology will be used for verification of the exclusion criteria. The results of the tests must be available for review before a subject is allocated to IMP. Parameters specified in the exclusion criteria need to be reviewed. This does not preclude the need to take a sample for central laboratory analysis.	… Clinical chemistry and hematology – central laboratory *(for subjects aged 2 years to less than 18 years)* … Clinical chemistry and hematology – local laboratory *(all subjects)* Blood samples for clinical chemistry and hematology for the local laboratory will be taken at the same time as the blood sample for the central laboratory before allocation/randomization to IMP *for subjects aged 2 years to less than 18 years. For subjects less than 2 years old, only the blood sample for local analysis will be taken.* The results of blood analyzed in a local laboratory for clinical chemistry and hematology will be used for verification of the exclusion criteria. The results of the tests must be available for review before a subject is allocated to IMP. Parameters specified in the exclusion criteria need to be reviewed. This does not preclude the need to take a sample for central laboratory analysis *for subjects aged 2 years to less than 18 years.*
Section 14.2.3: Analysis of subject characteristics data	
… Pain intensity scores collected before each NCA/PCA activation will be analyzed descriptively by treatment group.	… Pain intensity scores collected before each NCA/PCA activation will be analyzed descriptively by treatment group. *Prohibited medication used by the mother of a newborn or breastfeeding mother will be listed by subject.*
Section 14.2.6.2: Analysis of safety laboratory data	
… Descriptive statistics will be calculated for each safety laboratory parameter at baseline and at each scheduled time point as described in Section 1.2.	… Descriptive statistics *(only for blood samples analyzed at the central laboratory)* will be calculated for each safety laboratory parameter at baseline and at each scheduled time point as described in Section 1.2.
Section 19.10.5: Contact	
~~Sponsor~~ ~~Grünenthal GmbH~~ [redacted] ~~Deputy:~~ [redacted] [redacted]~~@grunenthal.com~~ [redacted]~~@grunenthal.com~~ ~~+49 (0) 241-569-~~[redacted]	~~Bioanalytical laboratory~~ ~~Grünenthal GmbH~~ *Dr* [redacted] [redacted]*@grunenthal.com* *+49 (0) 241-569-*[redacted]

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~+49 (0) 241-569-~~ [redacted] +49 (0) 241-569-[redacted]	

18.6 Protocol Amendment 06

Amendment rationale

This amendment has been enacted to:

- Enable the EU PDCO data set to be analyzed for regulatory requirements prior to completion of the US FDA data set.
- Remove the analysis of non-opioid analgesic medication as a secondary endpoint for logistical reasons.
- Clarify an inconsistency with regard to the start of continuous oxygen saturation monitoring.
- Update information on post-marketing experience.
- Update the collaborator's signatories.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Title page	
Collaborator's signatories: [redacted], Chief Medical Officer & Senior Vice President, [redacted], ~~Senior Director~~, Clinical ~~Operations~~, Depomed, Inc, Newark, California	Collaborator's signatories: *Dr* [redacted], Chief Medical Officer & Senior Vice President, *Dr* [redacted], *Vice President*, Clinical *Affairs*, Depomed, Inc, Newark, California
Title page	
Sponsor's medically qualified person: Phone: ~~+49 241-569-~~ [redacted]	Sponsor's medically qualified person: Phone: *+1 (908) 745-* [redacted]

Section 1: Protocol synopsis: Definition of endpoints: The secondary efficacy endpoints are: **Section 8.1: Definition of endpoints: The secondary efficacy endpoints are:**	
• The total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP. ~~• The total amount of non-opioid analgesics used (irrespective of the indication, e.g., acetaminophen, which can also be given as antipyretic medication) during the treatment period within the first 24 hours (EU PDCO) or within the first 12 hours (US FDA) after the first dose of IMP.~~ • Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged 2 years to less than 18 years old (EU PDCO).	• The total amount of supplemental opioid analgesic medication received, assessed in 12 hour intervals from 24 hours to 96 hours after the first dose of IMP. • Palatability and acceptability of the IMP after the first and last doses of IMP in subjects aged 2 years to less than 18 years old (EU PDCO).
Section 1: Protocol synopsis: Sample size rationale: **Section 14.1: Sample size rationale**	
... The trial enrollment will ~~then~~ complete when the following ~~3 criteria are~~ met: • At least 159 treated subjects in the age range 2 years to less than 18 years of age (EU PDCO). • At least 159 treated subjects in the age range birth to less than 17 years of age (US FDA). • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses (US FDA). Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size. ~~Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.~~	... *Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.* ***Completion of trial enrollment*** The trial enrollment *for the EU PDCO set (see Section 14.2.1 for the definition of the analysis populations)* will complete when the following *criterion is* met: • At least 159 treated subjects in the age range 2 years to less than 18 years of age (EU PDCO). *The trial enrollment for the US FDA set will complete when the following 2 criteria are met:* • At least 159 treated subjects in the age range birth to less than 17 years of age (US FDA). • 100 subjects in the age range birth to less than 17 years of age on tapentadol for at least 2 doses (US FDA). Based on estimates from adult trials in acute pain, it is assumed that approximately 5% of subjects (approximately 8 subjects) may discontinue prior to receiving 2 doses of IMP, which is covered by the targeted sample size.
Section 1: Protocol synopsis: Sample size rationale:	
	... *Reporting* *Two reports will be prepared for the trial. The first report will be prepared after the date of the last contact with the last subject according to the protocol for the EU PDCO set (last subject out - EU PDCO). The second report will be prepared after the date of the last contact with the last subject according to the protocol for the US FDA set (last subject out - US FDA).*

Section 1: Protocol synopsis: Statistical methods:	
... Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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 method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.	... Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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*, as applicable for the EU PDCO set and US FDA set*) and by method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.
Section 3: Abbreviations and definition of terms: Definition of terms	
... Last subject out: Date of last contact with the last subject according to the protocol.	... Last subject out - *EU PDCO*: Date of last contact with the last subject according to the protocol *for the EU PDCO set*. *Last subject out - US FDA*: *Date of last contact with the last subject according to the protocol for the US FDA set.*
Section 6.2: Relevant non-clinical and clinical data: Safety experience from post-marketing data in adults	
The total cumulative post-authorization patient exposure to tapentadol (IR and PR) since the first launch in Jul 2008 up to 20 May ~~2014~~ was ~~142 923 321~~ patient treatment days with an estimated average daily dose for tapentadol IR of 280 mg. In the time period from first launch to 20 May ~~2014, 5286~~ spontaneous, medically confirmed cases were received, reporting tapentadol either as the suspect, co-suspect, or suspect-interacting drug. Among the ~~5286~~ cases, there were ~~85~~ cases with a fatal outcome, ~~1607~~ serious nonfatal cases, and ~~3594~~ not serious cases. Age was reported in ~~2465~~ cases and ranged from ~~<1 year~~ to 100 years. The cases involved ~~2552~~ female patients and ~~1557~~ male patients (the sex was not reported or was reported as unknown in ~~1177~~ cases). Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, headache~~, hallucination, and vomiting~~.	The total cumulative post-authorization patient exposure to tapentadol (IR and PR) since the first launch in Jul 2008 up to 20 May *2016* was *314 million* patient treatment days with an estimated average daily dose for tapentadol IR of 280 mg. In the time period from first launch to 20 May *2016, 7556* spontaneous, medically confirmed cases were received, reporting tapentadol either as the suspect, co-suspect, or suspect-interacting drug. Among the *7556* cases, there were *188* cases with a fatal outcome, *2195* serious nonfatal cases, and *5173* not serious cases. Age was reported in *3687* cases and ranged from *0 years* to 100 years. The cases involved *3690* female patients and *2243* male patients (the sex was not reported or was reported as unknown in *1623* cases). Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, *somnolence, vomiting, and* headache.
Section 7: Trial objectives	
The primary efficacy objective (either 12 hours or 24 hours) for 1 region is considered as the secondary efficacy objective in the other, for the different age range, as described below. Subjects can be treated for up to 72 hours, and efficacy and safety information will also be collected throughout this time period.	The primary efficacy objective (either 12 hours or 24 hours) for 1 region is considered as the secondary efficacy objective in the other, for the different age range, as described below. *Two reports will be prepared for the trial. The first report will be prepared after the last subject out of the EU PDCO set. The second report will be prepared after the last subject out of the US FDA set.* Subjects can be treated for up to 72 hours, and efficacy and safety information will also be collected throughout this time period.

Section 8.4: Discussion of the trial design: Blinding	
The trial is double-blinded to prevent bias.	The trial is double-blinded to prevent bias. *The EU PDCO set will be locked and unblinded before recruitment of the under 2 year olds in the US FDA set is completed. All subjects in the EU PDCO set (which includes completed subjects aged 2 years or older in the US FDA set) will remain locked after the analysis of the first report. Subjects under 2 years old in the US FDA set will remain blinded, as independent randomization lists are used for subjects aged less than 2 years old.*
Section 10.4.1: Methods of blinding	
Randomization and blinding will be done in accordance with the sponsor's standard operating procedures (SOPs).	Randomization and blinding will be done in accordance with the sponsor's standard operating procedures (SOPs). *There are 4 randomization lists for this trial;* *1 randomization list for each of the 3 youngest age groups (birth to <30 days, 30 days to <6 months, 6 months to <2 years), each stratified by supplemental opioid used (morphine versus hydromorphone), and* *1 randomization list for the older age groups stratified by age group (2 years to <6 years, 6 years to <12 years, 12 years to <17 years, 17 years to <18 years) and supplemental opioid use. Unblinding can be performed for 1 or more of these lists individually.*
Section 10.4.2: Methods of unblinding	
Personnel in the sponsor's department~~s~~ of clinical trials supply will be unblinded during the trial according to the sponsor's SOPs for randomization and unblinding during the trial. The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after ~~database lock at the end of the trial~~. Unblinding will be initiated by the sponsor's department of biostatistics according to the sponsor's SOPs for randomization and unblinding.	Personnel in the sponsor's department of clinical trials supply will be unblinded during the trial according to the sponsor's SOPs for randomization and unblinding during the trial. *Once the EU PDCO set has completed recruitment and data for these subjects is locked, unblinding will be performed for those subjects aged 2 years and older. The additional age groups under 2 years old will be unblinded at the end of the trial.* The qualified person for pharmacovigilance may be unblinded at any time during the trial. Persons involved in the conduct (including subjects and investigators), data management, and analysis of the trial will remain blinded until unblinding is performed after *data is locked.* Unblinding will be initiated by the sponsor's department of biostatistics according to the sponsor's SOPs for randomization and unblinding.
Section 12.1.2.1: Opioid analgesic medication given by NCA/PCA and background infusion **Section 12.1.2.2: Detailed information for other analgesic (opioid and non-opioid) medication**	
~~See Section 12.1.3 for medication used outside of this timeframe.~~	

Section 12.1.3: Prior and concomitant therapies	
All therapies~~, excluding anesthetics and medication used during the surgery,~~ used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded.	All therapies used within 28 days before allocation/randomization to IMP and up to the end of the trial must be recorded.
Section 12.3.7 Continuous monitoring of oxygen saturation	
Oxygen saturation will be monitored continuously using pulse oximetry before ~~allocation/randomization to IMP (but after surgery)~~ until 4 hours after the last administration of IMP.	Oxygen saturation will be monitored continuously using pulse oximetry *from* before *the first dose of IMP* until 4 hours after the last administration of IMP.
Section 13.3: Data management: External data	
... At the end of the trial, the contract research organization(s) providing these data will provide the data management center with a ~~complete and clean~~ data transfer.	... At the end of the trial, the contract research organization(s) providing these data will provide the data management center with a *final* data transfer.
Section 13.3: Data management: Database lock	
~~When~~ all data have been received and entered, all data checks and quality control checks have been performed, and all queries are resolved~~, the trial database will be considered clean and can be locked~~.	*There will be 2 data locks for this trial. For the first report, only data for the EU PDCO set will be locked within the electronic CRF, the CRF will not be shut down. Any potential subsequent unlocking of this set of data will be performed according to the sponsor's SOPs for database unlock. The subjects' data will be locked as soon as all data for the EU PDCO set are considered clean (i.e.,* all data have been received and entered, all data checks and quality control checks *on these data* have been performed, and all queries *for these data* are resolved*). The same procedure will apply for the final data lock at the end of the trial.*
Section 14: Statistical methods and sample size determination	
As applicable and appropriate for the individual endpoint, the endpoints will be analyzed in the age ranges for the EU PDCO and for the US FDA.	As applicable and appropriate for the individual endpoint, the endpoints will be analyzed in the age ranges for the EU PDCO and for the US FDA. *Two reports will be prepared for the trial. The first report will be prepared after the last subject out of the EU PDCO set. The second report will be prepared after the last subject out of the US FDA set. Further details on the reports are given in Section 16.6.*

Section 14.2.1: Analysis populations (analysis sets): Safety Set	
The Safety Set comprises all treated subjects in the required age ~~range~~ for the EU PDCO and US FDA. ~~For t~~he EU PDCO~~, this~~ will include subjects 2 years to less than 18 years of age; ~~for~~ the US FDA~~, this~~ will include subjects from birth to less than 17 years of age.	The Safety Set comprises all treated subjects in the required age *ranges* for the EU PDCO and US FDA. *The overall Safety Set will include all treated subjects in the trial. T*he EU PDCO *Safety Set* will include subjects 2 years to less than 18 years of age; the US FDA *Safety Set* will include subjects from birth to less than 17 years of age*. A subject will be considered as treated if administered any amount of IMP.* *If by error a subject does not receive the allocated medication, the subject will be evaluated according to the received IMP.*
Section 14.2.1: Analysis populations (analysis sets): Full Analysis Set	
~~The~~ Full Analysis Set ~~is identical to the respective Safety Set.~~	*The overall* Full Analysis Set *includes all subjects that are allocated and treated. The EU PDCO Full Analysis Set will include allocated and treated subjects aged 2 years to less than 18 years old; the US FDA Full Analysis Set will include allocated and treated subjects from birth to less than 17 years of age.* *If by error a subject does not receive the allocated medication, the subject will be evaluated as allocated within the Full Analysis Set following the intention-to-treat principle.*
Section 14.2.1: Analysis populations (analysis sets): Per Protocol Set	
The Per Protocol Set is a subset of the respective Full Analysis Set, excluding subjects with protocol deviations that may have an impact on the results of the primary efficacy analyses. Further details of the Per Protocol Set definition will be specified in the statistical analysis plan.	The *EU PDCO or US FDA* Per Protocol Set is a subset of the respective Full Analysis Set, excluding subjects with protocol deviations that may have an impact on the results of the primary efficacy analyses. Further details of the Per Protocol Set definition will be specified in the statistical analysis plan.
Section 14.2.5.1: Primary efficacy endpoint	
... For subjects who withdraw from the trial prior to the 12-hour or 24-hour time point due to any other reason than no further need of opioid analgesic medication, cumulative supplemental opioid analgesia over the respective time period will be based on the observed supplemental opioid use up to the time of the subject's discontinuation. If a subject used a total of X mg/kg of supplemental opioid through Hour T (≤24 hours), cumulative use over 24 hours will be estimated as (X/T)*24 mg/kg. If T is <12 hours, cumulative use over 12 hours will be estimated as (X/T)*12. This extrapolation assumes a constant use (in mg/kg per hour) of supplemental opioid over 24 hours. For subjects who withdraw from the trial due to no further need of opioid analgesic medication, the cumulative use of supplemental opioid will equal the total amount of supplemental opioid used up to the time of withdrawal. Other imputation methods will be used for sensitivity analyses. These will be described in detail in the statistical analysis plan.	... For subjects who withdraw from the trial prior to the 12-hour or 24-hour time point due to any other reason than no further need of *opioid analgesic medication or switch to exclusively oral* opioid analgesic medication, cumulative supplemental opioid analgesia over the respective time period will be based on the observed supplemental opioid use up to the time of the subject's discontinuation. If a subject used a total of X mg/kg of supplemental opioid through Hour T (≤24 hours), cumulative use over 24 hours will be estimated as (X/T)*24 mg/kg. If T is <12 hours, cumulative use over 12 hours will be estimated as (X/T)*12. This extrapolation assumes a constant use (in mg/kg per hour) of supplemental opioid over 24 hours. For subjects who withdraw from the trial due to no further need of *opioid analgesic medication or switch to exclusively oral* opioid analgesic medication, the cumulative use of supplemental opioid will equal the total amount of supplemental opioid used up to the time of withdrawal. Other imputation methods will be used for sensitivity

	analyses. These will be described in detail in the statistical analysis plan.
Section 14.2.5.2: Secondary endpoints and subgroup analyses	
... The ~~total amounts~~ of non-opioid analgesic medications ~~used~~ (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake will be grouped according the Anatomical Therapeutic Chemical Classification System (World Health Organization Drug Dictionary coding) ~~and route of administration, and descriptively summarized by treatment group~~ and presented in tables.	... The *number and proportion* of *subjects taking* non-opioid analgesic medications (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake will be grouped according *to* the Anatomical Therapeutic Chemical Classification System (World Health Organization Drug Dictionary coding)*,* and presented in tables *by treatment group*.
Section 14.2.5.2: Secondary endpoints and subgroup analyses: Subgroup analyses	
Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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 method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.	Summary statistics for the primary efficacy endpoint will be provided by age group (birth to <30 days, 30 days to <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*, as applicable for the EU PDCO set and US FDA set*) and by method of supplemental opioid administration (NCA vs. PCA) among other subgroup analyses.
Section 14.2.6: Analysis of safety data	
The analysis of safety data will be performed for the ~~respective Safety Set.~~	The analysis of safety data will be performed for the *EU PDCO Safety Set for the EU PDCO report and for the overall Safety Set for the US FDA report.*
Section 16.5: Publication policy	
The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy (e.g., on ClinicalTrials.gov), according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing, and applicable regulatory guidance. The sponsor will post clinical trial information in a lay person understandable form in a freely accessible sponsor internet portal.	The results of this trial will be publically disclosed in accordance with the sponsor's disclosure policy (e.g., on ClinicalTrials.gov), according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) Principles for Responsible Clinical Trial Data Sharing, and applicable regulatory guidance. The sponsor will post clinical trial information in a lay person understandable form in a freely accessible sponsor internet portal. *Due to the preparation of 2 reports, the data presented in the databases may differ.*

Section 16.6: Final report	
~~A final report~~ integrating clinical and statistical results will be prepared by the sponsor. The coordinating investigator will approve the ~~final report~~ on behalf of the participating investigators. The sponsor will provide the competent authority and relevant IEC/IRB with ~~a summary~~ of the ~~final report~~ in accordance with applicable regulatory requirements. The coordinating investigator will be provided with ~~a summary~~ of the ~~final report~~.	*Two reports for the trial,* integrating clinical and statistical results*,* will be prepared by the sponsor. *The first report will be prepared after the last subject out of the EU PDCO set. For the first report the efficacy and safety data will be reported for the EU PDCO set, the subgroup of subjects aged 2 years to less than 18 years old.* *The second report will be prepared after the last subject out of the US FDA set. For the second report the safety data will be reported for all subjects in the study; that is the subjects reported in the first report combined with subjects aged less than 2 years old. The second report will include 2 sets of efficacy results; the previously reported results for the EU PDCO set and the efficacy results for the US FDA set.* The coordinating investigator will approve the *reports* on behalf of the participating investigators. The sponsor will provide the competent authority and relevant IEC/IRB with *summaries* of the *reports* in accordance with applicable regulatory requirements. The coordinating investigator will be provided with *summaries* of the *reports*.

18.7 Protocol Amendment 07

Amendment rationale

This amendment has been enacted to:

- Specify the doses of tapentadol oral solution to give to subjects less than 6 months old.
- Limit the safety laboratory blood sampling for subjects with a low body weight to a subset of clinical chemistry evaluations only.
- Update the contact details of the international coordinating investigator.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

In the table below, deleted text is crossed out and new text is highlighted using italics.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Title page: International coordinating investigator:	
Prof [redacted] Children's National ~~Medical Center, Pharmacology & Physiology, George Washington University School of Medicine and Health Sciences,~~ 111 Michigan Avenue, N.W. Washington, D.C. 20010~~.~~ United States of America. [a]	Prof [redacted] *Division of Clinical Pharmacology,* Children's National *Health System,* 111 Michigan Avenue, N.W. Washington, D.C. 20010*,* United States of America. [a]

Changes to this protocol include:

Formerly read:

Section 1: Protocol synopsis: Trial treatments: Investigational medicinal products

Age of subject	Dose for the first 24 hours	Dose after the first 24 hours	Body weight	Tapentadol oral solution or placebo
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
~~Birth~~ to <6 months old	~~To be defined [a]~~		~~<20 kg~~	4 mg/mL
			~~≥20 kg~~	~~20~~ mg/mL

~~a) The doses for subjects aged less than 6 months old (as determined at the time of allocation to IMP) will be defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.~~

Now reads:

Section 1: Protocol synopsis: Trial treatments: Investigational medicinal products

Age of subject	Dose for the first 24 hours	Dose after the first 24 hours	Body weight	Tapentadol oral solution or placebo
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
Birth to <30 days old	*0.1 mg/kg*	*0.1 mg/kg or 0.075 mg/kg*	-	*4* mg/mL

Formerly read:

Section 1: Protocol synopsis: Trial treatments: Investigational medicinal products

...

The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level.

~~After 24 hours, the investigator may decrease~~ the dose of IMP ~~to 1.0 mg/kg~~ according to the investigator's judgment ~~of the subject's reduced need for analgesia.~~

Now reads:

...

The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level.

Dose reduction after 24 hours

The dose of IMP may be reduced after 24 hours if there is a reduced need for analgesia according to the investigator's judgment*, as follows:*

- *Age 6 months or more: 1.0 mg/kg.*
- *Age 30 days to less than 6 months: 0.3 mg/kg.*
- *Age birth to less than 30 days old: 0.075 mg/kg.*

Section 1: Protocol synopsis: Key data collected: Safety

Formerly read:

- Adverse events.
- Safety laboratory ~~(clinical chemistry and hematology).~~
- Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.

Now reads:

- Adverse events.
- Safety laboratory.
- Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.

Section 1.2: Schedule of events

Formerly read:

Take blood for safety laboratory ~~(clinical chemistry and hematology)~~

Now reads:

Take blood for safety laboratory

Section 1.3.1: Inclusion criteria
Section 9.2.1: Inclusion criteria

Formerly read:

2. Male or female subject aged from birth to less than 18 years.

Now reads:

2. Male or female subject aged from birth *(≥37 weeks gestational age)* to less than 18 years.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.3.2: Exclusion criteria **Section 9.2.2: Exclusion criteria**	
8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). ... 14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject is excluded if the: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • Total bilirubin is >2-times upper limit of normal (except if the cause is due to Gilbert's syndrome). • Glomerular filtration rate <60 mL/min (calculated according to Schwartz et al. 1984).	8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). *or* *Subject weight is less than 2500 gm.* ... 14. Subject has clinically relevant (in the investigator's judgment) abnormal values for clinical chemistry or hematology (local laboratory sample taken after surgery). A subject *aged 6 months to less than 18 years old* is excluded if the: • Aspartate transaminase or alanine transaminase is >3-times upper limit of normal. • Total bilirubin is >2-times upper limit of normal (except if the cause is due to Gilbert's syndrome). • Glomerular filtration rate <60 mL/min (calculated according to Schwartz et al. 1984). *A subject aged from birth to less than 6 months old is excluded if:* *• Aspartate transaminase or alanine transaminase is >3-times upper limit of normal.* *• There is pathological jaundice in the opinion of the investigator.* *• Glomerular filtration rate (calculated according to Schwartz et al. 1984) is:* *− <20 mL/min/1.73 m^2 for subjects <1 week post-partum.* *− <30 mL/min/1.73 m^2 for subjects 1 week to 8 weeks post-partum.* *− <50 mL/min/1.73 m^2 for subjects >8 weeks post-partum to <6 months old.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 6.2: Relevant non-clinical and clinical data: Pharmacokinetics in children	
... The addition of data from children aged ~~1 month~~ to less than 2 years ~~(KF5503/72)~~ resulted in minor changes ~~in~~ the model and was best described by incorporation of an E_{max} type maturation function. The pharmacometric parameters changed to: CL/F = ~~160~~ $L.h^{-1}$, V/F = 5~~46~~ L (the CL/F and V/F are typical estimates for a subject with a body weight of 3~~4~~ kg), Ka = 2.~~21~~ h^{-1}, T_{LAG} = 0.267 h, with the coefficients of weight on CL/F and V/F being estimated as 0.5~~51~~ and 0.8~~29~~, respectively. The maturation function, which describes the age at which half the maximum CL/F in the data set was estimated as ~~46~~ weeks. The inter-individual variabilities on CL/F and ~~V/F~~ remained the same ~~with only the variability on Ka increasing to 148%.~~	... The addition of *data from KF5503/72, i.e., adding* data from children aged *birth* to less than 2 years, resulted in minor changes *to* the model *(comprising children from birth to 18 years old)* and was best described by incorporation of an E_{max} type maturation function. The pharmacometric parameters changed to: CL/F = *155* $L.h^{-1}$, V/F = 5*33* L (the CL/F and V/F are typical estimates for a subject with a body weight of 3*2.6* kg), Ka = 2.*44* h^{-1}, T_{LAG} = 0.267 h, with the coefficients of weight on CL/F and V/F being estimated as 0.5*62* and 0.8*27*, respectively. The maturation function, which describes the age at which half the maximum CL/F in the data set was estimated as *39* weeks. The inter-individual variabilities on CL/F*, V/F,* and *Ka* remained *virtually* the same.
Section 8.4: Discussion of the trial design: Dosing	
... The population pharmacokinetic model used for the pediatric dose simulations was updated with exposure data obtained from children aged ~~1 month~~ to less than 2 years (KF5503/72), the simulations were then redone to determine the appropriate dose for the age group 6 months to less than 2 years. The simulations specified that the dose of 1.25 mg/kg would give similar exposures as that observed in the age group 2 years to less than 18 years. Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged 6 months to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the investigator's judgment of the effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. ~~The doses for younger subjects aged less than 6 months will be defined based on forthcoming pharmacokinetic data. Younger subjects will not be recruited into the trial until the dose has been defined for them.~~	... The population pharmacokinetic model used for the pediatric dose simulations was updated with exposure data obtained from children aged *birth* to less than 2 years (KF5503/72), the simulations were then redone to determine the appropriate dose for the age group 6 months to less than 2 years. The simulations specified that the dose of 1.25 mg/kg would give similar exposures as that observed in the age group 2 years to less than 18 years. *For the younger groups, a lower dose is required.* Based on these results, a dose regimen of 1.25 mg/kg will be used for the first 24 hours of treatment in this trial in children aged 6 months to less than 18 years old. After 24 hours after the start of IMP, and based on clinical judgment, the dose may either be continued at 1.25 mg/kg or it may be decreased to 1.0 mg/kg. A decision to maintain or alter the dose will depend on the investigator's judgment of the effectiveness of the analgesia and the adverse event profile observed in each child over the first 24 hour dosing period. *For children aged 1 month to less than 6 months, and birth to less than 1 month old, doses of 0.5 mg/kg and 0.1 mg/kg, respectively, are expected to produce similar exposures as that observed in the age group 6 months to less than 18 years.*
Section 9.1: Subject enrollment procedure	
… The trial enrollment will be initiated in a staggered approach. Enrollment starts with an older age group until pharmacokinetic data are available in younger age	… The trial enrollment will be initiated in a staggered approach. Enrollment starts with an older age group until pharmacokinetic data are available in younger age

Changes to this protocol include:

<table>
<tr><th>Formerly read:</th><th>Now reads:</th></tr>
<tr><td>groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years are to be recruited. The recruitment of subjects aged 6 months to less than 2 years is allowed following Amendment 05, based on pharmacokinetic and safety data gathered from a separate trial in the same age ~~group. Subjects from birth to less than 6 months of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age~~ groups. Allocation/randomization to IMP will be stratified by 7 age groups and by use of morphine or hydromorphone as supplemental opioid analgesia (Section 10.3).</td><td>groups from other trials in the pediatric clinical development program of tapentadol. Initially, subjects aged 2 years to less than 18 years are to be recruited. The recruitment of subjects aged 6 months to less than 2 years is allowed following Amendment 05 and the recruitment of subjects aged from birth to less than 6 months of age is allowed following Amendment 07, based on pharmacokinetic and safety data gathered from a separate trial in the same age group. Subjects from birth to less than 6 months of age will be recruited after pharmacokinetic and safety data are obtained and the dose selection has been defined for younger age groups. Allocation/randomization to IMP will be stratified by 7 age groups and by use of morphine or hydromorphone as supplemental opioid analgesia (Section 10.3).</td></tr>
<tr><td colspan="2">Section 10.1.3: Preparation</td></tr>
<tr><td>..
~~The IMP does not require preparation.~~
The IMP will be supplied as a liquid in 100 mL bottles intended for multiple use per subject.</td><td>..
The IMP will be supplied as a liquid in 100 mL bottles intended for multiple use per subject.</td></tr>
<tr><td colspan="2">Section 10.2.1: Dose</td></tr>
<tr><td>Table 2: Determination of tapentadol dose and oral solution concentration
<table>
<tr><th>Age of subject</th><th>Dose for the first 24 hours</th><th>Dose after the first 24 hours</th><th>Body weight</th><th>Tapentadol oral solution or placebo</th></tr>
<tr><td>6 months to <18 years old</td><td>1.25 mg/kg</td><td>1.25 mg/kg or 1.0 mg/kg</td><td><20 kg</td><td>4 mg/mL</td></tr>
<tr><td></td><td></td><td></td><td>≥20 kg</td><td>20 mg/mL</td></tr>
<tr><td>~~Birth~~ to <6 months old</td><td>~~To be defined~~ [a]</td><td></td><td>~~<20 kg~~</td><td>4 mg/mL</td></tr>
<tr><td></td><td></td><td></td><td>~~≥20 kg~~</td><td>~~20~~ mg/mL</td></tr>
</table>
~~a)~~ The ~~doses~~ for subjects ~~aged~~ less than 6 months old ~~(as determined at the time of allocation to IMP)~~ will be ~~defined based on forthcoming pharmacokinetic data. Recruitment of this age group will commence when the dose has been defined.~~
Volumes of 1 mL or less will be given using a 1 mL syringe with 0.05 mL graduations. Volumes of more than 1 mL will be given using a 5 mL syringe with 0.1 mL graduations.</td><td>Table 2: Determination of tapentadol dose and oral solution concentration
<table>
<tr><th>Age of subject</th><th>Dose for the first 24 hours</th><th>Dose after the first 24 hours</th><th>Body weight</th><th>Tapentadol oral solution or placebo</th></tr>
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<tr><td></td><td></td><td></td><td>≥20 kg</td><td>20 mg/mL</td></tr>
<tr><td>30 days to <6 months old</td><td>0.5 mg/kg</td><td>0.5 mg/kg or 0.3 mg/kg</td><td>-</td><td>4 mg/mL</td></tr>
<tr><td>Birth to <30 days old</td><td>0.1 mg/kg</td><td>0.1 mg/kg or 0.075 mg/kg</td><td>-</td><td>4 mg/mL</td></tr>
</table>
The IMP does not require preparation unless very small volumes would need to be administered, in which case the IMP may be suitably diluted. This may be necessary, for example, for subjects less than 6 months old. The investigators will be supplied with instruction sheets for the preparation of the IMP.
Volumes of 1 mL or less will be given using a 1 mL syringe with 0.05 mL graduations. Volumes of more than 1 mL will be given using a 5 mL syringe with 0.1 mL graduations.</td></tr>
</table>

Changes to this protocol include:

Formerly read:	**Now reads:**
Section 10.2.2: Total dosing time and dosing interval	
... The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level. After 24 hours, the ~~investigator may decrease the dose of IMP to 1.0 mg/kg~~ according to the investigator's judgment ~~of the subject's reduced need for analgesia~~.	... The administration of IMP is based on the investigator's judgment of the subject's condition and sedation level. *The dose of IMP may be reduced* after 24 hours *if there is a reduced need for analgesia* according to the investigator's judgment*, as follows:* • *Age 6 months or more: 1.0 mg/kg.* • *Age 30 days to less than 6 months: 0.3 mg/kg.* • *Age birth to less than 30 days old: 0.075 mg/kg.*
Section 11.1.1: Enrollment Period (Visit 1)	
... The following procedures will be performed during this period: ... • Record a 12-lead ECG. This must be performed after surgery. • Take blood for both local and central (children aged 2 years or older) or local (children younger than 2 years old) safety laboratory ~~(clinical chemistry and hematology)~~ investigations when the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.	... The following procedures will be performed during this period: ... • Record a 12-lead ECG. This must be performed after surgery. • Take blood for both local and central (children aged 2 years or older) or local (children younger than 2 years old) safety laboratory investigations when the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.
Section 11.2: Examination hierarchy and time windows	
Non-invasive procedures (including completion of questionnaires) should generally be performed first. Blood samples for safety laboratory should be taken after all non-invasive procedures have been completed. The ~~exact~~ order that procedures are performed may deviate due to local circumstances and ~~do~~ not constitute, per se, a protocol deviation.	Non-invasive procedures (including completion of questionnaires) should generally be performed first. Blood samples for safety laboratory should be taken after all non-invasive procedures have been completed. The order that procedures are performed may deviate due to local circumstances and *a change in the order does* not constitute, per se, a protocol deviation.
Section 11.7: Overview of blood sampling in this trial	
... Table 5: Approximate volume of blood to be collected from each subject	... Table 6: Approximate volume of blood to be collected from each subject

Table 5

Assessment	Approx-imate blood volume per sample	Number of samples		Approximate total blood volume per test [a]	
		2 years to <18 years	<2 years	2 years to <18 years	<2 years
Clinical chemistry	2 mL	2 for central, 1 for local	2 for local	6 mL	4 mL

Table 6

Assessment	Approx-imate blood volume per sample	Number of samples		Approximate total blood volume per test [a]	
		2 years to <18 years	<2 years [b]	2 years to <18 years	<2 years
Clinical chemistry	2 mL	2 for central, 1 for local	2 for local	6 mL	4 mL
Hematology	2 mL	2 for central, 1 for local	2 for local	6 mL	4 mL

Changes to this protocol include:

Formerly read:	**Now reads:**
Hematology 2 mL 2 for central, 1 for local 2 for local 6 mL 4 mL **Total** 12 mL 8 mL The volume of blood taken may be individually variable due to flushing, resampling etc. a) Calculated as number of samples multiplied by amount of blood per sample. For subjects aged 2 years and older, the total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even if additional blood is drawn for a pharmacokinetic analysis if a serious adverse event occurs) (Table 3). For subjects aged less than 2 years old, blood sampling for clinical chemistry and hematology should be performed such that blood volumes taken do not exceed 0.8 mL/kg body weight for each sampling time point, and 2.4 mL/kg in total (EMEA ad hoc working party 2008). ~~The volume of blood drawn from subjects who participate in the trial will not exceed the recommended limits (Section 8.4).~~	**Total** 12 mL 8 mL The volume of blood taken may be individually variable due to flushing, resampling etc. a) Calculated as number of samples multiplied by amount of blood per sample. *b) For subjects with a low body weight, blood sampling for clinical chemistry and hematology may be limited to a subset of clinical chemistry evaluations only to keep the total blood volume drawn low.* *The volume of blood drawn from subjects who participate in the trial will not exceed the recommended limits (Section 8.4).* For subjects aged 2 years and older, the total blood volume drawn per subject will not exceed approximately 15 mL during the trial (even if additional blood is drawn for a pharmacokinetic analysis if a serious adverse event occurs) (Table 3). For subjects aged less than 2 years old, blood sampling for clinical chemistry and hematology should be performed such that blood volumes taken do not exceed 0.8 mL/kg body weight for each sampling time point, and 2.4 mL/kg in total (EMEA ad hoc working party 2008). *For subjects less than 6 months old with a low body weight, such that the drawing of sufficient blood sample volumes for both clinical chemistry and hematology are precluded, the tests may be limited to a subset of clinical chemistry evaluations only (the tests to be performed are alanine transaminase and aspartate transaminase, alkaline phosphatase, and creatinine [with calculation of the glomerular filtration rate]). Local site-specific guidelines must also be adhered to. Other chemistry and hematology values from samples taken for the standard of care may be used to supplement the safety laboratory profile.*
Section 12.3: Collection of safety data	
The following safety data will be collected: • Adverse events. • Safety laboratory ~~(clinical chemistry and hematology).~~ • Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.	The following safety data will be collected: • Adverse events. • Safety laboratory. • Pregnancy test for female subjects aged 12 years or older, or post-menarchal, or sexually active.
Section 12.3.2: Safety laboratory	
... The following tests will be performed:	... The following tests will be performed *unless the weight of the subject precludes full blood sampling, in which case the tests may be limited (see Section 11.7)*:

19 APPENDIX

19.1 List of medical concepts for consideration of seriousness stratified by system organ class

Blood and lymphatic system disorders		
Agranulocytosis	Aplastic anaemia	Blast cell proliferation (myeloproliferative and lymphoprolipherative disorders)
Bone marrow depression	Disseminated intravascular coagulation (DIC)	Haemolytic anaemia
Histiocytosis	Loss of anticoagulation control	Pancytopenia
Splenic haemorrhage, infarction or thrombosis	Thrombocytopenia (<30000)	Thrombotic thrombocytopenic purpura
Cardiac disorders		
Angina unstable	Atrial flutter	Atrioventricular block complete
Cardiac arrest	Cardiac failure acute	Cardiac fibrillation
Cardiac tamponade	Cardiogenic shock	Cardiomyopathy acute
Coronary artery spasm	Cor pulmonale decompensated	Myocardial infarction
Torsade de pointes	Ventricular fibrillation	Ventricular tachycardia
Ear and labyrinth disorder		
Deafness	Vestibular ataxia	
Endocrine disorders		
Adrenocortical insufficiency acute		
Eye disorders		
Cataract/lens opacity	Glaucoma	Keratitis/corneal opacification
Macular degeneration	Optic neuropathy, atrophy	Papilloedema
Ptosis	Retinal artery/vein occlusion	Retinitis
Scotoma	Sudden visual loss	Uveitis
Vitreous detachment		
Gastrointestinal disorders		
Colitis haemorrhagic	Gastric ulcer haemorrhage	Gastric ulcer perforation
Haematemesis	Haemoperitoneum	Ileus
Intestinal ischaemia	Intestinal perforation	Melaena
Mesenteric occlusion	Mesenteric vein thrombosis	Pancreatitis
Peritonitis		
General disorders and administration site conditions		
Malignant hyperthermia		
Hepato-biliary disorders		
Hepatic failure	Hepatitis fulminant	Hepatic necrosis
Hepatorenal syndrome	Portal hypertension	Reye’s syndrome

Immune system disorders		
Amyloidosis	Anaphylactic reaction	Anaphylactic shock
Graft versus host disease		
Infections and infestations		
Endotoxic shock	Sepsis	Toxic shock syndrome
Transmission of an infectious agent via a medicinal product		
Injury, poisoning and procedural complications		
Transplant failure	Wound dehiscence	
Metabolism and nutrition disorders		
Diabetic coma	Failure to thrive	Hypercalcaemia (CTC IV)
Hyperkalaemia (CTC IV)	Hypocalcaemia (CTC IV)	Hypokalaemia (CTC IV)
Lactic acidosis	Porphyria	Shock hypoglycaemic
Tetany		
Musculoskeletal and connective tissue disorders		
Aseptic necrosis bone	Fracture pathological	Muscle necrosis
Osteomalacia	Rhabdomyolysis	Systemic lupus erythematosus
Systemic sclerosis		
Nervous system disorders		
Amnesia	Anticholinergic syndrome	Aphasia
Cerebral oedema	Chorea	Coma
Convulsions	Demyelination	Encephalitis
Encephalopathy	Epilepsy	Guillain Barré syndrome
Hydrocephalus	Intracranial haemorrhage	Meningitis
Multiple sclerosis	Myasthenia gravis	Myelitis
Neuroleptic malignant syndrome	Opisthotonus	Paralysis
Paresis	Parkinson syndrome	Serotonin syndrome
Stroke	Tunnel vision	
Pregnancy, puerperium and perinatal conditions		
Abortion	Eclampsia	Intra-uterine death
Psychiatric disorders		
Anorexia nervosa	Delirium	Drug abuse
Drug dependence	Homicidal ideation	Intentional misuse
Self-injurious ideation/attempt	Suicidal ideation/attempt	Suicide completed
Renal and urinary disorders		
Anuria	Goodpasture’s syndrome	Haemolytic uraemic syndrome
Nephritis/nephritic syndrome	Nephrotic syndrome	Oliguria
Renal failure acute	Renal tubular necrosis	Urinary obstruction/retention
Reproductive system and breast disorders		
Metrorrhagia/uterine haemorrhage	Priapism	

Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	Adult respiratory distress syndrome	Alveolitis allergic
Asphyxia	Bronchospasm	Laryngeal oedema
Pulmonary fibrosis	Pulmonary haemorrhage	Pulmonary infarction
Pulmonary vasculitis	Respiratory arrest	Status asthmaticus
Pulmonary oedema		
Skin and subcutaneous tissue disorders		
Angioneurotic oedema	Erythema nodosum	Pemphigus
Stevens-Johnson syndrome	Toxic epidermal necrolysis	Vascular purpura
Vascular disorders		
Acute circulatory failure	Embolism	Malignant hypertension
Necrosis ischaemic	Thrombosis	

CTC = Common Toxicity Criteria also referred to as the Common Terminology Criteria for Adverse Events (CTCAE).
Dated Jul 2012

19.2 Face, Legs, Activity, Cry, Consolability scale

This is an example and the version used may differ.

DMS version: 1.0 ID: 1028201

FLACC Behavioral Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort
Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.			

Source: Merkel et al. 1997.

19.3 Faces pain scale – Revised

FPS-R - Canada/English - Mapi.
ID7858 / FPS-R_AU2.0_eng-CAori.doc

Faces Pain Scale – Revised (FPS-R)

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.

"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to right-most face]* **- it shows very much pain. Point to the face that shows how much you hurt** [right now]."

*Score the chosen face **0**, **2**, **4**, **6**, **8**, or **10**, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" and "sad". This scale is intended to measure how children feel inside, not how their face looks.*

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. Pain 1990;41:139-150.

(fold along dotted line)

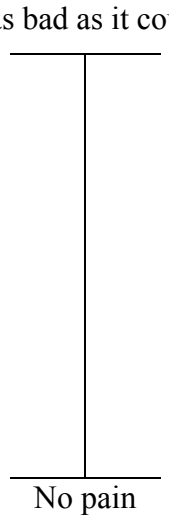
10 **8** **6** **4** **2** **0**

19.4 Visual analog scale

This is an example and the version used may differ.

The subject will evaluate pain intensity by answering the following question:

"My pain right now is"



The line will be 100 mm in length. The subject will be instructed to make a mark on the line to indicate the pain intensity.

Using a standard ruler, a trained observer (an individual under the supervision of the principal investigator who observes and instructs subjects regarding trial procedures) will measure the distance in millimeter (0-100) from the bottom of the scale to the subject's mark and record this distance in the CRF.

19.5 Columbia–Suicide Severity Rating Scale

Source: http://www.cssrs.columbia.edu/scales_cssrs.html

19.5.1 Columbia–Suicide Severity Rating Scale – children's baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

19.5.2 Columbia–Suicide Severity Rating Scale – children's since last visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact *posnerk@nyspi.columbia.edu*

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

19.6 Palatability and acceptability questionnaire

Questions on palatability and acceptability

- How does the medication taste?

- Swallowing the medication is

Literature: Guinard JX. Sensory and consumer testing with children. Trends in Food Science & Technology 2001; 11: 273–283.

PAQ (UK-English) 19MAR2013 FINAL

Source: Guinard 2011.

19.7 Algorithm to detect potential severe cases of drug-induced liver injury

Check laboratory values at the times specified in the trial protocol for increases of alanine transaminase, aspartate transaminase, and total bilirubin after administration of IMP.

If alanine transaminase or aspartate transaminase is >3 x upper limit of normal, repeat the lab test within 48 hours to 72 hours. The test should be performed for aspartate transaminase, alanine transaminase, creatine kinase, total, direct and indirect bilirubin, alkaline phosphate, lipase and gamma-glutamyl transferase.

If alanine transaminase or aspartate transaminase is >3 x upper limit of normal, (confirmed by retesting), and total bilirubin is <2 x upper limit of normal, the investigator and the sponsor should discuss the following recommendations:

- Initiate a close observation of the subject/patient.
- Repeat testing of alanine transaminase, aspartate transaminase, alkaline phosphate, total, direct and indirect bilirubin, creatine kinase, gamma-glutamyltransferase, international normalized ratio, eosinophilic granulocytes and lipase 2 times to 3 times weekly.
- Decrease the frequency of retesting to once a week or less if abnormalities stabilize or if the IMP has been discontinued.

If alanine transaminase or aspartate transaminase is >3 x upper limit of normal and total bilirubin is >2 x upper limit of normal, the investigator and the sponsor should discuss following recommendations:

- Repeat testing of alanine transaminase, aspartate transaminase, alkaline phosphate, total, direct and indirect bilirubin, creatine kinase, gamma-glutamyltransferase, international normalized ratio, eosinophilic granulocytes and lipase.
- Consult a hepatologist/gastroenterologist who must then conduct an obligatory abdominal ultrasound and other examinations (e.g., liver biopsy) as necessary.
- Obtain more detailed history of symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]).
- Obtain history of concomitant medication, including herbal drugs, alcohol use or other drugs of abuse.
- Obtain local laboratory tests as listed in Table 7.

Table 7: Local laboratory tests to be performed for the evaluation of alternative causes of drug-induced liver injury

Cause	Test/parameter
Hepatitis A	Anti-HAV-IgM
Hepatitis B	HBsAg and Anti-HBc IgM
Hepatitis C	Anti-HCV (if positive, HCV-RNA by PCR)
Hepatitis D	HBsAG and Anti-HDV IgM
Hepatitis E	Anti-HEV
Autoimmune hepatitis	ANA or SMA, elevated IgG-levels, liver kidney microsomal antibodies
Primary biliary cirrhosis	Mitochondrial antibody, elevated IgM-levels
Primary sclerosing cholangitis	P-ANCA
Epstein-Barr virus	Anti-VCA IgG and IgM
Cytomegalovirus	Anti-CMV IgM and IgG
Alcoholic liver disease	CDT (Carbohydrate-Deficient-Transferrin)
α_1 Antitrypsin disease	α_1 Antitrypsin
Wilson disease	Ceruloplasmin
Hemachromatosis	Ferritin
Hepatocellular cancer	α –fetoprotein

Ag = antigen; ANA = anti-nuclear antibody; HB = hemoglobin; Ig = immune globulin; P-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; PCR = polymerase chain reaction; RNA = ribonucleic acid; SMA = smooth muscle antibody; V = virus; VCA = viral capsid antigen.

19.8 Global impression of change

Clinical Global Impression of Change (CGIC)

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

[1] ☐ Very much improved	[5] ☐ Minimally worse
[2] ☐ Much improved	[6] ☐ Much worse
[3] ☐ Minimally improved	[7] ☐ Very much worse
[4] ☐ No change	[0] ☐ Not assessed

Source: National Institute of Mental Health (NIMH)

Patient (or parent/legal guardian) Global (overall) Impression of Change (PGIC)

Please select the number that best describes how you feel.

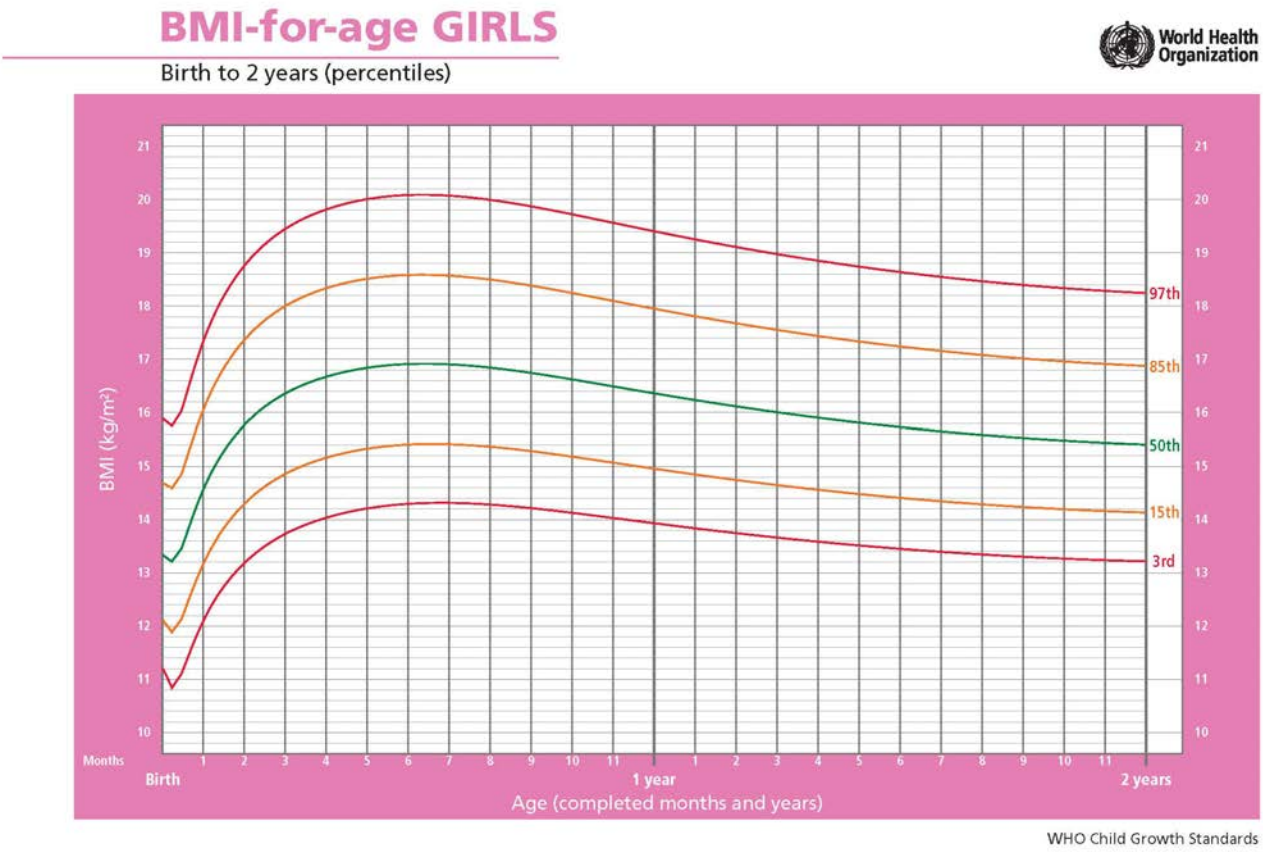
Since the start of the study, my overall status is:

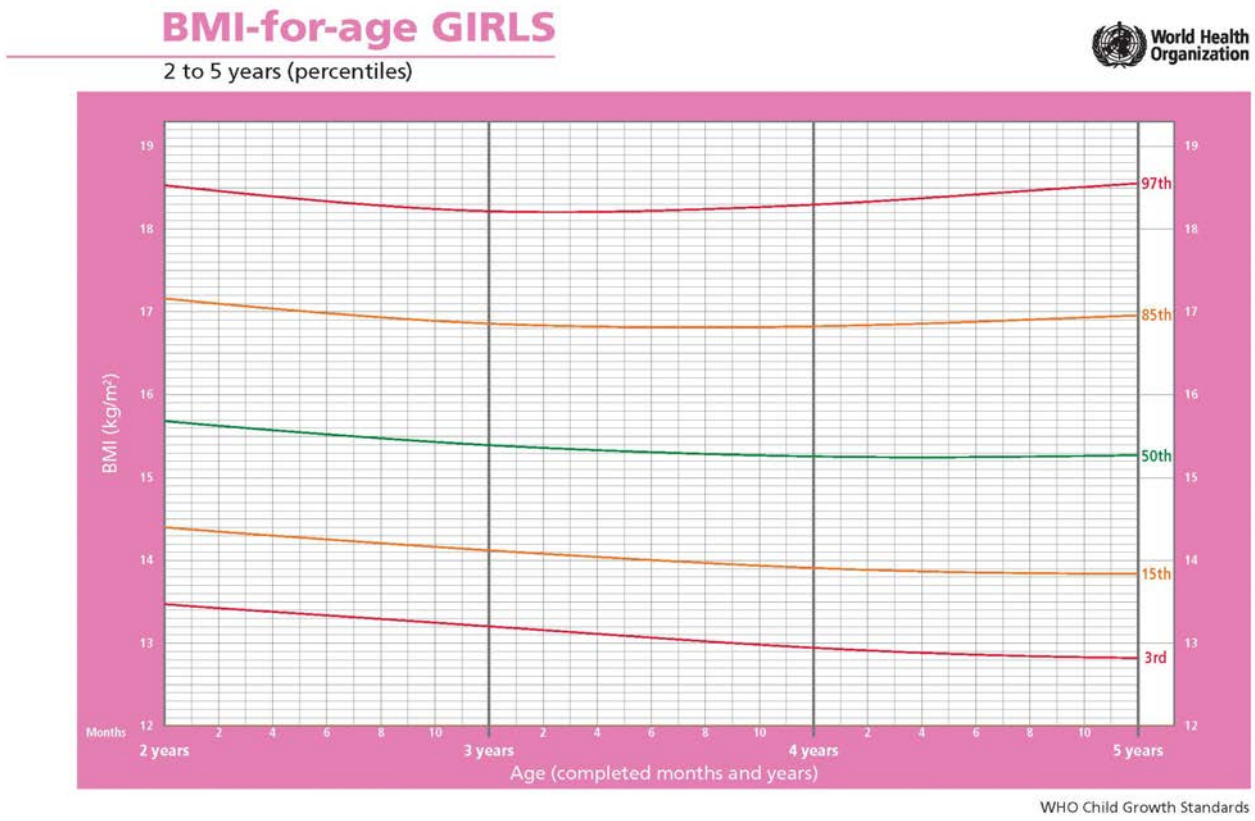
✓*one box only:*

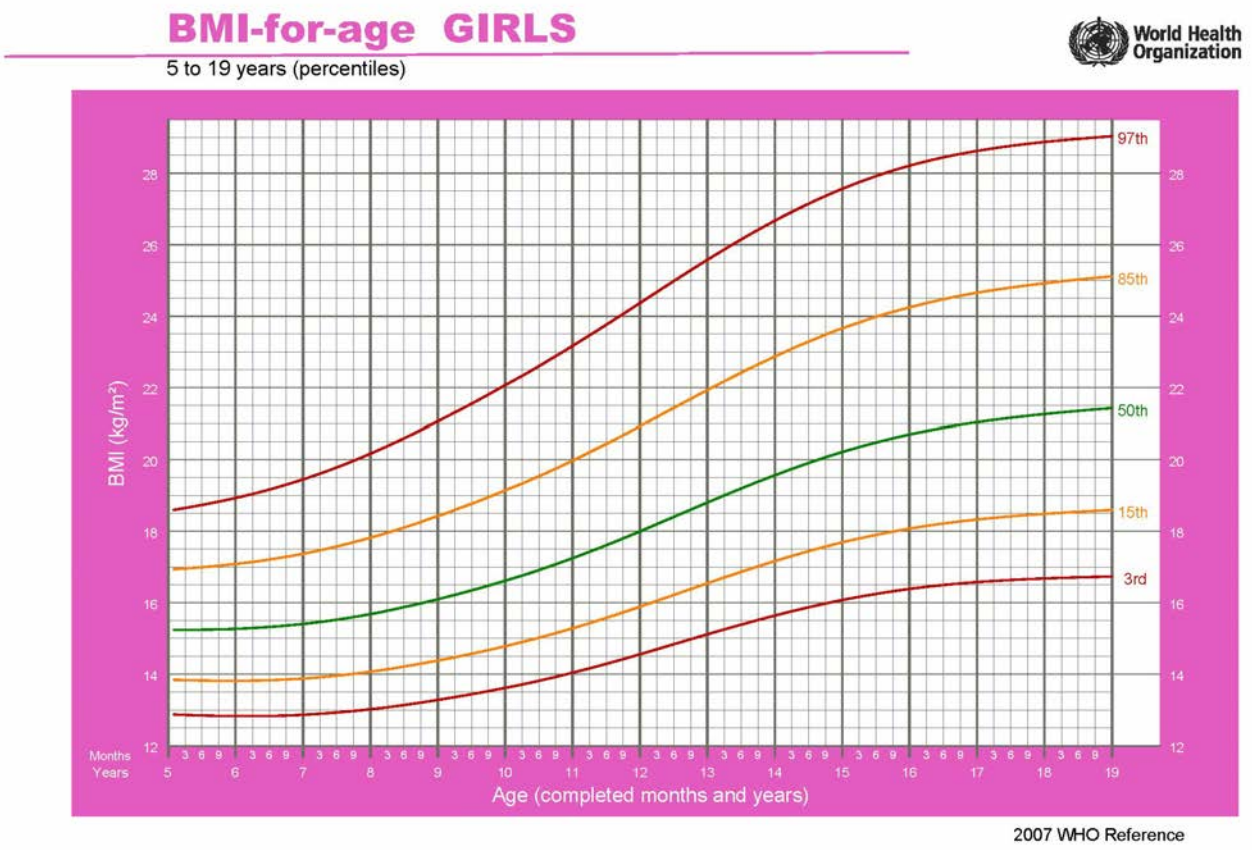
[1] ☐	Very Much Improved
[2] ☐	Much Improved
[3] ☐	Minimally Improved
[4] ☐	No Change
[5] ☐	Minimally Worse
[6] ☐	Much Worse
[7] ☐	Very Much Worse

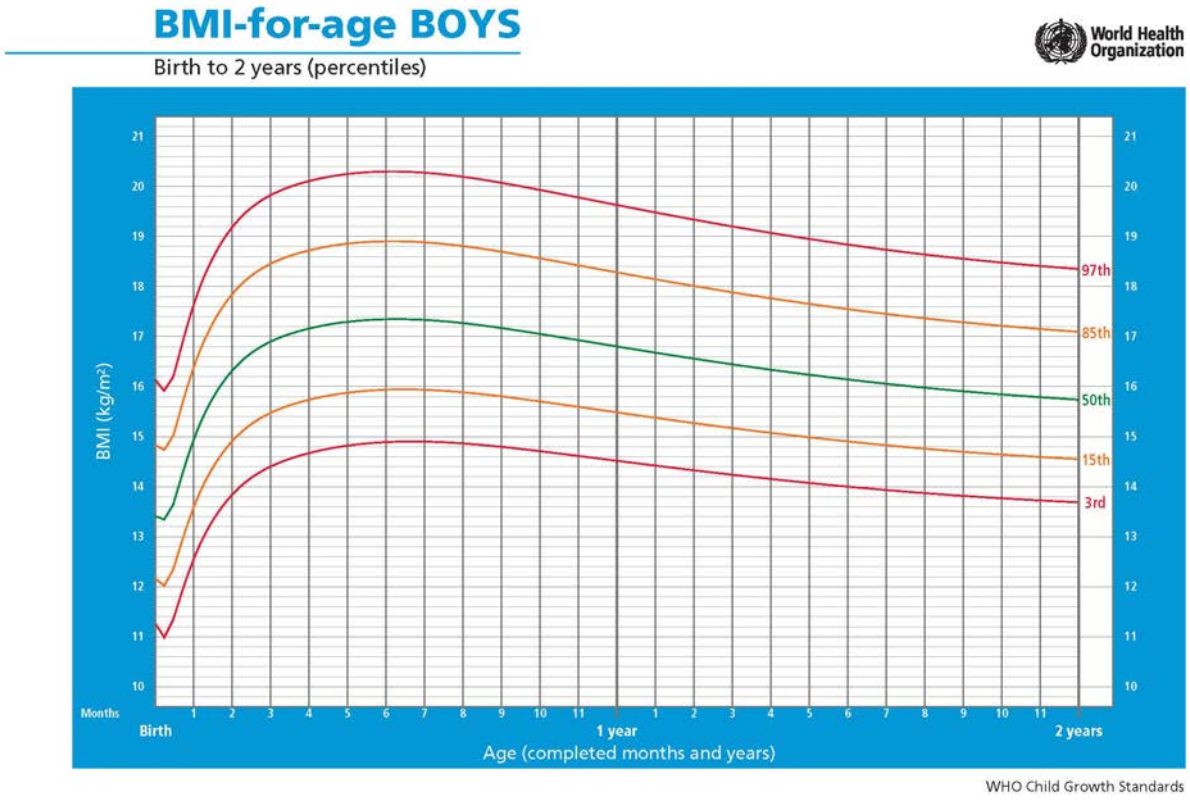
(US/English)

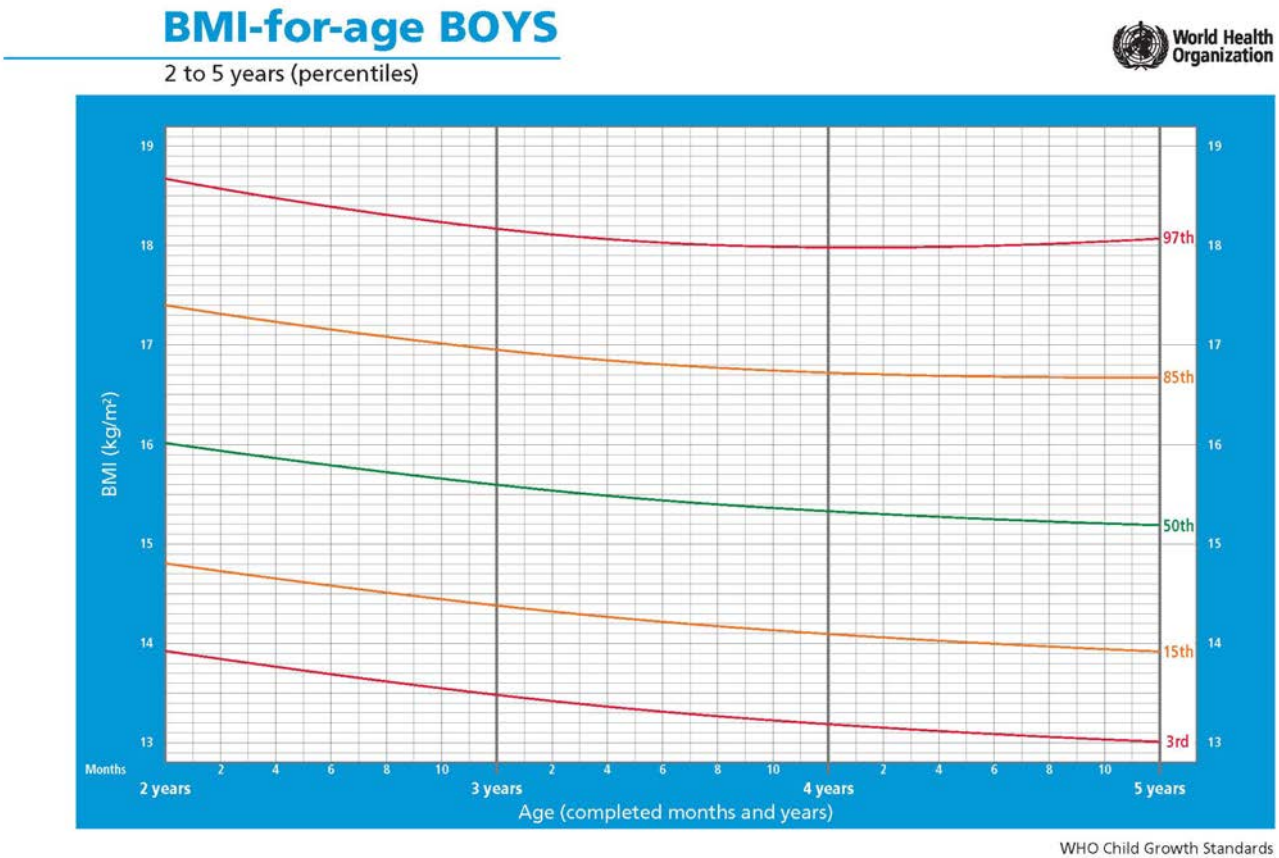
19.9 World Health Organization body mass index growth charts

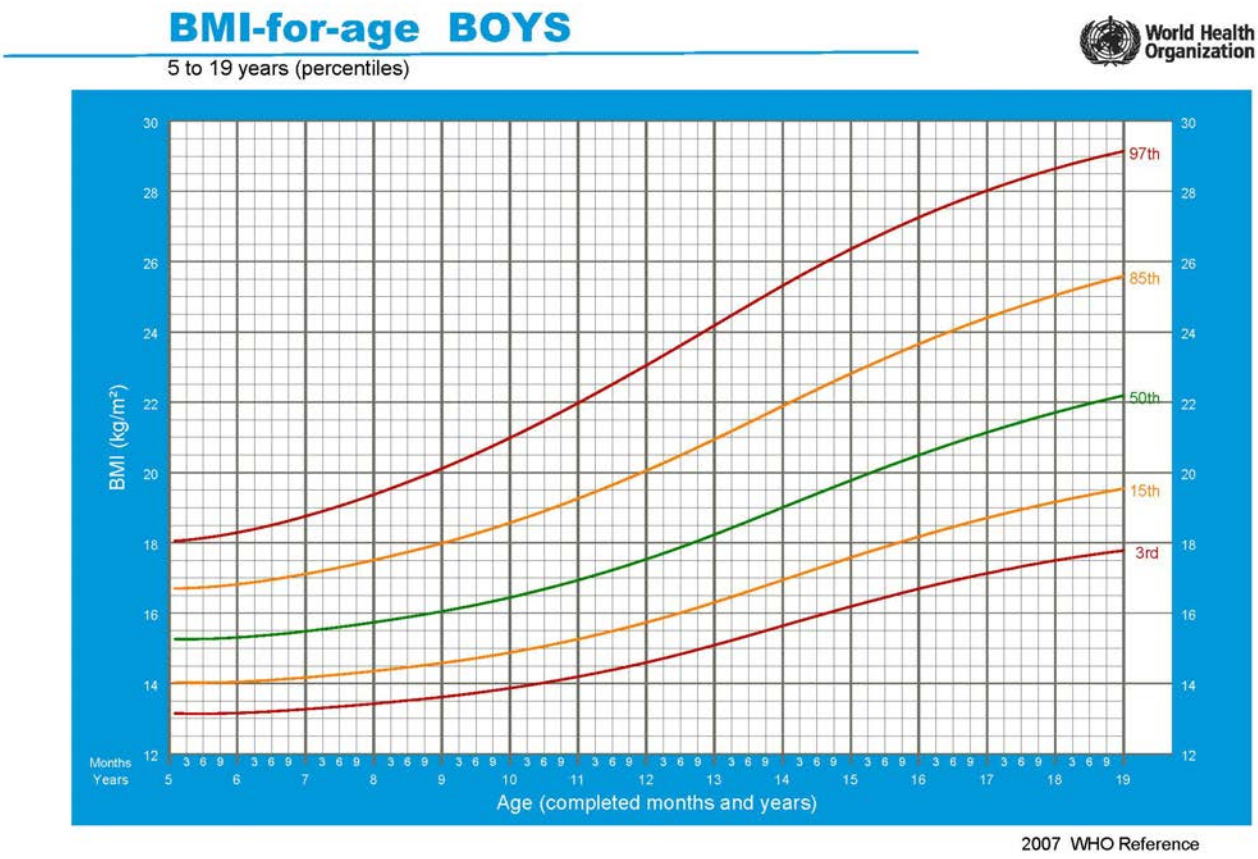



BMI-for-age GIRLS
2 to 5 years (percentiles)
World Health Organization
BMI (kg/m²)
97th
85th
50th
15th
3rd
Months
2 years
3 years
4 years
5 years
Age (completed months and years)
WHO Child Growth Standards


BMI-for-age GIRLS
5 to 19 years (percentiles)
World Health Organization
BMI (kg/m²)
97th
85th
50th
15th
3rd
Months
Years
Age (completed months and years)
2007 WHO Reference


BMI-for-age BOYS
Birth to 2 years (percentiles)
World Health Organization
BMI (kg/m²)
97th
85th
50th
15th
3rd
Months
Birth
1 year
2 years
Age (completed months and years)
WHO Child Growth Standards


BMI-for-age BOYS
2 to 5 years (percentiles)
World Health Organization
BMI (kg/m²)
97th
85th
50th
15th
3rd
Months
2 years
3 years
4 years
5 years
Age (completed months and years)
WHO Child Growth Standards


BMI-for-age BOYS
5 to 19 years (percentiles)
World Health Organization
BMI (kg/m²)
97th
85th
50th
15th
3rd
Months
Years
Age (completed months and years)
2007 WHO Reference

19.10 Collecting, handling and shipment of pharmacokinetic serum samples

19.10.1 Labeling

The labels should include the following information:

- Trial number.
- Subject number.
- Time and date of sample.
- Nominal sampling time after the last administered dose of IMP.

19.10.2 Devices

- S-Monovette® (e.g., 1.2 mL, Sarstedt, Order No.06.1663.001)
- Cryovials (e.g., 1.5 mL, VWR, Order No. 479-3225)
- Other devices may be used if equivalent after approval by the sponsor.

19.10.3 Procedure

- Fill S-Monovette® with 0.5 mL of blood.
- Register sample collection date and time in the CRF.
- Before processing: mix immediately by inverting the S-Monovette gently 1-2 times and incubate at room temperature for 20 minutes to 30 minutes.
- Centrifuge at room temperature at 1500 g for 10 minutes. Clot and serum must be well separated. If necessary, centrifuge once again.
- Carefully pipette all the serum into appropriately labeled cryotubes.
- Discard collection tube.
- Freeze cryovial at –15°C or lower until shipment on dry ice.

19.10.4 Shipment

The samples will be sent to the bioanalytical facility according to the schedule stated in the Scope of Work with the Central Laboratory. An inventory list must be included with each shipment. The inventory list must note each specimen drawn for each subject, and note any missing specimens.

- For shipment, ensure that the samples are packed with sufficient dry ice to maintain frozen state throughout transport.
- Send the samples by premium courier door-to-door delivery to the bioanalytical laboratory (address given in Section 19.10.5). Choice of courier has to be approved by the sponsor.
- Notify sponsor contact by e-mail and the bioanalytical laboratory before shipment of the samples.

19.10.5 Contact

Contact person	Dr [redacted]	Dr [redacted]
E-mail address	[redacted]@grunenthal.com	[redacted]@grunenthal.com
Phone	+49 (0) 241-569-[redacted]	+49 (0) 241-569-[redacted]
Postal address	Zieglerstraße 6 52078 Aachen Germany	
Fax	+49 (0) 241-569-[redacted]	

19.11 University of Michigan Sedation Scale

0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

Source: Malviya et al. 2002.