PROTOCOL

Trial number:	KF5503-66
Title of trial:	An open-label trial, enrolling subjects aged 6 years to less than 18 years suffering from pain requiring prolonged release opioid treatment, to evaluate the safety and efficacy of tapentadol PR versus morphine PR, followed by an open-label extension.
EudraCT number:	2012-004360-22.
Trial sponsor:	Grünenthal GmbH, 52099 Aachen, Germany.
International coordinating investigator:	[redacted], UCL Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK [a]. Phone: [redacted]. Email: [redacted]
Trial site(s):	Multi-site trial in ~50 sites. Documentation of the involved trial sites will be maintained.
Trial design:	This is a 2-part trial: Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial. Part 2 is an open-label Extension Period with tapentadol treatment (Tapentadol Period) or an observation period without tapentadol treatment (Observation Period) lasting for up to 12 months.
Investigational medicinal products:	Tapentadol prolonged release (PR) tablets. Morphine PR tablets.
Sponsor's medically qualified person:	[redacted], Associate Principal Clinical Scientist. Phone: +49 (0) 241-569-[redacted]. Email: [redacted]@grunenthal.com [a].
Sponsor's signatory:	[redacted], Senior International Clinical Lead, Grünenthal GmbH.
Publication number:	[redacted]. **Universal Trial Number:** U1111-1154-4572.
Pharmacokinetic study code:	PK1492.

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

NCT02151682

Version	Date	DMS Version:	Valid for
Original:	28 Apr 2014	DMS version 4.0	All countries
Amendment 01	26 Jun 2014	DMS version 5.0	All countries
Amendment 02	23 Jun 2015	DMS version 6.0	All countries
Amendment 03	07 Dec 2016	DMS version 7.0	United States (US)
Amendment 04	23 May 2017	DMS version 8.0	All countries
Amendment 05	27 Jul 2017	DMS version 9.0	All countries

1 PROTOCOL SYNOPSIS

Trial objectives:

The trial objectives for Part 1 of the trial are:

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

The trial objective for Part 2 of the trial is:

- To describe the long-term safety profile covering up to a 12-month period with treatment of tapentadol PR taken twice daily (Tapentadol Period) in subjects aged 6 years or older suffering from long-term pain requiring prolonged release opioid treatment, or in subjects without tapentadol treatment (Observation Period) aged 6 years or older who have received at least 1 dose of investigational medicinal product (IMP).

Trial design:

This is a 2-part trial:
Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring prolonged release opioid treatment. The target is to allocate 69 subjects in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily.

Blood samples for pharmacokinetic evaluations will only be drawn from subjects on tapentadol PR.

Part 2 is an open-label Extension Period with tapentadol treatment (Tapentadol Period) or an observation period without tapentadol treatment (Observation Period) lasting for up to 12 months.

Definition of the primary endpoint

Part 1 (primary analysis of the trial)

The primary endpoint is a binary variable “responder”. A subject is defined as “responder” if both of the following criteria are met:

- Completion of the 14-day Treatment Period (Part 1).
- One of the following calculated from the scheduled pain assessments (“pain right now”) documented during the last 3 days of the Treatment Period:
  - Average pain <50 on a visual analog scale (VAS) for subjects aged 12 years to less than 18 years; or <5 on the Faces Pain Scale–revised (FPS-R) for subjects aged 6 years to less than 12 years.
  - Average reduction from baseline of pain ≥20 on a VAS for subjects aged 12 years to less than 18 years; or ≥2 on the FPS-R for subjects aged 6 years to less than 12 years.

The proportion of subjects classified as responders will be assessed and compared between the treatment groups.

Age groups are determined at Visit V2. Baseline pain is defined as "pain right now" at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.

Definition of the secondary endpoints

The main secondary endpoints are:

Part 1

- Constipation as assessed by changes from baseline (Visit V2) of total scores for the modified constipation assessment scale (CAS).

Part 1 and Part 2

- Tolerability as assessed by the number and type of adverse events and adverse drug reactions by treatment group during the different trial periods, on a subject and event level.

Definition of other endpoints

Other endpoints compared between treatment groups at each measurement time point are:

Part 1 - Treatment Period, other endpoints (baseline is the value at Visit V2):

- Pain as assessed by changes from baseline using the VAS.
- Pain as assessed by changes from baseline using the FPS-R.
- Use of rescue medication as assessed by number of doses of rescue medication taken at different dose levels of IMP.
- Description of population pharmacokinetics of tapentadol and tapentadol-O-glucuronide.
- Palatability and acceptability as assessed by differences within treatment groups of the 5-point hedonic faces scale with the verbal rating score at Visit V3 and Visit VE (the End of Treatment Visit).

Part 2 - Tapentadol Period, other endpoints (baseline is the value at Visit VE):

- Pain as assessed by changes from baseline using the VAS.
- Pain as assessed by changes from baseline using the FPS-R.
- Constipation as assessed by changes from baseline of total scores for the modified CAS.

Part 2 - Observation Period, other endpoints (baseline is the value at Visit VE or Visit ET [Early Termination Visit]):

- Constipation as assessed by changes from baseline of total scores for the modified CAS.

Part 1 or Part 2 - other endpoints:

- Opiate withdrawal symptoms as assessed by the scale score of the subjective opiate withdrawal scale (SOWS) questionnaire at individual time points and changes to baseline.
- Time to discontinuation of IMP assessed by a survival analysis.

Trial population

Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2 (Allocation Visit; Day 1), and who comply with the inclusion/exclusion criteria given in Section 1.3. Long-term pain is defined as any pain condition that requires a minimum of 14 days of treatment with a strong oral opioid. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., spinal

surgery), cancer-related pain (including pain caused by treatment) as well as chronic indications with moderate to severe pain.

The age groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined.

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

Trial treatments

The 2 IMPs are:

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

The IMP will be taken for 14 days in Part 1.

Regardless of the treatment received during the treatment period, subjects who are still in need of a prolonged release opioid will be given the possibility to enter the Tapentadol Period (Part 2) for up to 12 months. Dosing will be twice daily with a dosing interval of ~12 hours (but not less than 6 hours).

The initial dose administered will be adjusted to the weight of the subject and then titrated to the subject's optimal dose (see Section 10.2.3 of the body of the protocol). Subjects will be titrated to the therapeutic effect, defined as a balance between self-reported analgesia and side effects based on the judgment of the investigator and within the given limits as defined per weight group (see Table 2 for tapentadol PR and Table 3 for morphine PR in the body of the protocol) after consulting the investigator at visits or by using telephone contacts throughout the period of treatment with IMP, in Part 1 and Part 2.

Doses may only be increased after a minimum of 2 days (4 scheduled intakes of IMP) on a dose. The dose can be reduced at any time, but the investigator must be informed as soon as possible.

Rescue medication

During Part 1 only, morphine oral solution will be supplied by the sponsor as rescue medication for both treatment groups.

Concomitant medications/therapies

All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed.

Subjects will be allowed to participate in trials of marketed therapeutic medications and therapies (including trials of antibody therapies) at the same time as participating in this trial.

Allowed concomitant medications/therapies with timely or dose restrictions are:

On the day of allocation to IMP (Visit V2):

- Weak and strong opioids up to a morphine-equivalent dose of <3.5 mg/kg per day.

During the Treatment Period (from Visit V2 to Visit VE):

- Rescue medication (morphine oral solution) provided by the sponsor.

During the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Intravenous opioids during surgery.

During the Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Immediate release strong opioids for treatment of breakthrough pain and incidental pain.

Forbidden prior and concomitant medication/therapies are:

Before allocation to IMP (Visit V2) and during the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- From 14 days prior to Visit V2 until the last intake of IMP: Monoamine oxidase inhibitors.
- From 30 days prior to Visit V2 until the last intake of IMP: Any medication or medical devices without a marketing authorization for human use.

Subjects may not undergo a washout of the above for the purposes of the trial.

During the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Non-trial supplied opioids (unless covered by allowed concomitant treatments).

Caution should be exercised with concomitant medication that:

- May enhance the risk of central nervous or respiratory depression.
- Is a serotoninergic medicinal product (e.g., selective serotonin re-uptake inhibitors).
- Is a strong enzyme inducer (e.g., rifampicin, phenobarbital, St John's Wort) that is started or stopped during the intake of IMP.

Trial period

Estimated date of first subject in: Oct 2014.

Part 1, estimated date of last subject out: Sep 2018.

Part 2, estimated date of last subject out: Sep 2019.

Each subject is expected to be treated with IMP for 14 days in Part 1. Subjects will be in Part 2 for up to 12-months. In total, for each subject, the trial duration will be ~13 months.

Course of the trial

The trial will comprise 2 parts.

Part 1: After the Enrollment Visit, all subjects complying with the inclusion/exclusion criteria will enter Part 1. Part 1 of the trial will be completed after the last subject has attended Visit VE. Data of Part 1 will comprise the primary analysis of the trial.

Blood samples for pharmacokinetic evaluations will only be drawn from subjects on tapentadol PR.

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

Tapentadol Period (12 months): Subjects completing the Treatment Period (Part 1) with tapentadol PR or morphine PR and who have need for continued opioid treatment can enter the Tapentadol Period. They will be treated with tapentadol PR for up to 12 months until Visit F12M (a 12-month visit relative to Visit VE). As withdrawal symptoms may occur in subjects transferring

from morphine PR to tapentadol PR, because they start tapentadol PR at 70% of the equivalent morphine dose, these subjects will have 2 additional visits at the beginning of the Part 2 Tapentadol Period (Visit M1 and Visit M2).

Observation Period (12 months): Subjects not completing the Treatment Period (Part 1), but who have taken at least 1 dose of IMP, and those who complete the Treatment Period but do not want to continue with tapentadol PR, will enter the Observation Period (12 months). Subjects will be followed until Visit F12M. Subjects in the Tapentadol Period of Part 2 may stop treatment early (before Visit F12M) and switch to Observation period for the remainder of Part 2.

Part 2 of the trial will be completed after the last subject has completed or discontinued from the trial.

See Section 1.1 for a summary of the trial as a flow diagram and Section 1.2 for tabular schedules of events for each period.

Blood sampling volumes

The volumes of blood taken for each assessment may vary due to trial site requirements; however, the expected total blood volume drawn per subject during the trial (Part 1: 12 mL and Part 2: 25 mL) should not generally exceed 37 mL (excluding any blood that is discarded). Additional blood may be drawn if a (serious) adverse event occurs or if the investigator considers it necessary.

Key data collected

Subject characteristics data:

- Demographic data (date of signing the informed consent/assent form, sex, age, and race/ethnicity).
- Medical history including pain history.
- Prior and concomitant medication and therapies.

Other data:

- Acceptability and palatability of IMP.

Pharmacokinetic data:

- Serum pharmacokinetics (serum concentrations of tapentadol and tapentadol-O-glucuronide). Blood samples for pharmacokinetic evaluations will only be drawn from subjects on tapentadol PR.

Safety data:

- Adverse events.
- Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Twelve-lead electrocardiogram (ECG).
- Safety laboratory (hematology, clinical chemistry, and urinalysis).
- Urine test for drugs of abuse outcome.
- Urine pregnancy test outcome.
- Physical examination.
- Height and body weight.
- SOWS questionnaire.

- Modified CAS questionnaire.

Efficacy data:

- Pain intensities assessed using a VAS and the FPS-R.
- Rescue medication use.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic methods

Pharmacokinetic data collected in this trial will be used to validate exposure predictions obtained with a pediatric tapentadol PR population-pharmacokinetic model developed previously by the sponsor. The validation process will enable assessment of tapentadol accumulation in this pediatric population during administration of tapentadol PR. The model will be subsequently updated with the pharmacokinetic data collected in this trial.

Sample size rationale

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

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

Statistical methods

Separate analyses will be performed for Part 1 and Part 2. The analysis for Part 1 will take into consideration the Treatment Period of Part 1. The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2.

Part 1

For the Treatment Period, baseline measurements are defined as the last evaluation performed before starting IMP (i.e., Visit V1, Visit V2, or an unscheduled visit).

For pain assessments, the baseline pain is defined as “pain right now” at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.

Part 2

For the Tapentadol Period, baseline measurements are defined as the last evaluation performed before or at Visit VE.

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

- Visit VE for subjects entering the Observation Period directly after Part 1.
- Visit ET for subjects switching from the Tapentadol Period to the Observation Period.

General

For continuous variables, descriptive statistics will include the 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. If applicable, changes from the baseline or predefined time points will be presented descriptively.

Data will also be listed and summarized using graphical displays, as appropriate.

Main analysis of the trial

The main analysis of the trial will be performed after all subjects have completed the first 12 weeks (Visit TP3 or Visit OP3) of Part 2.

Primary efficacy endpoint

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

As this endpoint is a binomial event rate, it will be summarized by descriptive statistics grouped by treatment group. The standard maximum likelihood estimators for the proportion of subjects classified as responders in each group will be the estimated proportions adjusted for the baseline pain intensity, age group, and underlying pain condition. To obtain these estimators, a logistic regression model will be fitted to the response using the baseline pain intensity, age group, treatment, and underlying pain condition as explanatory variables. The Farrington-Manning test will then be applied and an 80% confidence interval calculated.

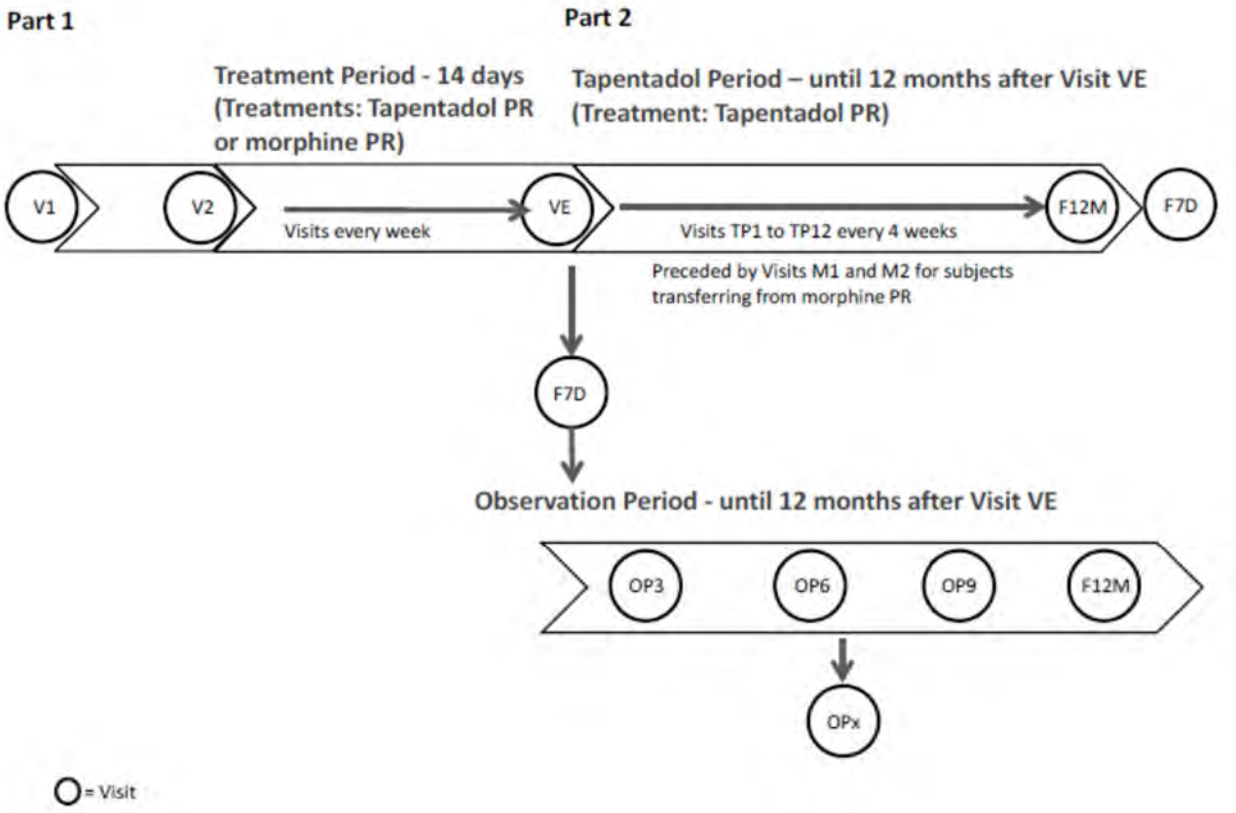
In addition, a Bayesian logistic regression model will be fitted as a sensitivity analysis.

Analysis of safety data

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

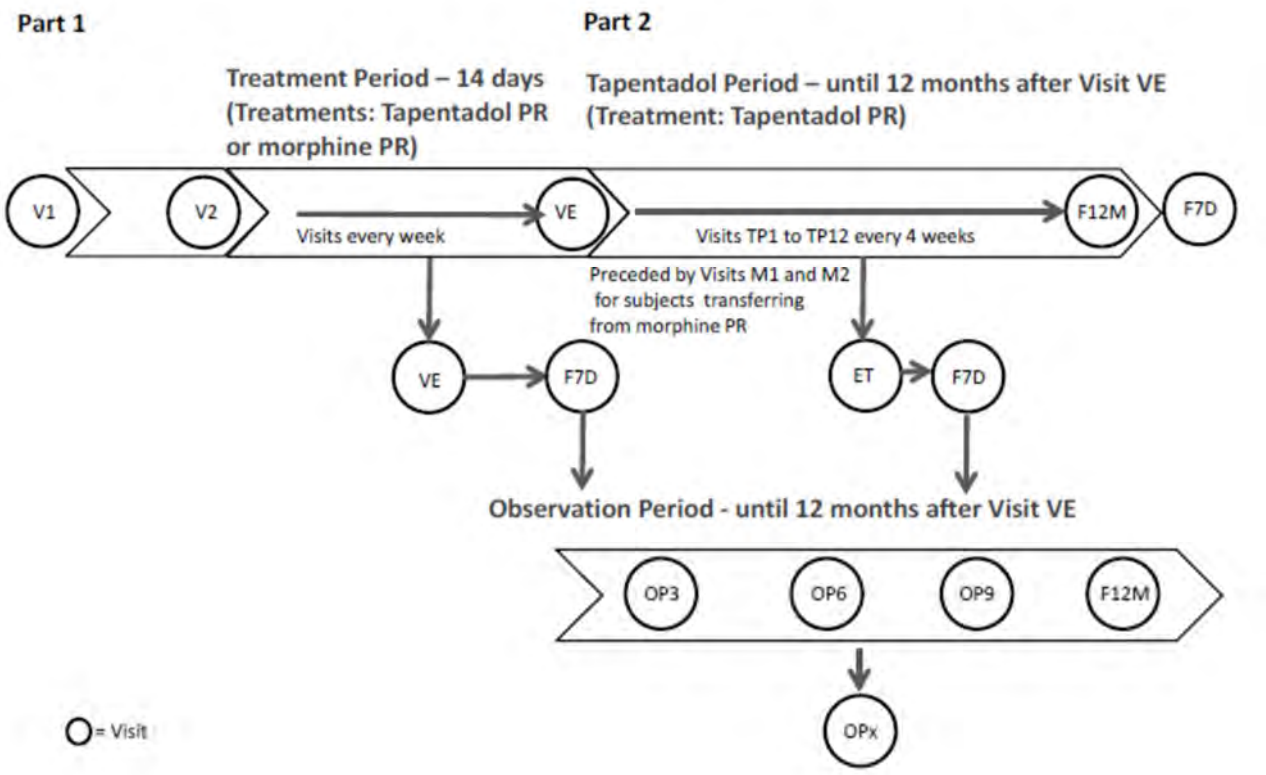
1.1 Flow diagram summary of the trial (Part 1 and Part 2)

1.1.1 Flow diagram for subjects completing Part 1 and Part 2



Vx = visit number x; VE = End of Treatment Visit for the Treatment Period; F12M = visit 12 months after Visit VE; F7D = final post treatment visit; OPx = an unscheduled visit in the Observation Period when the subject stops further participation in the trial; Visit OPn = visit at n months in the Observation Period; PR = prolonged release.

1.1.2 Flow diagram for subjects discontinuing investigational medicinal product or the trial during Part 1 or Part 2



Subjects transferring before Visit F12M from the Tapentadol Period to the Observation Period will continue in the Observation Period starting from the same trial day number.

Vx = visit number x; VE = End of Treatment Visit for the Treatment Period; ET = early termination Visit after stopping investigational medicinal product during the Tapentadol Period; F12M = visit 12 months after Visit VE; F7D = final post treatment visit; OPx = an unscheduled visit in the Observation Period when the subject stops further participation in the trial; Visit OPn = visit at n months in the Observation Period; PR = prolonged release.

1.2 Schedule of events

The visit time windows are not cumulative, and visits should be performed at the times specified within the given time window.

Phone contacts can be made at any time, e.g., if the subject wants to report adverse events, or has questions regarding concomitant medication intake/therapies. If no trial site visit takes place, phone contacts are mandatory if the subject would like to up or down titrate the IMP. A trial site visit may be performed as a home visit after prior approval by the sponsor.

1.2.1 Part 1: Enrollment Visit and Treatment Period (Visit V1 to Visit VE)

Period	Enrollment	Treatment Period			
Visit	**V1**	**V2**	**V3**	**VE[a]**	**F7D[b]**
Day (range)	-14 to 1	1	8 (±1)	15 (±1)	
Obtain informed consent/assent [s]	X				
Record demographic data	X				
Record age	X	X[c]		X	
Record medical history	X				
Record pain history	X				
Record prior medication intake/therapies	X				
Record concomitant medication intake/therapies	X	X[c]	X	X	X
Perform physical examination	X	X[c,d]		X[d]	X[d]
Record height	X			X	
Record body weight	X	X[c]	X	X	
Record vital signs	X	X[c]	X	X	X
Record 12-lead ECG [t]	X			X	
Take blood for central laboratory	X			X	
Take blood for local laboratory [e]	X				
Perform urine pregnancy test [f]		X		X	
Collect urine/perform dip stick urinalysis (safety laboratory)	X			X	
Perform urine test for drugs of abuse	X				
Evaluate subject suitability for trial participation: Check inclusion/exclusion criteria [g]	X	X			
Diary set up		X			
Dispense diary		X			
Train/instruct subjects, parents, or legal guardian how:					
1. To use the diary to record pain assessments twice daily (VAS and FPS-R) [k] until Visit VE.					
2. To record intake of IMP and rescue medication, including time of administration.		X	X	X[h]	
Check diary compliance			X	X	
Collect diary				X[i]	
Record pain assessment in diary (VAS, FPS-R)		X[j]			
Record “pain right now” in CRF (VAS, FPS-R)				X[h]	
Complete questionnaires [l]					
- Modified constipation assessment scale		X	X	X	
- Subjective opiate withdrawal scale				X[m,b]	X[m]
- Acceptability and palatability of IMP			X	X	
Allocate subjects		X			
Collect returned IMP and rescue medication			X	X	
Perform drug accountability [n]			X	X	
Dispense IMP (the first dose of IMP will be taken during Visit V2, within 24 hours after randomization. Day 1 is the		X	X	X[h]	

Period	Enrollment	Treatment Period			
Visit	V1	V2	V3	VE[a]	F7D[b]
Day (range)	-14 to 1	1	8 (±1)	15 (±1)	
day of first IMP intake)					
Dispense rescue medication		X	X		
Discuss IMP titration/dose adjustment		X	X	X[h]	
Train/instruct subject, parent(s), guardian(s), or caregiver on IMP/rescue medication use. Exchange instruction sheet if necessary (e.g., due to weight change).		X	X	X[h,o]	
Take blood sample for serum pharmacokinetics[p]		X	X	X	
Dispense subject trial card	X				
Assess/record adverse events	X	X[c]	X	X	X
Document changes of each ongoing adverse event				X	
Check discontinuation criteria for IMP intake			X	X	
Check subject eligibility for the Tapentadol Period or Observation Period and assign subject to Tapentadol Period or Observation Period				X[q,r]	
Instruct the subject, parent(s), legal guardian(s), or caregiver about the Tapentadol and Observation Periods				X	
Complete end of trial tasks, e.g., collect subject trial cards (if the subject is discontinuing from the trial)					X

Non-invasive procedures, e.g., recording of pain assessment, should be performed before invasive procedures.

a) Visit VE must also be performed within 3 days after last intake of IMP if IMP is stopped during the Treatment Period.

b) Only for subjects going in to the Observation Period. This visit is performed 7 (±2) days after the last intake of IMP.

c) If Visit V1 and Visit V2 are on the same day, assessments scheduled for both visits will not be repeated at Visit V2.

d) Document that a physical examination was performed and record the changes from the previous assessment.

e) Local laboratory parameters needed are: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine (the creatinine clearance will be calculated in the electronic CRF). The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.

f) In female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.

g) Compliance with the exclusion criteria will be checked based on local laboratory values.

h) Only for subjects going into the Tapentadol Period (except for recording rescue medication).

i) Not for subjects entering the Tapentadol Period (Part 2).

j) “Pain right now” will be documented in the diary at Visit V2 using the VAS and FPS-R before any painful or unpleasant procedure, and before the first intake of IMP as a baseline value.

k) “Pain right now” will be documented in the diary twice daily (preferably before dosing).

l) The caregiver, parent, or legal guardian may assist the subject completing the questionnaires.

m) Complete once daily until the seventh day after the last intake of IMP. At Visit VE, or earlier if applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires.

n) Comprises:

- Confirm and document compliance with IMP intake.
- Confirm whether returned amount of rescue medication matches expected amount to be returned.
- Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.

o) Train subject, parent(s), or guardian(s) on tapentadol PR use for subjects entering the Tapentadol Period of Part 2.

p) Samples will only be drawn from subjects on tapentadol PR for the determination of serum concentrations of tapentadol and tapentadol-O-glucuronide: 1 sample at Visit V2 (1 hour to 6 hours after IMP intake for out-patients and 3 hours to 6 hours after IMP intake for hospitalized subjects), 1 sample at Visit V3, and 1 sample at Visit VE (at any time during the visit, but after pain assessments).

q) Subjects completing the Treatment Period (Part 1) with tapentadol PR or morphine PR and who have need for continued opioid treatment can enter the Tapentadol Period. Subjects not completing the Treatment Period (Part 1), but who have taken at least 1 dose of IMP, and those who complete the Treatment Period but do not want to continue with tapentadol PR, will enter the Observation Period (12 months). Subjects will be followed until Visit F12M. Subjects in the Tapentadol Period of Part 2 may stop treatment early (before Visit F12M) and switch to Observation period for the remainder of Part 2.

r) Assignment needs to be documented in the case report form and the interactive response technology system.

s) The informed consent/assent may be obtained earlier than Day -14.

t) The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.

Demographic data = date of signing the informed consent/assent form, sex, age, and race/ethnicity; Safety laboratory = hematology, clinical chemistry, and urinalysis; Serum pharmacokinetics = serum concentrations of tapentadol and tapentadol-O-glucuronide; Vital signs = respiratory rate, systolic and diastolic blood pressure, and pulse rate.

VE = End of Treatment Visit after stopping IMP during the Treatment Period; Vx = visit number x; F7D = final post treatment visit; F12M = visit 12 months after Visit VE.

CRF = case report form; ECG = electrocardiogram; IMP = investigational medicinal product; FPS-R = Faces Pain Scale-revised; VAS = visual analog scale; PR = prolonged release.

1.2.2 Part 2: Tapentadol Period

Period	Tapentadol Period															
Visit	M1 [a]	M2 [a]	TP1	TP2	TP3	TP4	TP5	TP6	TP7	TP8	TP9	TP10	TP11	TP12	ET [bc]	F12M [b]	F7D [d]
Day (range)	7 (±2)	14 (±2)	28 (±5)	56 (±5)	84 (±5)	112 (±5)	140 (±5)	168 (±5)	196 (±5)	224 (±5)	252 (±5)	280 (±5)	308 (±5)	336 (±5)	Early Termin-ation	365 (±14)	
Record concomitant medication intake/therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform physical examination															X[e]	X[e]	X[e]
Record height					X			X			X			X	X	X	
Record body weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete questionnaires [f] - Modified constipation assessment scale															X	X	
- Subjective opiate withdrawal scale															X[g]	X[g]	X[g]
Record “pain right now” in CRF (VAS, FPS-R)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Take blood for central laboratory					X			X			X			X	X	X	
Collect urine/perform dip stick urinalysis (safety laboratory)					X			X			X			X	X	X	
Perform urine pregnancy test [h]					X			X			X			X	X	X	
Train/instruct subject how to use diary to record intake of IMP, including time of administration.	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Period	Tapentadol Period															
Visit	M1 [a]	M2 [a]	TP1	TP2	TP3	TP4	TP5	TP6	TP7	TP8	TP9	TP10	TP11	TP12	ET [bc]	F12M [b]	F7D [d]
Day (range)	7 (±2)	14 (±2)	28 (±5)	56 (±5)	84 (±5)	112 (±5)	140 (±5)	168 (±5)	196 (±5)	224 (±5)	252 (±5)	280 (±5)	308 (±5)	336 (±5)	Early Termin-ation	365 (±14)	
Check diary compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect diary															X	X	
Collect returned IMP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Perform drug accountability [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense IMP	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Discuss IMP titration/dose adjustment	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Train/instruct subject, parent(s), guardian(s), or caregiver on IMP use. Exchange instruction sheet if necessary (e.g., due to weight change)	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Assess/record adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check discontinuation criteria for IMP intake	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Complete end of trial tasks, e.g., collect subject trial cards																	X

Days are referenced by last intake of IMP in Part 1.

a) Visit M1 and Visit M2 are only for subjects who were allocated to morphine PR in the Treatment Period.

b) If Visit F12M and Visit ET are performed on the same day, assessments scheduled for both visits will not be repeated at Visit F12M.

c) Visit ET must be performed within 3 days after last intake of IMP if IMP is stopped before Visit F12M in Part 2.

d) Visit F7D is performed 7 (±2) days after the last intake of IMP.

e) Document that a physical examination was performed and record the changes from the previous assessment.

f) The caregiver, parent, or legal guardian may assist the subject completing the questionnaires.

g) Once daily until the seventh day after the last intake of IMP (normally Visit F12M or at Visit ET in case of early termination). At Visit F12M, or as applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires.

h) In female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.

i) Comprises:

- Confirm and document compliance with IMP intake.
- Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.

Safety laboratory = hematology, clinical chemistry, and urinalysis; Vital signs = respiratory rate, systolic and diastolic blood pressure, and pulse rate.

VE = End of Treatment Visit after stopping IMP during the Treatment Period; ET = Early termination Visit after stopping IMP during the Tapentadol Period; F12M = visit 12 months after Visit VE; F7D = final post treatment visit; Visit TPx = visit at n months during the Tapentadol Period.

FPS-R = Faces Pain Scale-revised; Modified CAS = modified constipation assessment scale; SOWS = subjective opiate withdrawal scale; VAS = visual analog scale; CRF = case report form; IMP = investigational medicinal product.

1.2.3 Part 2: Observation Period

Period	Observation Period				
Visit	OP3	OP6	OP9	OPx	F12M [a]
Month (range: ±14 days)	3	6	9	(unscheduled)	12
Record concomitant medication intake/therapies	X	X	X	X	X
Perform physical examination				X[a,b]	X[b]
Record height				X[a]	X
Record body weight				X[a]	X
Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate)				X[a]	X
Complete modified constipation assessment scale questionnaire [c]				X[a]	X
Take blood for central laboratory (hematology, clinical chemistry)				X[a]	X
Collect urine/perform dip stick urinalysis				X[a]	X
Assess/record adverse events	X	X	X	X	X
Complete end of trial tasks, e.g., collect subject trial cards				X	X

Months are referenced by last intake of IMP in Part 1.

a) Assessments are performed for all subjects who discontinue from the Observation Period, unless informed consent is withdrawn.

b) Document that a physical examination was performed and record the changes from the previous assessment.

c) The questionnaire will be filled in by the subject, caregiver, parent or legal guardian.

Visit OPx = an unscheduled visit in the Observation Period when the subject stops further participation in the trial; F12M = visit 12 months after Visit VE; Visit OPn = visit at n months in the Observation Period.

IMP = investigational medicinal product.

1.2.4 Phone contacts

Phone contacts can be made at any time, e.g., if the subject wants to report adverse events, or has questions regarding concomitant medication intake/therapies. If no trial site visit takes place, phone contacts are mandatory if the subject would like to up or down titrate the IMP. A trial site visit may be performed as a home visit after prior approval by the sponsor.

	Phone contact
Record concomitant medication intake/therapies	X
Discuss titration/dose adjustment	X
Record reason for dose adjustment and new dose, if applicable	X
Assess/record adverse events	X
Check discontinuation criteria	X

1.3 Inclusion/exclusion criteria

1.3.1 Inclusion criteria

Subjects are eligible for the trial at Visit V1 if all the following apply:

Inclusion criteria	Rationale for criterion
1. Informed consent/(if applicable) assent obtained.	Legal requirement.
2. Male or female subject at least 6 years of age at the Enrollment Visit and less than 18 years of age on the predicted day of Visit VE.	Standardization of trial population.
3. Subject has an underlying long-term pain condition (e.g., cancer, chronic disease, planned or performed surgery) that is, according to the judgment of the investigator, expected to require a twice-daily prolonged release opioid treatment until at least the end of the 14-day Treatment Period (Visit VE).	Standardization of trial population.
4. Subject can swallow tablets of appropriate size.	Logistical requirement.
5. Subject is able to participate in the trial as planned and willing to comply with the requirements of the protocol including refraining from drinking beverages containing alcohol and recreational intake of drugs while on IMP.	Safety, standardization of trial population, and practical consideration.

Subjects must satisfy the following criteria at Visit V2 to be allocated to IMP:

Inclusion criteria	Rationale for criterion
6. Less than 18 years of age on the planned day of Visit VE.	Standardization of trial population.
7. No opioid intake or last calculated morphine equivalent dose at day of allocation of <3.5 mg/kg per day.	Standardization of trial population.
8. Subject has a body weight of ≥17.5 kg.	Standardization of trial population.
9. If a female of childbearing potential (post-menarchal and not surgically incapable of childbearing) and sexually active, must practice an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch) before allocation to IMP until the end of intake of IMP.	Safety.
10. If a female and post-menarchal or older than 12 years, has a negative urine pregnancy test on the day before or on the day of allocation to IMP.	Safety.

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

1.3.2 Exclusion criteria

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

The following will be checked at Visit V1:

Exclusion criteria	**Rationale for criterion**
1. Has been previously enrolled in this trial or a previous trial with tapentadol.	Ethics and interference with trial assessments.
2. Has a clinically relevant history of hypersensitivity, allergy, or contraindication to morphine or tapentadol or any ingredient, including galactose intolerance (see investigator's brochure for tapentadol PR and summary of product characteristics for morphine PR), or naloxone.	Safety.
3. History or current condition of any one of the following: • Seizure disorder or epilepsy. • Serotonin syndrome. • Traumatic or hypoxic brain injury, brain contusion, stroke, transient ischemic attack, intracranial hematoma, posttraumatic amnesia, brain neoplasm, or episode(s) of more than 24 hours duration of unconsciousness.	Safety and interference with trial assessments.
4. 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). • Complex regional pain syndrome. • A pain indication with a strong psycho-somatic component that, in the judgment of the investigator, is unlikely to respond to opioids.	Safety and interference with trial assessments.
5. History of alcohol or drug abuse in the investigator's judgment, based on history and physical examination. Drugs of abuse detected in urine screen unless explained by allowed concomitant medication (see synopsis section Concomitant medications/therapies).	Safety.
6. Subject has: • A clinically relevant abnormal ECG. • Signs of pre-excitation syndrome. • Brugada's syndrome. • QT or QTcF (Fridericia) interval >470 ms.	Safety.
7. Any surgery scheduled during Part 1 of the trial that is expected to require post-surgical intensive care unit (ICU) treatment, or that	Safety.

Exclusion criteria	Rationale for criterion
requires post–surgical parenteral pain-treatment, or may, in the opinion of the investigator, affect the safety of the subject.	
8. 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.	Ethical requirement and interference with trial assessments.
9. Subject, parent or the legal representative is an employee of the investigator or trial site, with direct involvement in the proposed trial or other studies under the direction of that investigator or trial site, or family member of the employees or the investigator.	Good Clinical Practice.

The following will be checked at Visit V1 and Visit V2:

Exclusion criteria	**Rationale for criterion**
10. Has a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection) that in the opinion of the investigator may affect or compromise subject safety during the trial participation.	Safety.
11. Pancreatic/biliary tract disease (e.g., pancreatitis) or paralytic ileus.	Safety.
12. Intake of forbidden concomitant medication/use of forbidden therapies (see synopsis section Concomitant medications/therapies).	Safety and standardization of trial population.
13. Female subject breast-feeding a child.	Safety.

The following will be checked at Visit V2:

Exclusion criteria	**Rationale for criterion**
14. Has received a drug or used a medical device not approved for human use within 30 days prior to Visit V2.	Safety and standardization of trial population.
15. Based on data from the local laboratory, one or more of: • Total serum bilirubin >2.0 mg/dL. • Serum albumin <2.8 g/dL. • Aspartate transaminase or alanine transaminase >5-times upper limit of normal.	Safety.
16. Based on data from the local laboratory, creatinine clearance <30 mL/min per 1.73 m^2 (calculated according to a formula that is appropriate for the respective age group).	Safety.
17. [criteria deleted]	Ethics and interference with trial assessments.

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

1.3.3 Inclusion criteria for the Tapentadol Period (Part 2)

Inclusion criteria	**Rationale for criterion**
18. Subject has completed the 14-day Treatment Period.	Standardization of trial population.
19. Subject is still in need of prolonged release opioid treatment.	Ethics and standardization of trial population.
20. Subject does not meet any of the compulsory discontinuation criteria (described in Section 9.3.1 of the body of the protocol).	Safety.

Note: Subjects will only receive tapentadol PR in the Tapentadol Period if documentation is available showing that they comply with these inclusion criteria.

2 TABLE OF CONTENTS

1	PROTOCOL SYNOPSIS	3
1.1	Flow diagram summary of the trial (Part 1 and Part 2)	10
1.1.1	Flow diagram for subjects completing Part 1 and Part 2	10
1.1.2	Flow diagram for subjects discontinuing investigational medicinal product or the trial during Part 1 or Part 2	11
1.2	Schedule of events	11
1.2.1	Part 1: Enrollment Visit and Treatment Period (Visit V1 to Visit VE)	12
1.2.2	Part 2: Tapentadol Period	15
1.2.3	Part 2: Observation Period	18
1.2.4	Phone contacts	18
1.3	Inclusion/exclusion criteria	19
1.3.1	Inclusion criteria	19
1.3.2	Exclusion criteria	20
1.3.3	Inclusion criteria for the Tapentadol Period (Part 2)	23
2	TABLE OF CONTENTS	24
3	ABBREVIATIONS AND DEFINITION OF TERMS	29
4	ETHICS	30
4.1	Independent ethics committee(s) or institutional review board(s)	31
4.2	Subject information and informed consent	31
4.3	Informing the subject's healthcare provider	31
5	INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE	32
5.1	Investigators and trial site personnel	32
5.1.1	Investigators	32
5.1.2	Trial site personnel assigned trial-related duties	32
5.2	Contract research organizations	33
5.3	The sponsor and sponsor's personnel	33
5.4	Data monitoring committee	33
6	INTRODUCTION AND TRIAL BACKGROUND	33
6.1	Background to the investigational medicinal product	33
6.2	Relevant non-clinical and clinical data	33
7	TRIAL OBJECTIVES	37
8	TRIAL DESIGN	37
8.1	Definition of endpoints	38
8.1.1	Primary endpoint definition	38

8.1.2	Secondary endpoint definitions	39
8.1.3	Other endpoints	39
8.2	Trial rationale	39
8.3	Special agreements with regulatory authorities	40
8.4	Discussion of the trial design	40
8.5	Benefit/risk analysis	45
9	SUBJECT ENROLLMENT AND TRIAL DISCONTINUATION	46
9.1	Subject enrollment procedure	46
9.2	Inclusion/exclusion criteria	47
9.2.1	Inclusion criteria	47
9.2.2	Exclusion criteria	47
9.2.3	Inclusion criteria for the Tapentadol Period (Part 2)	47
9.2.4	Criteria for entry into the Tapentadol Period or Observation Period	47
9.3	Trial discontinuation and treatment not completed	47
9.3.1	Reasons for discontinuation of a subject from IMP (treatment not completed)	47
9.3.2	Reasons for discontinuation of a subject from the trial	49
9.3.3	Procedure for the handling of prematurely discontinued subjects	49
9.3.4	Premature termination or suspension of the trial	50
10	TREATMENTS	50
10.1	Investigational medicinal product	50
10.1.1	Identity and composition – tapentadol PR (test)	50
10.1.2	Identity and composition – morphine PR (comparator)	50
10.1.3	Packaging and labeling	51
10.1.4	Delivery, storage and disposal	51
10.2	Administration of trial treatments	51
10.2.1	Administration	51
10.2.2	Total number of doses and dosing interval	51
10.2.3	Dose	51
10.2.4	Titration and dosing tables	54
10.3	Method of assigning subjects to treatment (allocation)	55
10.3.1	Part 1	55
10.3.2	Part 2	56
10.4	Blinding and unblinding	56
10.5	Allowed and forbidden and prior/concomitant medications/therapies	56
10.5.1	Allowed prior and concomitant medications/therapies	57
10.5.2	Forbidden prior and concomitant medication/therapies	57

10.5.3	Cautionary use	57
10.6	Rescue medication	58
10.6.1	Dose	58
10.6.2	Reasons for administration	58
10.6.3	Documentation	58
10.7	Documentation of drug accountability	59
11	TRIAL PROCEDURES	59
11.1	Course of the trial	59
11.1.1	Part 1	59
11.1.2	Part 2 – Tapentadol Period	63
11.1.3	Visit F7D (Final post treatment visit, at 7 days after stopping IMP, range ±2 days)	66
11.1.4	Part 2 – Observation Period	67
11.1.5	Phone contacts	68
11.1.6	Additional trial site attendance	68
11.2	Examination hierarchy and time windows	68
11.3	Conditions during the trial	69
11.3.1	Medical care	69
11.3.2	General restrictions	69
11.3.3	Counseling of female subjects of reproductive age	69
11.4	Subject trial cards	69
11.5	Provisions of any additional care of subject after trial termination	70
11.6	Low enrollment	70
12	DATA COLLECTION	70
12.1	Overview of blood sampling in this trial	70
12.2	Collection of subject characteristics data	71
12.2.1	Demographic data	71
12.2.2	Medical history	71
12.2.3	Pain history	71
12.2.4	Prior and concomitant medications and therapies	71
12.3	Collection of pharmacokinetic data	72
12.3.1	Blood sampling for serum pharmacokinetics	72
12.3.2	Bioanalytical assays	72
12.4	Collection of efficacy data	72
12.4.1	Pain intensity	72
12.5	Questionnaires	73
12.5.1	Modified constipation assessment scale	73

12.5.2	Acceptability and palatability of investigational medicinal product	73
12.5.3	Subjective opiate withdrawal scale	73
12.6	Collection of safety data	74
12.6.1	Adverse events	74
12.6.2	Vital signs	80
12.6.3	Height and body weight	80
12.6.4	Twelve-lead electrocardiogram	80
12.6.5	Safety laboratory	80
12.6.6	Urine test for drugs of abuse	82
12.6.7	Physical examination	82
12.6.8	Pregnancy test	82
12.7	Appropriateness of measurements	83
12.8	Compliance	83
13	DOCUMENTATION OF TRIAL DATA	84
13.1	Case report forms	84
13.2	Subject reported outcomes	84
13.3	Data management	85
13.4	Source data	85
13.5	Investigator's site file and the trial master file	86
14	STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION	87
14.1	Sample size rationale	87
14.2	Analysis of the trial – statistical analysis	87
14.2.1	Analysis populations (analysis sets)	87
14.2.2	General descriptive and graphical methods	88
14.2.3	Analysis of subject characteristics data	89
14.2.4	Analysis of subject disposition	89
14.2.5	Analysis of pharmacokinetic data	89
14.2.6	Analysis of efficacy data	89
14.2.7	Analysis of safety data	91
14.2.8	Acceptability and palatability	93
14.2.9	Final analysis	93
14.3	Population pharmacokinetic modeling and simulation	93
15	QUALITY SYSTEM, AUDIT AND INSPECTION	93
15.1	Quality system	93
15.2	Data quality assurance	93
15.2.1	Clinical research organization/investigator selection	93
15.2.2	Trial site monitoring	94

15.2.3 Audits 94
15.3 Inspections 94
16 GENERAL CONDITIONS AND AGREEMENTS 94
16.1 Insurance 94
16.2 Legal regulations 94
16.3 Contracts 95
16.4 Subject data and data protection 95
16.5 Publication policy 95
16.6 Final report and reporting of the trial 96
16.7 Approval 97
16.7.1 Sponsor 97
16.7.2 International coordinating investigator 97
17 REFERENCES 97
18 PROTOCOL AMENDMENTS 100
18.1 Protocol amendment 01 100
18.2 Protocol amendment 02 101
18.3 Protocol amendment 03 111
18.4 Protocol amendment 04 112
18.5 Protocol amendment 05 125
19 APPENDIX 127
19.1 List of medical concepts for consideration of seriousness stratified by system organ class 127
19.2 Visual analog scale 130
19.3 Faces Pain Scale – Revised 131
19.4 Modified constipation assessment scale 132
19.5 Subjective opiate withdrawal scale 133
19.6 Palatability and acceptability 134
19.7 Algorithm to detect potential severe cases of drug-induced liver injury 135
19.8 Collecting, handling, and shipment of pharmacokinetic serum samples 137
19.8.1 Labeling 137
19.8.2 Devices 137
19.8.3 Procedure 137
19.8.4 Shipment 137

LIST OF TABLES

Table 1: Reasons for compulsory and optional discontinuation of subjects from investigational medicinal product (treatment not completed) 47
Table 2: Tapentadol PR dosing table 54
Table 3: Morphine PR dosing table 55
Table 4: Approximate volume of blood to be collected from each subject during Part 1 70
Table 5: Approximate volume of blood to be collected from each subject during the Tapentadol Period of Part 2 71
Table 6: Laboratory tests to be performed for the evaluation of alternative causes of drug-induced liver injury 136

3 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

Abbreviation	Explanation
CAS	Constipation assessment scale
CP	Conditional power
CRF(s)	Case report form(s)
DMC	Data monitoring committee
ECG	Electrocardiogram
FAS	Full Analysis Set
FPS-R	Faces Pain Scale–revised
GCP	Good clinical practice
ICU	Intensive care unit
IEC	Independent ethics committee
IMP(s)	Investigational medicinal product(s)
IR	Immediate release
IRB	Institutional review board
PR	Prolonged release
SpO_2	Oxygen saturation
SAP	Statistical analysis plan
SOP	Standard operating procedure(s). A synonym for all standard procedural documents.
SOWS	Subjective opiate withdrawal scale (questionnaire)
TEAE	Treatment emergent adverse event
VAS	Visual analog scale
WHO	World Health Organization

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

Definition of terms

Term	Definition
Allocated subjects	Enrolled subjects who are allocated 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.
Discontinuation (of trial)	The act of concluding the participation of an enrolled subject in a trial prior to completion of all activities required by the protocol.
Treatment not completed	IMP discontinued before scheduled end of the Treatment Period of Part 1 or the Tapentadol Period of Part 2.
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 form signed. If required by local law and assent form signed.
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	A generic term describing the preparations under investigation in this trial, i.e., tapentadol PR tablets and morphine PR tablets.
Last subject out	Date of last contact with the last subject according to the protocol.
Modified CAS	Modified constipation assessment scale (questionnaire).
Opioid naïve	No intake of opioids within the 4 weeks prior to enrollment.
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 completers Part 1	Subjects who have completed the 14-day Treatment Period.
Treatment completers Part 2	Subjects who have completed the 12-month Tapentadol Period.
Trial completers Part 1	Subjects who have completed the 14-day Treatment Period and Visit F7D or who entered the Tapentadol Period of Part 2.
Trial completers Part 2	Subjects who fully completed the extension period, i.e., either subjects completing the Tapentadol Period and the follow-up visit (F7D) or subjects completing the Observation Period (F12M) not earlier than 351 days after Visit VE).

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 relating to this trial that are required to fulfill its responsibilities. Any updates thereof will be provided according to GCP and applicable regulatory requirements.

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

Documentation of all involved IECs and 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 or 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.

As the inclusion of exclusively minors at the Enrollment Visit (Visit V1) 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. An assent form should be signed by the child in adherence to local regulations.

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

During Part 2 of the trial, subjects may reach the age of majority (e.g., 18 years old, depending on local laws). They must sign an informed consent as soon as they reach this age to continue in the trial.

4.3 Informing the subject's healthcare provider

The subject's healthcare provider will be informed about the subject's participation in the trial at trial enrollment in applicable countries if the subject is treated by a healthcare provider, e.g., general

practitioner, and if the subject, parent, or legal guardian, as applicable, agrees in writing in the informed consent form. This is to be documented in the case report form (CRF). The subject must also be informed and the subject's opinion taken into consideration. This must be documented 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 will be required to sign a declaration of their responsibilities (the "investigator confirmation sheet") before any trial-related procedure is performed.

An international 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 in the target population.

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 accepts the responsibilities of the sponsor.

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 data from selected pediatric trials with tapentadol administration performed by Grünenthal. Operational aspects of the DMC will be given in a charter which will be issued before the first subject-in in this trial. For more details about the planned evaluations of the DMC, see Section 8.5.

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

Tapentadol is a centrally acting analgesic combining opioid- and non-opioid activities. It has agonistic activity at the mu-opioid receptor and it inhibits noradrenaline reuptake as a non-opioid activity. Both actions act synergistically in analgesia. 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. Both opioid and non-opioid properties are relevant for the management of clinical pain.

The non-clinical safety pharmacology data indicate a low potential for side effects upon the vital functions like respiratory depression and gastrointestinal inhibition in humans. Tapentadol has no adverse cardiovascular effects in the antinociceptive dose range.

Clinical experience

In the clinical program to date, tapentadol (as the hydrochloride salt) has been mostly administered to adults. It has been given intravenously or orally as an oral solution, as immediate-release (IR) tablets or capsules, and as prolonged release tablets (including a tamper resistant formulation).

More recently, 2 trials have been performed (or are ongoing) in children and adolescents to evaluate the pharmacokinetics of a single dose of tapentadol oral solution 1 mg/kg after scheduled surgical procedures that routinely produce acute postsurgical pain [redacted]. No safety issues have so far been identified.

Pharmacodynamics

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 immediate release (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

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

After oral administration, ~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 (Vz) of 540 L. The terminal half-life was ~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 ~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. Consistent with linear pharmacokinetics, the accumulation ratio of tapentadol based on the maximum serum concentrations at steady-state ($C_{max,ss}$) was close to the theoretically expected value.

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 function 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.

Safety in Phase I trials (tapentadol intravenous, tapentadol oral solution, tapentadol IR, and tapentadol prolonged release [PR] including tamper resistant formulation)

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 treatment emergent adverse events (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 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 Phase II and Phase III (tapentadol PR) in clinical trials

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 in Phase II trials in children (tapentadol oral solution)

To date, in a single dose trial [redacted] 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 6 subjects were discontinued due to an adverse event (vomiting, which was also considered a stopping criteria). In a second trial [redacted] 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 experience from post-marketing data

The total cumulative post-authorization patient exposure to tapentadol IR and tapentadol 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. [redacted] 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 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. The 5 trials (2 in chronic painful osteoarthritis, 1 in chronic low back pain, and 2 in painful diabetic peripheral neuropathy) central to the evaluation of the efficacy of tapentadol PR were adequate and well-controlled, and statistical separation from placebo for the primary efficacy endpoints was demonstrated in 4 of these trials. Numerical superiority to placebo was seen in the fifth trial.

Stable pain reduction was shown for 12 weeks in efficacy trials, and maintenance of effect was demonstrated for up to 1 year in a safety trial using the same dose range (tapentadol PR 100 mg to 250 mg twice daily) with no indication of tolerance to the analgesic effect.

In addition, the efficacy of tapentadol PR for the treatment of moderate to severe cancer pain was demonstrated in an active- and placebo-controlled, double blind, trial in subjects with moderate to severe chronic malignant tumor-related pain. In this trial, the maximum dose after titration was 250 mg twice daily for tapentadol PR and 100 mg twice daily for morphine PR. Tapentadol PR was shown to be effective in the treatment of moderate to severe cancer pain on the primary efficacy endpoint (responder rates in the Maintenance Phase) and to be non-inferior to morphine PR with respect to efficacy (responder rate) during the Titration Phase.

7 TRIAL OBJECTIVES

The trial objectives for Part 1 are:

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

The trial objective for Part 2 is:

- To describe the long-term safety profile covering up to a 12-month period with treatment of tapentadol PR taken twice daily (Tapentadol Period) in subjects aged 6 years or older suffering from long-term pain requiring prolonged release opioid treatment, or in subjects without tapentadol treatment (Observation Period) aged 6 years or older who have received at least 1 dose of IMP.

8 TRIAL DESIGN

This is a 2-part trial:

Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring prolonged release opioid treatment. The target is to allocate 69 subjects in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily.

After the Enrollment Visit, subjects complying with the inclusion/exclusion criteria will enter Part 1.

Blood samples for pharmacokinetic evaluations will only be drawn from subjects on tapentadol PR.

Part 1 of the trial will be completed after the last subject has attended Visit VE. Data of Part 1 will comprise the primary analysis of the trial.

Part 2 is an open-label Extension Period with tapentadol treatment (Tapentadol Period) or an observation period without tapentadol treatment (Observation Period) lasting for up to 12 months.

Tapentadol Period (12 months): Subjects completing the Treatment Period (Part 1) and who are still in need of treatment with a prolonged release opioid can enter the Tapentadol Period. They will be treated with tapentadol PR for up to 12 months until Visit F12M (a 12-month visit relative to Visit VE).

Observation Period (12 months): Subjects not completing the Treatment Period (Part 1), but who have taken at least 1 dose of IMP, and those who complete the Treatment Period but do not want to continue with tapentadol PR, will enter the Observation Period (12 months). Subjects will be followed up until Visit F12M to assess any long-term effects after discontinuing treatment with the IMP. Subjects in the Tapentadol Period of Part 2 may stop treatment early (before Visit F12M) and switch to the Observation Period for the remainder of Part 2.

Part 2 of the trial will be completed after the last subject has completed or discontinued from the trial.

Trial population

Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from severe long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2 (Allocation Visit; Day 1), and who comply with the inclusion/exclusion criteria given in Section 1.3. Long-term pain is defined as any pain condition that requires a minimum of 14 days of treatment with a strong oral opioid. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., spinal surgery), cancer-related pain (including pain caused by treatment) as well as chronic indications with moderate to severe pain.

The age groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined.

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

Trial period

Estimated date of first subject in: Oct 2014.

Part 1, estimated date of last subject out: Sep 2018.

Part 2, estimated date of last subject out: Sep 2019.

Each subject is expected to be treated with IMP for 14 days in Part 1, followed by a 12-month Extension Period (Part 2). In total, for each subject, the trial duration will be ~13 months.

8.1 Definition of endpoints

For details of the analysis sets, see Section 14.2.1.

8.1.1 Primary endpoint definition

Part 1 (primary analysis of the trial)

The primary endpoint is a binary variable “responder”. A subject is defined as “responder” if both of the following criteria are met:

- Completion of the 14-day Treatment Period (Part 1).
- One of the following calculated from the scheduled pain assessments (“pain right now”) documented during the last 3 days of the Treatment Period:
  - Average pain <50 on a VAS for subjects aged 12 years to less than 18 years; or <5 on the FPS-R for subjects aged 6 years to less than 12 years.
  - Average reduction from baseline of pain ≥20 on a VAS for subjects aged 12 years to less than 18 years; or ≥2 on the FPS-R for subjects aged 6 years to less than 12 years.

The proportion of subjects classified as responders will be assessed and compared between the treatment groups.

Age groups are determined at Visit V2. Baseline pain is defined as “pain right now” at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.

8.1.2 Secondary endpoint definitions

The main secondary endpoints are:

Part 1

- Constipation as assessed by changes from baseline (Visit V2) of total scores for the modified CAS.

Part 1 and Part 2

- Tolerability as assessed by the number and type of adverse events and adverse drug reactions by treatment group during the different trial periods, on a subject and event level.

8.1.3 Other endpoints

Other endpoints compared between treatment groups at each measurement time point are:

Part 1 - Treatment Period, other endpoints (baseline is the value at Visit V2):

- Pain as assessed by changes from baseline using the VAS.
- Pain as assessed by changes from baseline using the FPS-R.
- Use of rescue medication as assessed by number of doses of rescue medication taken at different dose levels of IMP.
- Description of population pharmacokinetics of tapentadol and tapentadol-O-glucuronide.
- Palatability and acceptability as assessed by differences within treatment groups of the 5-point hedonic faces scale with the verbal rating score at Visit V3 and Visit VE.

Part 2 - Tapentadol Period, other endpoints (baseline is the value at Visit VE):

- Pain as assessed by changes from baseline using the VAS.
- Pain as assessed by changes from baseline using the FPS-R.
- Constipation as assessed by changes from baseline of total scores for the modified CAS.

Part 2 - Observation Period, other endpoints (baseline is the value at Visit VE or Visit ET):

- Constipation as assessed by changes from baseline of total scores for the modified CAS.

Part 1 or Part 2 - other endpoints:

- Opiate withdrawal symptoms as assessed by the scale score of the SOWS questionnaire at individual time points and changes to baseline.
- Time to discontinuation of IMP assessed by a survival analysis.

8.2 Trial rationale

Pain in children is a public health concern of major significance in most parts of the world. Although the means and knowledge to relieve pain exists, children's pain is often not recognized, is ignored or even denied (WHO 2012). This might also be due the fact that only few trials have been conducted in children with opioids to provide evidence of their safety and efficacy (Finkel et al. 2005). There is a need for comparative trials of opioids in terms of effectiveness, side-effects and feasibility of use in children with persisting pain due to medical illnesses (WHO 2012).

Marketing approval was granted for tapentadol for the treatment of severe acute pain and severe chronic pain (in the US also moderate pain) in adults. Tapentadol PR was shown to be efficacious and better tolerated than oxycodone controlled release (CR) in adults for the treatment of chronic pain in different pain models such as neuropathic pain, osteoarthritis and low back pain. In addition, tapentadol PR was superior to placebo and showed comparable efficacy to morphine PR in adult patients suffering from chronic cancer-related pain.

Tapentadol may also offer notable advantages for the management of pain in children and adolescents. The better gastrointestinal tolerability profile than oxycodone makes tapentadol especially attractive for use in children and adolescents.

This trial is designed to compare the efficacy and safety profiles of morphine PR and tapentadol PR, and to characterize the pharmacokinetic parameters based on population pharmacokinetics and physiologically based pharmacokinetic modeling of tapentadol PR in children. The pharmacokinetic sampling will enable assessment of tapentadol accumulation in this pediatric population via modeling and simulation. In addition, long-term safety data on tapentadol PR will be collected from subjects aged 6 years or older suffering from long-term pain requiring prolonged release opioid treatment.

The standard indications for chronic pain in adults, such as low back pain and osteoarthritis are not comparable to those in children and treatment approaches are different. Therefore, the definition of long-term pain requiring prolonged release opioid treatment appears to be more appropriate and reflects the population that would benefit from tapentadol PR treatment. If tapentadol PR proves to be an effective analgesic with fewer opioid side effects than morphine in this population, then tapentadol PR will meet an unmet medical need.

8.3 Special agreements with regulatory authorities

[redacted]

8.4 Discussion of the trial design

Overall design

Taking into account the trial population and previous trials performed in children suffering from long-term pain, a 14-day duration for the Treatment Period (Part 1), in which tapentadol PR and morphine PR treatment are compared, seems to be appropriate. Data from a similarly designed trial (Finkel et al. 2005) showed that only a small percentage of subjects remained for more than 1 month on trial medication. With this background, it does not seem useful to extend the duration of the proposed trial for the assessment of efficacy beyond 14 days. However, the possibility for subjects to be treated with tapentadol PR for up to 12 months in the setting of a clinical trial enables the collection of valuable safety data on long-term treatment.

Choice of population and trial sites

The trial includes children with different indications requiring treatment with an oral strong opioid for at least 14 days. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., orthopedic surgery), cancer-related pain (including pain caused by treatment), as well as chronic indications with moderate to severe pain.

Tapentadol PR has shown to be an efficacious and safe drug for the treatment of different chronic pain indications that are common in the adult population, such as low back pain, osteoarthritis and cancer-related pain. The data from pivotal clinical trials have been confirmed by post-marketing data in further clinical trials as well as in non-clinical trial settings.

The data gained for tapentadol suggest that also children may benefit from treatment with tapentadol PR (Section 6.2).

Chronic daily pain can occur in children in the context of chronic daily headaches, neurodegenerative disorders, inflammatory disorders, post-traumatic neuropathic pain conditions, and in children with advanced cancer and other life-limiting diseases. Overall, however, chronic daily pain is much less prevalent in children than in adults (Berde et al. 2012). This is even more the case for painful conditions requiring long-term opioid treatment.

In children with progressive malignant disease, two thirds experience pain requiring opioid analgesia (Goldman and Bowman 1990). However, cancer in children is rare. In the United States, cancer has been found to occur most frequently in the first year of life with incidence rates of ~250 cases per million per year. The incidence then drops to only ~100 cases per million per year by the age of 10 years, after which the incidence increases again to approach 250 per million cases per year at the age of 18 years (Kadan-Lottick 2007). Furthermore, Berde et al. (2012) reported that within a single year, only 386 children with cancer pain received oral round-the-clock opioid treatment for the duration of 1 month or more in the United States.

Other conditions that often require treatment with prolonged release opioids for at least 2 weeks include severe burns and major or complicated surgery. A mail-in survey of pediatric pain control practices in North American Burn Centers (Martin-Herz et al. 2003) showed that although intravenous morphine was the most frequently used analgesic for the treatment of background pain from burns, 21% of the responders used prolonged release opioids for school-age children, and 39% for adolescents.

Surgical correction for scoliosis is associated with high levels of pain that extend beyond the initial inpatient hospital stay. These patients, as well as others undergoing major surgery with expected extended pain duration, may benefit more from early transition to prolonged release formulations than from continuous PCA, because prolonged release formulations are associated with lower pain levels on average, and present a more convenient route of administration (Czarnecki et al. 2004). This is in line with the results shown in clinical trials in adults undergoing major surgery, e.g., hip and knee replacement: patients treated with prolonged release opioids 48 hours after surgery had improved pain scores compared to those who received continuous treatment with immediate release formulations and patient controlled analgesia (PCA), and they had a shorter duration of their hospital stay (de Beer et al. 2005).

In conclusion, opioids, especially in a prolonged release formulation, are not only used in children suffering from classical chronic pain conditions (e.g., cancer-related pain), but also frequently in a

patient population with other long-term pain conditions (e.g., due to major surgery or burns). Therefore, it is appropriate to investigate tapentadol PR in the conditions reflective of those that will be treated with tapentadol PR when commercially available.

Furthermore, the inclusion of subjects suffering from cancer-related pain participating in other trials investigating drugs with marketing authorization is considered to be appropriate, when they constitute the standard treatment for particular patient population. As it is known that most drugs are administered to children off-label, but represent the current standard of care, it is considered that allowing the participation of subjects in trials with marketed drugs does not impose further uncertainties or safety risks to the subjects compared to their standard treatment.

Multiple trial sites, e.g., specialized in pediatric oncology and hematology, burns and orthopedics, in multiple countries will be required for the recruitment of 69 subjects in the specified time. See Section 14.1 for the sample size rationale.

Morphine as active control

Since its discovery, morphine has been widely accepted as a gold standard in the analgesic management of severe pain (De Conno and Kress 2006) and its analgesic efficacy in cancer pain has been proven (Broomhead et al. 1997). Morphine is among the top 10 medications given to children in the inpatient setting (Lasky et al. 2012). It is one of the few pain medications, and notably one of the few WHO Step III pain medications, that are authorized for use in children.

Blinding

An open-label trial was selected because it is not appropriate to over-encapsulate tapentadol PR and morphine PR tablets as the size of capsules would become too big for children and adolescents to swallow.

A double dummy method is also not feasible due to the large number of tablets that would be required to be taken by each subject.

Randomization

Subjects will be allocated in the ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily. A ratio of 2:1 was selected to gain more experience of tapentadol PR in a long-term pain requiring prolonged release opioid treatment setting within a pediatric population.

Stratification

Stratification by age and underlying pain condition (cancer/non-cancer-related pain) is planned. Stratification by underlying pain condition is foreseen because of the different progression of the underlying diseases and thus different progression of pain scores over time. The predefined age groups are 6 years to less than 12 years, and 12 years to less than 18 years, and subjects will be stratified so that at least 25% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years.

Sample size

See Section 14.1 for the sample size rationale.

Pain evaluations

During the trial, exploratory subject-reported pain assessments and supplemental analgesic rescue dosing information will be collected. To measure pain intensity, 2 pain intensity scales will be used: a VAS and the FPS–R. The appropriateness of these assessments is discussed in Section 12.7.

Dosing

The selection of the tapentadol PR dose (see Section 10.2.3 for dosing in this trial) to be evaluated in pediatric subjects was based largely upon pharmacokinetic considerations.

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 subjects aged above 3 years compared with adults, particularly in the adolescent group of 12 years to less than 18 years old. 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) such that again no major differences in excretion characteristics of tapentadol are anticipated in the children and adolescent age groups.

Data from a multiple dose trial in healthy adult subjects [redacted] 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 ~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 and adolescents will be predictable and time independent after single and multiple dosing.

Based on the pharmacokinetic evidence described above for tapentadol, the sponsor considers it justified to move into an adolescent safety and efficacy trial without a prior pharmacokinetic trial in this age group using the prolonged release formulation. An advisory committee meeting (in March 2012) initiated by the FDA to discuss “clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development” recommended, based on an FDA review of 22 products recently approved for adolescent use, that for dose confirmation in adolescents (12 years to less than 18 years), no pharmacokinetic trials are needed, but that doses can be derived using adult data.

Non-linear mixed effects modeling was performed to develop a population pharmacokinetic model in the pediatric population for the tapentadol oral solution and in the adult population for the tapentadol PR formulation. The adult tapentadol PR and pediatric tapentadol oral solution models were integrated to obtain a combined pediatric tapentadol PR model. This integrated model served as a basis for dose selection in the current trial.

Based on these results, a starting dose of ~1.25 mg/kg to 1.5 mg/kg every 12 hours, with a maximum dose of ~4.5 mg/kg every 12 hours, were chosen in this trial. As the IMP used in this trial is only available as tapentadol PR 25 mg and tapentadol PR 100 mg tablets, the doses in the age subgroups (Table 2) are chosen to be as close as possible to the estimated doses.

Blood sampling

Sparse blood sampling for the quantification of serum concentrations of tapentadol and tapentadol-O-glucuronide will be performed for subjects on tapentadol PR only. This will be done to confirm assumptions on dosing strategy based on modeling and simulation data and to confirm that tapentadol and metabolites do not accumulate in the pediatric population.

A total of 3 samples for the quantification will be taken from subjects allocated to tapentadol: at Visit V2 (1 hour to 6 hours after first dose for out-patients and 3 hours to 6 hours after first dose for hospitalized patients), at Visit V3, and at Visit VE. The serum concentrations from this number of samples are considered sufficient to enable a population pharmacokinetic analysis of the serum concentrations to estimate the exposure in each age group. No blood samples for pharmacokinetic evaluations will be drawn from subjects on morphine PR.

The volumes of blood taken for each assessment may vary due to trial site requirements. However, the total blood volume drawn per subject during the trial (Part 1 and Part 2) should not exceed 37 mL (excluding any blood that is discarded), i.e., will stay well within the maximum acceptable level of blood loss recommended in a pediatric population (EMEA ad hoc working party 2008). The EMEA ad hoc working party recommends that the total blood drawn in pediatric clinical trials does not exceed 3% of the total blood volume. For example, given the approximate blood volume in subjects 6 years to 18 years of age is 83 mL/kg to 90 mL/kg; the maximum allowed blood drawn in a 6 year-old girl with a body weight of 17.5 kg is therefore 43.6 mL to 47.3 mL.

Safety

The safety of tapentadol PR tablets in the trial population will be assessed at the end of the Treatment Period and again at the end of the Extension Period by evaluating the safety data

collected (adverse events, vital signs, 12-lead ECG, safety laboratory, physical examinations, height and body weight, SOWS, and modified CAS questionnaire).

To allow early signal detection and to ensure the safety of the trial subjects, an independent DMC (see Section 5.4) will be established to oversee and evaluate data from selected pediatric trials with tapentadol administration performed by Grünenthal.

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). Although data on the specific efficacy of opioids in children and adolescents is limited, it is not expected that these will deviate notably from those observed in adults. A single dose pharmacokinetic trial [redacted] in the same age group as the population in this trial has been recently performed by the sponsor, the data of which confirmed the dosing of tapentadol PR used in this trial.

The comparator in this trial, morphine PR, is a well-known opioid analgesic with proven efficacy in adults.

In addition, subjects enrolled in this trial will be intensively monitored during the treatment period, more closely than in routine clinical practice.

Risks

Lack of efficacy

Tapentadol may not be as efficacious in children and adolescents as it is in adults, even if the exposure is comparable. However, this is considered to be unlikely.

During the Treatment Period, rescue medication, in the form of morphine oral solution, will be available for use as rescue medication if pain relief is insufficient. Thereafter, subjects may receive immediate release strong opioids for treatment of breakthrough pain and incidental pain.

Safety

The potential risks to subjects in this trial include exposure to tapentadol and morphine, with a potential for side effects. Since most of these side effects are related to the use of opioids, i.e., class related, and the subjects would anyway require opioid treatment, the added safety risk is considered acceptable.

Data on the specific risks of opioids in children and adolescents is limited. However, it is not expected that the specific risks of opioids in children and adolescents will deviate from those observed in adults.

Subjects will be monitored for adverse events throughout the trial, and experts in pediatric pain will conduct the trial.

Safety – tapentadol

The assessment of risk for the tapentadol PR is mainly based on experience in adults with the solid oral formulations tapentadol IR and tapentadol PR (and a related tamper resistant formulation).

The safety profile of tapentadol has been well characterized through a completed clinical program in adults and post-marketing experience is now available. The safety of tapentadol PR has been demonstrated in a 1 year safety trial in adults.

The potential risks to subjects in this trial include long-term exposure to tapentadol PR, with a potential for side effects not discovered during single dose treatment in children and long-term treatment in adults. However, 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.

Safety – general and blood sampling

This trial has been designed to protect the interests of the subjects, minimizing the risk to them, and ensuring compliance with recommendations (EMEA ad hoc working party 2008) for the amount of blood drawn (see Section 12.1). Blood sampling for pharmacokinetic assessments and safety monitoring will be performed. These are the only invasive procedures associated with the trial. Risks to subjects include stress and discomfort, and the risks associated with the blood sampling process (venipuncture) and the volume of blood drawn.

To reduce the subject stress and discomfort, only staff with experience working with children or adolescents will draw blood and the application of a local anesthetic before venipuncture is recommended. Also, no more than 2 attempts to collect blood for pharmacokinetic evaluations will be done at any visit.

To keep the volume of blood drawn to a minimum, only laboratories will be used with expertise in handling and analyzing biological samples using small volumes. The number of venipunctures will also be kept to a minimum.

Data monitoring committee

To allow early signal detection and to ensure the safety of the trial subjects, an independent DMC (see Section 5.4) will be established to oversee and evaluate data from selected pediatric trials with tapentadol administration performed by Grünenthal. The DMC will review and evaluate the data provided, as defined in a DMC charter, on an ongoing basis. The DMC will provide recommendations to the sponsor's steering committee as described in the DMC Charter.

Conclusion

The efficacy of tapentadol is expected to be similar in children and adolescents to that seen in adults. The risks associated with the trial, and the risks associated with the administration of tapentadol and morphine, are adequately addressed by the mitigation procedures. As the trial generates data that will support the prescribing of tapentadol for control of pain in the pediatric population, 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 will 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 requested by the investigator to give consent/(if applicable) assent for the subject's enrollment in the trial as described in Section 4.2.

The investigator will keep a subject screening log and a subject identification and enrollment log.

9.2 Inclusion/exclusion criteria

9.2.1 Inclusion criteria

See Section 1.3.1.

9.2.2 Exclusion criteria

See Section 1.3.2.

9.2.3 Inclusion criteria for the Tapentadol Period (Part 2)

See Section 1.3.3.

9.2.4 Criteria for entry into the Tapentadol Period or Observation Period

Subjects completing the Treatment Period (Part 1) with tapentadol PR or morphine PR and who have need for continued opioid treatment can enter the Tapentadol Period (see Section 1.2.2).

Subjects not completing the Treatment Period (Part 1), but who have taken at least 1 dose of IMP, and those who complete the Treatment Period, but who do not want to continue with tapentadol PR treatment, will enter the Observation Period (12 months) (see Section 1.2.3).

9.3 Trial discontinuation and treatment not completed

Subjects may stop taking IMP (treatment not completed) during the trial, but continue in the Observation Period. Subjects may, however, also discontinue participation in the trial completely (trial not completed).

9.3.1 Reasons for discontinuation of a subject from IMP (treatment not completed)

The investigator must discontinue subjects from treatment with IMP (i.e., treatment not completed) for the compulsory reasons (stopping criteria) given in Table 1. For reasons marked as optional, the investigator may decide to stop IMP administration if the benefit/risk ratio for continued administration of IMP is considered not to be favorable.

Table 1: Reasons for compulsory and optional discontinuation of subjects from investigational medicinal product (treatment not completed)

	Discontinuation from IMP	
Main 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, laboratory parameters, vital signs, or other safety parameters (e.g., ECG).		X

	Discontinuation from IMP	
Main reason	**Compulsory**	**Optional**
- A confirmed QT or QTc interval of >470 ms.	X	
- Based on data from the central laboratory, clinically relevant change in liver parameters after dosing if the result is confirmed by 1 additional laboratory assessment (see Section 19.7), for 1 or more of: • 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 serum 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 (trial discontinuation)	X	
Lack of efficacy		
- The subject requires more than 4 doses per day of rescue medication on 2 consecutive days for persistent intolerable pain while taking the highest dose of IMP twice daily.	X	
Pregnancy	X	
Enrollment failure (trial discontinuation)	X	
Protocol deviation		
- The subject is non-compliant with requirements of the trial.		X
- Subject is using drugs or medical devices that have no marketing authorization for human use.	X	
- The subject continues to take more than the maximum allowed dose of IMP after being reminded not to do so.	X	
- Subject continues to take less than the minimum allowed dose of IMP according to weight group (see Table 2 and Table 3) after being reminded not to do so.		X
- A female subject becomes post-menarchal or turns 12 years of age and is not abstinent, or, if sexually active, is not practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch).	X	
- The subject is taking forbidden medication (see Section 10.5.2).		X
- Surgery during Part 1 (Treatment Period) of the trial that requires post-surgical ICU treatment, or that requires post–surgical parenteral pain-treatment, or, in the opinion of the investigator, affects the safety of the subject.	X	
Lost to follow-up (trial discontinuation)	X	
Technical reasons		
- Technical or logistical grounds (e.g., important technical equipment fails).		X
- Subject no longer requires opioid analgesia.	X	
- Subject requires a change of route of analgesic administration, e.g., because they can no longer swallow the tablets.	X	
Withdrawal of informed consent (trial discontinuation)	X	
Trial terminated by the sponsor (trial discontinuation)	X	

ECG = electrocardiogram; ICU = intensive care unit; IMP = investigational medicinal product.

9.3.2 Reasons for discontinuation of a subject from the trial

Following discontinuation of a subject from IMP, in certain cases (e.g., withdrawal of consent), the subject may also need to be discontinued from trial participation (see items marked trial discontinuation in Table 1).

9.3.3 Procedure for the handling of prematurely discontinued subjects

The investigator must inform the sponsor in writing about any discontinuation of a subject from the trial or from IMP (treatment not completed) and must document any such discontinuation of a subject. The investigator must update the interactive response technology system and CRF within 48 hours of a subject discontinuing. 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 or IRB must be informed with a detailed written explanation. Also, any technical devices provided to the subjects, e.g., electronic diaries, must be collected.

For all subjects discontinuing the trial or discontinuing IMP (treatment not completed; these subjects may continue the trial in the Observation Period), the following information must be documented:

- Reason for discontinuation.
- If the parent/legal guardian/subject agrees, perform all assessments for Visit VE or Visit ET as appropriate, and Visit F7D (Section 1.2).

For subjects discontinued from the trial, the following information must be documented:

- Status of all new and ongoing (serious) adverse events.
- All data captured until discontinuation as required at all attended visits, including the recording of concomitant medication taken until the day of discontinuation from the trial.
- Ensure the return of partially used and unused medication kits.
- Perform a final IMP and, if applicable, rescue drug accountability.
- Collect the diary and any other devices provided to the subject.
- If the subject agrees, perform all assessments/visits as given in Section 1.2.

For subjects discontinued from IMP (treatment not completed), all efforts should be made to:

- Ensure the return of partially used and unused medication kits.
- Perform a final IMP and, if applicable, rescue drug accountability.
- Collect the diary and any other devices provided to the subject.
- If the subject agrees, perform all assessments/visits as given in Section 1.2.

Subjects turning 18 years old before Visit VE may continue in the trial. However, an additional subject will then be enrolled and allocated to IMP. Otherwise treated subjects will not be replaced. See Section 3 for a definition of allocated and treated subjects. Replacement subjects will receive

the same sequence of treatments and undergo the same procedures and assessments up to Visit VE as the initially entered subjects.

9.3.4 Premature termination or suspension of the trial

The relevant IEC or 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 or IRB, the regulatory authorities, or the sponsor/the sponsor's authorized delegate, as applicable).

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

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

10 TREATMENTS

10.1 Investigational medicinal product

10.1.1 Identity and composition – tapentadol PR (test)

Name:	Tapentadol prolonged release tablets
Substance code:	CG5503
Substance name:	Tapentadol hydrochloride
Active component(s):	Tapentadol
Dose (strength):	25 mg, 100 mg tablets (tapentadol)
Manufacturer:	Grünenthal GmbH, Aachen, Germany

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

10.1.2 Identity and composition – morphine PR (comparator)

Name:	Morphine prolonged release tablets
Substance name:	Morphine sulfate
Active component(s):	Morphine
Dose (strength):	10 mg, 30 mg tablets (morphine sulfate)
Final release of the re-packaged product:	Grünenthal GmbH, Aachen, Germany

10.1.3 Packaging and labeling

The IMPs will be manufactured as single oral dosage forms and packed in blister packs. For detailed information about the packaging and labeling, see the clinical supply specification.

10.1.4 Delivery, storage and disposal

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

Storage conditions will be specified on the labels of the IMPs.

For countries in which tapentadol and morphine have been classified as a controlled/scheduled substance, all local requirements for handling, storage, and distribution of narcotics will be followed. Controls will be implemented at the trial site to ensure documented compliance with these requirements.

10.2 Administration of trial treatments

10.2.1 Administration

The route of administration is oral. Tablets should be taken with at least 50 mL of water or other suitable fluid. Tablets can be taken irrespective of food intake.

Subjects taking tapentadol PR 100 mg or more can decide if they prefer to take the smaller tapentadol PR 25 mg tablets or a combination of tapentadol PR 25 mg and tapentadol 100 mg tablets.

The time of IMP administration and the number of tablets per dose will be captured in the diary during Part 1 (Treatment Period).

All restrictions and precautions listed in the investigator's brochure for tapentadol PR and in the summary of product characteristics for morphine PR must be followed.

The first dose of IMP will be taken during Visit V2 (Allocation Visit).

A dose must not be repeated if a subject vomits or regurgitates part or all of a dose. Vomiting and/or regurgitation of a dose must be recorded as an adverse event.

10.2.2 Total number of doses and dosing interval

The IMP will be taken for 14 (±1) days in Part 1 (Treatment Period) and, thereafter (tapentadol PR only), for up to ~12 months in the Tapentadol Period of Part 2. Dosing will be twice daily with a dosing interval of ~12 hours (but not less than 6 hours).

10.2.3 Dose

10.2.3.1 Starting doses in Part 1 for subjects without previous opioid treatment

Subjects will start with the minimum dose (Dose level 1) of tapentadol PR (Table 2) or morphine PR (Table 3).

10.2.3.2 Starting doses in Part 1 for subjects with previous opioid treatment

Subjects taking previous opioid treatment will start at 70% of the equi-analgesic dose of their previous treatment or lower; depending on the available dose, but using at least the minimum dose according to weight group (see Table 2 for tapentadol PR and Table 3 for morphine PR).

Subjects pre-treated with morphine can continue on their previous dose or next lower dose according to Table 2 if the dose does not match a dose given on the dosing table, if randomized to morphine.

Conversion from other opioids to morphine should be done according to clinical routine. To calculate the dose of prolonged release opioids per intake, it is recommended to calculate the total daily dose of the immediate release opioid and divide the result by 2. To rotate subjects from other opioids to tapentadol PR, the morphine-equivalent dose should be calculated first followed by the calculation of the final tapentadol PR dose (1 mg morphine PR is equivalent to 2.5 mg tapentadol PR).

10.2.3.3 Starting dose of tapentadol PR in Part 2

Subjects converting from morphine PR (Treatment Period of Part 1) to tapentadol PR (Tapentadol Period of Part 2) will start tapentadol PR at 70% of the current morphine equivalent dose or lower, depending on the available dose, but using at least the minimum dose according to their weight group (Table 2).

Subjects treated with tapentadol PR during Part 1 (Treatment Period) will continue on the last dose taken during Part 1 and the dose can be adjusted within the pre-defined limits as required during Part 2.

10.2.3.4 Titration

The dose of IMP will be titrated within the given limits for dosing according to the body weight measured during the last visit (see Table 2 for tapentadol PR and Table 3 for morphine PR).

Subjects will have the dose of IMP titrated up or down according to the pre-specified criteria defined below after consulting the investigator at visits throughout the trial or by using telephone contacts. However, a subject can reduce the dose at any time without consulting the investigator beforehand if a TEAE occurs. The subject should be informed by the investigator to report any dose reduction as soon as possible to the investigator.

The decision for a dose increase is at the investigator's discretion, but should only be done after a minimum of 2 days (4 scheduled intakes of IMP) since the last increase to allow attainment of a steady state at the current dose.

Subjects who are already on the highest dose but who lose weight during the course of the trial may continue on that dose if needed.

10.2.3.4.1 Criteria for up-titration during Part 1

Subjects will have their dose of IMP increased if the subject reports to the investigator that all of the criteria below are met:

- Good tolerability (no signs of respiratory depression, tolerable nausea, constipation, etc.).
- Last up-titration was ≥2 days ago (4 scheduled intakes of IMP).

- 1 of the following is true:
  - ≥3 doses of rescue medication per 24 hours.
  - Average of pain assessments within the last 24 hours before dosing ("pain right now") ≥50 on VAS for subjects aged 12 years to less than 18 years at Visit V2.
  - Average of pain assessments within the last 24 hours before dosing ("pain right now") on the FPS-R ≥5 for subjects aged 6 years to less than 12 years at Visit V2.

10.2.3.4.2 Criteria for up-titration during Tapentadol Period of Part 2

Subjects will have their dose of IMP increased if the subject reports to the investigator that all of the criteria below are met:

- Good tolerability (no signs of respiratory depression, tolerable nausea, constipation, etc.).
- Last up-titration was ≥2 days ago (4 scheduled intakes of IMP).

10.2.3.4.3 Criteria for down-titration

Down-titration is recommended but not obligatory if at least 1 of the following criteria is met:

- Pain <30 on VAS for the last 72 hours for subjects aged 12 years to less than 18 years at Visit V2.
- Pain <3 on the FPS-R for the last 72 hours for subjects aged 6 years to less than 12 years at Visit V2.
- The dose can be decreased any time due to TEAEs.

10.2.4 Titration and dosing tables

Table 2: Tapentadol PR dosing table

Weight (kg)	Minimum/Starting dose [a] Dose level 1		Titration						Maximum dose Dose level 5	
			Dose level 2		Dose level 3		Dose level 4			
	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)
17.5 to <22.5	25	25	50	50	-	-	-	-	75	75
22.5 to <27.5	25	25	50	50	75	75	-	-	100	100
27.5 to <32.5	25 [b]	50 [b]	75	75	100	100	-	-	125	125
32.5 to <40.0	50	50	75	75	100	100	125	125	150	150
40.0 to <45.0	50	50	100	100	125	125	150	150	175	175
45.0 to <50.0	75	75	100	100	150	150	175	175	200	200
50.0 to <55.0	75	75	100	100	150	150	200	200	225	225
55.0 to <60.0 [c]	75	75	100	100	150	150	200	200	250	250
≥60.0 [c]	100	100	125	125	150	150	200	200	250	250

a) Subjects taking less than the minimum dose according to their weight group may be discontinued from investigational medicinal product.

b) The first intake is 25 mg (irrespective whether first taken in the morning of evening) and the second and subsequent intakes are 50 mg.

c) Subjects with a bodyweight of 55.0 kg or higher will receive a maximum dose of tapentadol PR 250 mg twice daily.

M = morning; E = evening; PR = prolonged release.

Table 3: Morphine PR dosing table

Weight (kg)	Minimum/Starting dose [a] Dose level 1		Titration Dose level 2		Titration Dose level 3		Titration Dose level 4		Maximum dose Dose level 5	
	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)	M (mg)	E (mg)
17.5 to <22.5	10	10	20	20	-	-	-	-	30	30
22.5 to <27.5	10	10	20	20	30	30			40	40
27.5 to <32.5	10 [b]	20 [b]	30	30	40	40	-	-	50	50
32.5 to <40.0	20	20	30	30	40	40	50	50	60	60
40.0 to <45.0	20	20	40	40	50	50	60	60	70	70
45.0 to <50.0	30	30	40	40	60	60	70	70	80	80
50.0 to <55.0	30	30	40	40	60	60	80	80	90	90
55.0 to <60.0 [c]	30	30	40	40	60	60	80	80	100	100
≥60.0 [c]	40	40	50	50	60	60	80	80	100	100

a) Subjects taking less than the minimum dose according to their weight group may be discontinued from investigational medicinal product.

b) The first intake (irrespective whether first taken in the morning of evening) is 10 mg and the second and subsequent intakes are 20 mg.

c) Subjects with a bodyweight of 55 kg or higher will receive a maximum dose of morphine PR 100 mg twice daily.

M = morning; E = evening; PR = prolonged release.

10.3 Method of assigning subjects to treatment (allocation)

An interactive response technology system (voice and web based) will be used to assign a subject number at the Enrollment Visit (Visit V1) of Part 1 and to support the drug supply chain management processes of distribution and return. Details of the vendor and the system will be defined in a separate document and filed in the trial master file at the end of trial.

The investigator or person assigned by the investigator must log into the system using their own user identification number and a password. The investigator or person assigned by the investigator will enter the subject's number and other information required by the system to obtain a medication number. The medication number is then used to select the correct package of IMP to give to the subject.

10.3.1 Part 1

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 at Visit V2 (Allocation Visit) for the duration of the Treatment Period.

Subjects will be stratified using the interactive response technology system by age group (6 years to less than 12 years and 12 years to less than 18 years, at Visit V2 [Allocation Visit]) so that at least 25% of the subjects are in the younger age group, and by underlying pain condition (cancer/non-cancer-related pain).

The following aspects will be requested by the interactive response technology system: body weight, age group of the subject, underlying pain condition, previous opioid treatment for first IMP supply, and preferred strength (25 mg or a combination of 25 mg and 100 mg), if applicable.

10.3.2 Part 2

At Visit VE, subjects will be discontinued from treatment in the interactive response technology system or be offered further treatment with tapentadol PR. Subjects who were treated with morphine PR will be offered further treatment with tapentadol PR in the interactive response technology system.

The following aspects will be reflected by the system: body weight, previous treatment in Part 1 (morphine PR or tapentadol PR) for first IMP supply in Part 2, and preferred strength (25 mg or a combination of 25 mg and 100 mg), if applicable.

10.4 Blinding and unblinding

This is an open-label trial.

10.5 Allowed and forbidden and prior/concomitant medications/therapies

Where appropriate, the following only apply to subjects taking IMP.

Restrictions apply to prior medication/therapy use, and subjects will be instructed to only use allowed concomitant medication/therapy during the trial.

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

For information about potential interactions with concomitant medication/therapy, see the current investigator's brochure for tapentadol PR or the summary of product characteristics for morphine PR.

In emergency situations, medication according to standard medical knowledge should be initiated.

All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed.

10.5.1 Allowed prior and concomitant medications/therapies

Allowed concomitant medications/therapies with timely or dose restrictions are:

On the day of allocation to IMP (Visit V2):

- Weak and strong opioids up to a morphine-equivalent dose of <3.5 mg/kg per day.

During the Treatment Period (from Visit V2 to Visit VE):

- Rescue medication (morphine oral solution) provided by the sponsor.

During the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Intravenous opioids during surgery.

During the Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Immediate release strong opioids for treatment of breakthrough pain and incidental pain.

10.5.2 Forbidden prior and concomitant medication/therapies

Forbidden prior and concomitant medication/therapies are:

Before allocation to IMP (Visit V2) and during the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- From 14 days prior to Visit V2 until the last intake of IMP: Monoamine oxidase inhibitors.
- From 30 days prior to Visit V2 until the last intake of IMP: Any medication or medical devices without a marketing authorization for human use.

Subjects may not undergo a washout of the above for the purposes of the trial.

During the Treatment Period (from Visit V2 to Visit VE) and Tapentadol Period (from Visit VE until Visit ET/Visit F12M):

- Non-trial supplied opioids (unless covered by allowed concomitant treatments).

10.5.3 Cautionary use

Caution should be exercised with concomitant medication that:

- May enhance the risk of central nervous or respiratory depression.
  General anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other central nervous system depressants (including alcohol and illicit drugs) taken concomitantly with tapentadol may exhibit interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma.
- Is a serotoninergic medicinal product (e.g., selective serotonin re-uptake inhibitors).
  In isolated cases, there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tapentadol in combination with serotoninergic medicinal products such as selective serotonin re-uptake inhibitors.
- Is a strong enzyme inducer (e.g., rifampicin, phenobarbital, St John's Wort) that is started or stopped during the intake of IMP, since this may lead to decreased efficacy or risk of adverse effects, respectively.

10.6 Rescue medication

During Part 1 (Treatment Period) only, morphine oral solution will be supplied by the sponsor as rescue medication for both treatment groups.

An interactive response technology system (voice and web based) will be used to assign subjects to rescue medication.

Name:	Morphine oral solution
Substance name:	Morphine sulfate or morphine hydrochloride
Active component(s):	Morphine
Dose (strength):	0.5% and/or 2.0%
Final release of the re-packaged product:	Grünenthal GmbH, Aachen, Germany

During Part 2, the use of immediate release strong opioids for treatment of breakthrough pain and incidental pain is allowed.

10.6.1 Dose

The dose of morphine oral solution per intake of rescue medication is ~1/6 of the total daily dose of morphine PR treatment or ~1/6 of the morphine equivalent dose of tapentadol PR treatment.

The investigators and parent or legal guardian of the subject will be provided with a table showing clearly what dose of morphine oral solution the subject should take as rescue medication.

Subjects on the highest dose of IMP are not allowed to take more than 4 doses of rescue medication per day on 2 consecutive days as this indicates a lack of efficacy (defined as a discontinuation criteria, see Section 9.3.1). No more than 10 doses of rescue medication at any dose level are allowed per day.

10.6.2 Reasons for administration

Rescue medication may be given in Part 1 for:

- Breakthrough pain without clear cause.
- End-of-dose failure indicating a requirement of adjustment of the dose of IMP.
- Increased activity or movement (incidental pain).
- Withdrawal symptoms such as hyperalgesia that appeared during the first days of titration after the previous treatment with an opioid were stopped.
- Prevention of pain during titration, if considered necessary by the investigator.

10.6.3 Documentation

The intake of rescue medication (time and dose [mg]) will be documented by the subject, parent or legal guardian on a daily basis in the diary preferably after each intake of rescue medication in the Treatment Period.

10.7 Documentation of drug accountability

For tapentadol PR and morphine PR tablets, drug accountability must be performed on a tablet basis per assigned IMP kit.

The bottles of rescue medication oral solution (morphine) will be weighed using appropriately calibrated scales before handing out to the subject/parent or legal guardian and at return to allow 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, 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.

Before the unused IMPs and other medications supplied to the investigator are returned or destroyed, the investigator must allow sponsor representatives 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. The documentation should also be checked regarding the expected amount to be returned according to the expected treatment dose.

See Section 12.8 for compliance limits.

11 TRIAL PROCEDURES

See Section 1.1 for a summary of the trial as a flow diagram and Section 1.2 for tabular schedules of events for each period. A trial site visit may be performed as a home visit after prior approval by the sponsor.

11.1 Course of the trial

11.1.1 Part 1

11.1.1.1 Enrollment Visit (Visit V1; Day -14 to Day 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 following procedures will be performed:

- Obtain informed consent and (if required by local law) assent (see Section 4.2 for the procedure). The informed consent/assent may be obtained earlier than Day -14.
- Record demographic data (date of signing the informed consent/assent form, sex, age, and race/ethnicity).
- Record relevant medical history and pain history.

- Record prior and concomitant medication and therapies.
- Perform a physical examination and document findings.
- Record height and body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Record a 12-lead ECG. The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.
- Take blood for safety laboratory investigations (for both the central and local laboratories). The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.
- Collect urine/perform dip stick urinalysis.
- Perform a urine test for drugs of abuse.
- Evaluate subject suitability for trial participation according to the inclusion/exclusion criteria as applicable (e.g., excluding results of central laboratory tests not yet available). Compliance with the exclusion criteria pertaining to laboratory analyses will be checked based on local laboratory values. The parameters needed for this assessment comprise: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine. The creatinine clearance will be calculated by the electronic CRF.
- Assess and record adverse events that occur after signing the informed consent form.
- Dispense the subject trial card to the subject/parent/guardian.

11.1.1.2 Visit V2 (Allocation Visit; Day 1)

If Visit V1 and Visit V2 are on the same day, the following procedures will not be repeated:

- Record age.
- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Assess and record adverse events.

The following Day 1 specific evaluations will be carried out:

- Perform a urine pregnancy test in female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.
- Check inclusion and exclusion criteria. Compliance with the exclusion criteria will be checked based on local laboratory values. The parameters needed for this assessment comprise: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine. The creatinine clearance will be calculated automatically by the electronic CRF.

- Set up diary.
- Dispense diary.
- Instruct subject, parent(s), or legal guardian(s) on how to use diary.
  - Give instructions to record pain assessment twice daily in the diary (VAS and FPS-R) until Visit VE.
  - Give instructions to record intake of IMP and rescue medication in the diary, including time of administration.
- Record "pain right now" in the diary (VAS and FPS-R) before any painful or unpleasant procedure, and before the first intake of IMP as a baseline value.
- Complete the modified CAS.
- Allocate subject to treatment (see Section 10.3).
- Dispense IMP and rescue medication (see Section 10.6).
- Administer the first dose of IMP to the subject (see Section 10.2.1). The first dose of IMP will be taken during this visit, within 24 hours after randomization. Day 1 is the day of first IMP intake. Record administration in the diary.
- Train/instruct subject, parent(s), guardian(s), or caregiver on IMP/rescue medication use (handling and intake).
- Discuss IMP titration/dose adjustment.
- Take a single blood sample for serum pharmacokinetics from subjects on tapentadol PR at 1 hour to 6 hours after IMP for out-patients or at 3 hours to 6 hours after IMP intake for hospitalized subjects.

11.1.1.3 Visit V3 (Day 8 ± 1)

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Train/instruct subject(s), parent(s), or legal guardian(s) how to use the diary.
  - Give instructions to record pain assessment twice daily in diary (VAS and FPS-R) until Visit VE.
  - Give instructions to record intake of IMP and rescue medication in the diary, including time of administration.
- Check diary compliance.
- Complete the modified CAS questionnaire.
- Complete the acceptability and palatability of IMP questionnaire.
- Collect returned IMP and rescue medication.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.

- Confirm whether returned amount of rescue medication matches expected amount to be returned.
- Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.

- Dispense IMP and rescue medication.
- Train/instruct subject, parent(s), guardian(s), or caregiver on IMP/rescue medication use (handling and intake). Exchange instruction sheet if necessary (e.g., due to weight change).
- Discuss IMP titration/dose adjustment.
- Take blood sample for serum pharmacokinetics (at any time during the visit, but after measuring the pain scores) from subjects on tapentadol PR.
- Assess and record adverse events.
- Assess discontinuation criteria.

11.1.1.4 Visit VE (Day 15 ± 1, End of Treatment Visit)

This visit is planned for Day 15 ± 1, but must also be performed within 3 days after last intake of IMP if a subject discontinues IMP during the Treatment Period.

The following procedures will be performed:

- Record age of subject.
- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record height.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Record a 12-lead ECG.
- Record “pain right now” in the CRF (VAS and FPS-R) - only for subjects going into the Tapentadol Period.
- Complete the following questionnaires:
  - Modified CAS.
  - Acceptability and palatability of IMP.
  - Dispense SOWS questionnaire for completion at home if this is the visit of the last intake of IMP (only for subjects going in to the Observation Period). To be completed once daily until the seventh day after the last intake of IMP. To be collected at Visit F7D.
- Check diary compliance.
- Collect the diary for subjects not entering the Tapentadol Period (Part 2).
- Collect returned IMP and rescue medication.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.

- Confirm whether returned amount of rescue medication matches expected amount to be returned.
- Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.

- Take blood sample for serum pharmacokinetics (at any time during the visit, but after measuring the pain scores) from subjects on tapentadol PR.
- Take blood for central laboratory (hematology, clinical chemistry).
- Collect urine/perform dip stick urinalysis.
- Perform a urine pregnancy test in female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.
- Assess and record adverse events. Document changes (e.g., in the intensity) of each ongoing adverse event.
- Check discontinuation criteria for IMP intake.
- Check subject eligibility and assign eligible subjects to the Tapentadol Period or Observation Periods.

For subjects entering the Tapentadol Period:

- Instruct the subject, parent(s), legal guardian(s) or caregiver about the Tapentadol Period, including:
  - Discuss titration/dose adjustment if subject transfers from morphine PR.
  - Dispense IMP.
  - Retrain subject, parent(s), legal guardian(s), or caregiver on use of IMP (handling and intake).
- Train/instruct subject(s), parent(s), or legal guardian(s) how to use the diary.
  - Give instructions to record intake of IMP in the diary, including time of administration. Exchange instruction sheet if necessary (e.g., due to weight change).

For subjects assigned to the Observation Period:

- Instruct the subject, parent(s), or legal guardian(s) about the Observation Period.

11.1.2 Part 2 – Tapentadol Period

Subjects completing the Treatment Period (Part 1) with tapentadol PR or morphine PR and who have need for continued opioid treatment can enter the Tapentadol Period. Assignment to the Tapentadol Period needs to be documented in the CRF and the interactive response technology system. Subjects will be followed until Visit F12M. Subjects in the Tapentadol Period of Part 2 may stop treatment early (before Visit F12M) and switch to Observation period for the remainder of Part 2.

11.1.2.1 Visit M1 (Day 7 ± 2) and Visit M2 (Day 14 ± 2)

As withdrawal symptoms may occur in subjects transferring from morphine PR to tapentadol PR, because they start tapentadol PR at 70% of the equivalent morphine dose, these subjects will have 2 additional visits at the beginning of the Part 2 Tapentadol Period (Visit M1 and Visit M2).

Visit M1 and Visit M2 in the Tapentadol Period are only for subjects who had been previously allocated to morphine PR in the Treatment Period.

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Record "pain right now" in the CRF (VAS and FPS-R).
- Train/instruct subject(s), parent(s) or legal guardian(s) how to use the diary.
  - Give instructions to record intake of IMP in the diary, including time of administration.
- Check diary compliance.
- Collect returned IMP.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.
  - Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.
- Dispense IMP.
- Discuss titration/dose adjustment.
- Train/instruct subject, parent(s), legal guardian(s), or caregiver on the use of IMP (handling and intake). Exchange instruction sheet if necessary (e.g., due to weight change).
- Assess and record adverse events.
- Check discontinuation criteria.

11.1.2.2 Visit TP1 to TP12 (every 28 days after Visit VE, range: ±5 days)

Visits TP1 to TP12 are performed at ~28 day intervals in all subjects in the Tapentadol Period. The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Record body weight.
- Record height (only at Visit TP3, Visit TP6, Visit TP9, and Visit TP12).
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Record "pain right now" in the CRF (VAS and FPS-R).
- Take blood for central laboratory (hematology, clinical chemistry; only at Visit TP3, Visit TP6, Visit TP9, and Visit TP12).
- Collect urine/perform dip stick urinalysis (only at Visit TP3, Visit TP6, Visit TP9, and Visit TP12).
- Perform a urine pregnancy test in female subjects who are post-menarchal or older than 12 years (only at Visit TP3, Visit TP6, Visit TP9, and Visit TP12) at the time of the scheduled visit.
- Train/instruct subject(s), parent(s), or legal guardian(s) how to use the diary.
  - Give instructions to record intake of IMP in the diary, including time of administration.
- Check diary compliance.

- Collect returned IMP.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.
  - Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.
- Dispense IMP.
- Discuss titration/dose adjustment
- Train/instruct subject, parent(s), legal guardian(s), or caregiver on IMP (handling and intake). Exchange instruction sheet if necessary (e.g., due to weight change).
- Assess and record adverse events.
- Check discontinuation criteria.

11.1.2.3 Visit ET (Early Termination Visit)

Visit ET must be performed within 3 days after last intake of IMP if IMP is stopped before Visit F12M in Part 2. If Visit F12M and Visit ET are performed on the same day, assessments scheduled for both visits will not be repeated at Visit F12M.

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record height.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Complete the following questionnaires:
  - Modified CAS questionnaire.
  - Dispense SOWS questionnaire for completion at home if this is the visit of the last intake of IMP. To be completed once daily until the seventh day after the last intake of IMP. To be collected at Visit F7D.
- Record “pain right now” in the CRF (VAS and FPS-R).
- Take blood for central laboratory (hematology, clinical chemistry).
- Collect urine/perform dip stick urinalysis.
- Perform a urine pregnancy test in female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.
- Check diary compliance.
- Collect the diary.
- Collect returned IMP.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.
  - Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.
- Assess and record adverse events.

11.1.2.4 Visit F12M (at 12 months after Visit VE, range ±14 days)

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record height.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Complete the following questionnaires:
  - Modified CAS questionnaire.
  - Dispense SOWS questionnaire for completion at home if this is the visit of the last intake of IMP. To be completed once daily until the seventh day after the last intake of IMP. To be collected at Visit F7D.
- Record "pain right now" in the CRF (VAS and FPS-R).
- Take blood for central laboratory (hematology, clinical chemistry).
- Collect urine/perform dip stick urinalysis.
- Perform a urine pregnancy test in female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit.
- Check diary compliance.
- Collect the diary if IMP has been stopped at this visit, if not already collected.
- Collect returned IMP.
- Perform drug accountability:
  - Confirm and document compliance with IMP intake.
  - Verify discrepancies with subject, or parent(s), legal guardian(s), or caregiver.
- Assess and record adverse events.

11.1.3 Visit F7D (Final post treatment visit, at 7 days after stopping IMP, range ±2 days)

Visit F7D is the final post treatment visit, performed 7 days (±2) after stopping IMP, i.e., after Visit F12M, or after Visit VE for subjects stopping IMP in Part 1, or Visit ET for subjects stopping IMP before Visit F12M in Part 2.

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Collect the completed SOWS questionnaires.
- Assess and record adverse events.

- Complete end of trial tasks, e.g., collect subject trial cards (if the subject is discontinuing from the trial).

11.1.4 Part 2 – Observation Period

Subjects not completing the Treatment Period (Part 1), but who have taken at least 1 dose of IMP, and those who complete the Treatment Period but who do not want to continue with tapentadol PR, will enter the Observation Period (12 months). Assignment to the Observation Period needs to be documented in the CRF and the interactive response technology system Subjects will be followed until Visit F12M. Subjects in the Tapentadol Period of Part 2 may stop treatment early (before Visit F12M) and switch to Observation period for the remainder of Part 2. Subjects transferring before Visit F12M from the Tapentadol Period to the Observation Period will continue in the Observation Period starting from the same trial day number.

11.1.4.1 Visit OP3, Visit OP6, and Visit OP9 (at 3, 6, 9 months after Visit VE, range ±14 days)

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Assess and record adverse events.

11.1.4.2 Visit OPx (unscheduled final visit)

Visit OPx is an unscheduled visit during the Observation Period when the subject stops further participation in the trial. The assessments are performed for all subjects who discontinue from the Observation Period, unless informed consent is withdrawn.

The following procedures will be performed:

- Record concomitant medication intake/therapies.
- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record height.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Complete the following questionnaires:
  - Modified CAS questionnaire.
- Take blood for central laboratory (hematology, clinical chemistry).
- Collect urine/perform dip stick urinalysis.
- Assess and record adverse events.
- Complete end of trial tasks, e.g., collect subject trial cards.

11.1.4.3 Visit F12M (at 12 months after Visit VE, range ±14 days)

The following procedures will be performed:

- Record concomitant medication intake/therapies.

- Perform a physical examination, document that it was performed, and record changes to previous assessment.
- Record height.
- Record body weight.
- Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
- Complete the following questionnaires:
  - Modified CAS questionnaire.
- Take blood for central laboratory (hematology, clinical chemistry).
- Collect urine/perform dip stick urinalysis.
- Assess and record adverse events.
- Complete end of trial tasks, e.g., collect subject trial cards.

11.1.5 Phone contacts

Phone contacts can be made at any time, e.g., if the subject wants to report adverse events, or has questions regarding concomitant medication intake/therapies. If no trial site visit takes place, phone contacts are mandatory if the subject would like to up or down titrate the IMP. A trial site visit may be performed as a home visit after prior approval by the sponsor.

The following will be recorded:

- Record concomitant medication intake/therapies.
- Discuss titration/dose adjustment.
- Record reason for dose adjustment and new dose, if applicable.
- Assess and record adverse events.
- Check discontinuation criteria.

11.1.6 Additional trial site attendance

A parent or legal guardian (or subject if 18 years or older) may additionally visit the investigator's site solely for the purpose of obtaining further supplies of IMP, especially at trial sites where provision of narcotics to subjects is limited. This may be performed without the presence of the subject.

11.2 Examination hierarchy and time windows

No procedures for this trial are allowed to be performed before the informed consent/(if required) assent is obtained.

Non-invasive procedures, e.g., recording of pain assessment, should be performed before invasive procedures. Blood samples for safety laboratory and pharmacokinetics should be taken after all non-invasive procedures are completed and should be taken together when scheduled for the same visit. The exact order in which procedures are performed may deviate due to local circumstances and will not constitute, per se, a protocol deviation.

The visit time windows are not cumulative, and visits should be performed at the times specified within the given time window (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 tapentadol PR and the summary of product characteristics for morphine PR for precautions and emergencies relevant for this trial, e.g., for the management of overdose.

11.3.2 General restrictions

Subjects must refrain from drinking beverages containing alcohol and recreational intake of drugs while on IMP.

All restrictions and precautions, e.g., regarding prior food intake, listed in the investigator's brochure for tapentadol PR and in the summary of product characteristics for morphine PR must also be followed. Otherwise, there are no general restrictions on the subjects.

11.3.3 Counseling of female subjects of reproductive age

All female subjects of childbearing potential (post-menarchal and not surgically incapable of childbearing), including those with the menarche during the trial or are or become 12 years old, should be counseled on the need to practice medically acceptable methods of birth control during the trial and on the importance of avoiding pregnancy while on IMP. Counseling should take place at the start of the trial or during the trial if the child is post-menarchal. Counseling must be documented in the source documents and CRF.

Medically acceptable methods of birth control include:

- 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 trial site staff immediately if pregnancy is suspected.

11.4 Subject trial cards

Subjects/parent(s)/legal guardian(s), as applicable, will receive a "subject trial card". The trial card will list at a minimum the following information:

- Name of the subject and a statement that he/she is currently participating in a clinical trial.
- Trial code.
- Dates of all individual visits.
- Name of investigator.
- Contact (telephone) number at the trial site.

11.5 Provisions of any additional care of subject after trial termination

After stopping the IMP, subjects will be treated by their physicians according to the specific standard treatment in the country concerned.

11.6 Low enrollment

Trial sites with a low enrollment rate 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 16 weeks of IMP availability at the trial site, and no subject allocation to IMP within 1 year after the last subject was allocated to IMP.

12 DATA COLLECTION

12.1 Overview of blood sampling in this trial

The application of a local anesthetic (patch, cream or gel) to the skin of 2 potential locations for vein puncture before the blood samples are taken is recommended. Immediately before the blood sampling, the locations must be cleaned to remove any residuals of the local anesthetic.

Blood can be taken through a central venous line if in place and there is a spare line through which no medication is administered. The amount of blood that needs to be discarded when collecting it via the central line needs to be taken into account so as not to exceed the maximum allowed amount of blood.

If possible, blood samples for safety laboratory evaluations and serum pharmacokinetics should be taken at the same time. Sampling times are given in the schedule of events (Section 1.2). The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.

Table 4: Approximate volume of blood to be collected from each subject during Part 1

Examination	Blood per test	Number of samples	Total per test [b]
Blood sampling for serum pharmacokinetics [a]	0.5 mL	3	1.5 mL
Clinical chemistry – central laboratory	2 mL	2	4 mL
Hematology – central laboratory	2 mL	2	4 mL
Clinical chemistry – local laboratory	2 mL	1	2 mL
Total			11.5 mL

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

a) Blood samples for serum pharmacokinetics will only be drawn from subjects on tapentadol PR.

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

PR = prolonged release.

Table 5: Approximate volume of blood to be collected from each subject during the Tapentadol Period of Part 2

Examination	Blood per test	Number of samples	Total per test [a]
Clinical chemistry – central laboratory	2 mL	6	12 mL
Hematology – central laboratory	2 mL	6	12 mL
Total			24 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.

The expected total blood volume drawn per subject will not exceed 12 mL during the Part 1 of the trial, and 25 mL during the Tapentadol Period of Part 2. Approximately 4 mL blood (2 mL for hematology and 2 mL for clinical chemistry) will be taken at Visit F12M of the Observation Period.

Additional blood may be drawn if a (serious) adverse event occurs or if the investigator considers it necessary.

The volumes of blood taken for each assessment may vary due to trial site requirements; however, the total planned blood volume drawn per subject during the trial (Part 1 and Part 2) should not generally exceed 37 mL (excluding any blood that is discarded), i.e., will stay well within the maximum acceptable level of blood loss recommended in a pediatric population (EMEA ad hoc working party 2008).

12.2 Collection of subject characteristics data

12.2.1 Demographic data

Demographic data (date of signing the informed consent/assent form, sex, age, and race/ethnicity) will be recorded in the CRF.

12.2.2 Medical history

The clinically relevant medical history of the subject per investigator's opinion will be documented in the CRF.

12.2.3 Pain history

The history, underlying pain condition (cancer/non-cancer-related pain), and treatments given in the last 30 days for pain before enrollment will be recorded in the CRF.

12.2.4 Prior and concomitant medications and therapies

All therapies, medication requiring prescriptions (including oral contraceptives) and/or over-the-counter medication used within 30 days prior to enrollment and up to the end of the trial must be recorded in the CRF.

All additions to or changes in therapy, prescriptions and/or over-the-counter medication after enrollment must be recorded in the CRF, for changes in therapy as a new entry.

12.3 Collection of pharmacokinetic data

12.3.1 Blood sampling for serum pharmacokinetics

Blood samples for pharmacokinetic evaluations will only be drawn from subjects on tapentadol PR. No blood samples will be drawn from subjects on morphine PR for pharmacokinetic evaluations.

The instructions given in Section 12.1 should be followed for blood sampling for serum pharmacokinetics. No more than 2 attempts to collect blood for pharmacokinetic evaluations should be done at any visit. The exact dates and times of blood sample collection must be recorded in the CRF. See Section 19.8, for instructions for the handling and shipping of the pharmacokinetic samples.

12.3.2 Bioanalytical assays

Serum concentrations of tapentadol and tapentadol-O-glucuronide will be determined using a validated bioanalytical assay under the supervision of the sponsor's department of pharmacokinetics.

The bioanalytical report, including a description of the assays and a summary of the assay performance data, will be included in the final integrated clinical trial report.

12.4 Collection of efficacy data

12.4.1 Pain intensity

During the trial, the following pain evaluations will be performed at the time points indicated in the schedule of events (see Section 1.2). Information related to the rationale for these evaluations and the validation of the pain scales is given in Section 12.7.

During Part 1, subjects will document the pain they have at present, twice daily (preferably directly before IMP administration) in their diary. Subjects will document the pain by using first the VAS and directly thereafter the FPS-R. If required, the subjects may be helped by their parent or legal guardian or a health care provider.

For the Tapentadol Period of Part 2, the investigator will document the pain that the subject has at each visit in the CRF based on the FPS-R and VAS.

Documentation of the pain scales actually used will be maintained.

12.4.1.1 Visual analog scale

The subject will be asked to indicate the current level of pain intensity at the time of assessment on a validated vertical VAS scale (see example in Section 19.2). It will be scored such that a score of 0 is equivalent to "no pain" and a score of 100 is equivalent to "pain as bad as it could be".

12.4.1.2 Faces Pain Scale – Revised

The subject will be asked to indicate the current level of pain intensity at the time of assessment using the FPS-R (see 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.

12.5 Questionnaires

The subject will fill in the questionnaires at the visits as described in the schedule of events (Section 1.2). The caregiver, parent, or legal guardian may assist the subject completing the questionnaires. If the subject is not able to read, the caregiver, parents, or legal guardians will fill in the questionnaires together with the subject. The investigator will document the scores of the questionnaires in the CRF.

Documentation of the questionnaires actually used will be maintained.

12.5.1 Modified constipation assessment scale

The constipation assessment scale was developed and validated for people with cancer (McMillan and Williams 1989), and was revised for use in children with cancer (Woolery et al. 2006). Strong validity and reliability data have been obtained in several small samples, including adults and children with cancer. Because the assessment takes only 2 minutes to complete, it is useful in the clinical setting.

The scale has 8 items that inquire about subjective symptoms that commonly occur with constipation (see Section 19.4). Total scoring goes from 0 = no constipation to 16 = worst possible constipation.

12.5.2 Acceptability and palatability of investigational medicinal product

Responses for palatability and acceptability will be evaluated on 5 point hedonic scales in combination with a verbal rating (Guinard 2001) (see Section 19.6).

Palatability will be assessed by asking the following question “How does the tablet 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 tablet was ...”. The verbal rating is really easy, easy, a bit easy/a bit difficult, difficult, and really difficult.

12.5.3 Subjective opiate withdrawal scale

The SOWS questionnaire is a self-administered scale for grading opioid withdrawal symptoms (Handelsman et al. 1987). It contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extremely) (see Section 19.5). The original scale including 16 questions has been used in a detoxification setting of opioid addicts. More recently, it is being used in rapid detoxification with 15 questions. The first 15 questions of the 16-question SOWS questionnaire are appropriate for the studied population. It takes less than 10 minutes to complete. The scale has been demonstrated to be a valid and reliable indicator of the severity of the opiate withdrawal syndrome over a wide range of common signs and symptoms.

The SOWS questionnaire will be completed by the subjects at home daily until the seventh day after the last intake of IMP. It will be collected at Visit F7D.

12.6 Collection of safety data

12.6.1 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).

Changes in any of the attributes of an ongoing adverse event will be documented separately, by recording a separate episode of the same adverse event (details will be given in the CRF completion guideline).

All adverse events will be sorted into the categories: non-treatment emergent adverse events (non-TEAEs) and TEAEs.

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.

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.

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.

Definition of treatment emergent adverse events

All adverse events occurring in a subject who was administered a trial treatment and that do not necessarily have a causal relationship with the trial treatment. In addition, pre-treatment adverse events which worsen during the treatment period are also considered TEAEs.

The therapeutic reach (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 (SAP).

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 event.

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.

If possible, after serious adverse events considered related to IMP (≥possible: see the section Classification of causation), a blood sample for the quantitation of systemic exposure of tapentadol and metabolites should be drawn in close temporal relationship to the serious adverse event.

Definition of expected treatment emergent adverse events

An unexpected TEAE is one where the nature or intensity is not consistent with the information in the investigator's brochure for tapentadol PR or in the summary of product characteristics for morphine PR.

Expectedness will be assessed by the sponsor.

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 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 IMPs are given in the current version of the investigator's brochure for tapentadol PR and in the summary of product characteristics for morphine PR.

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.

Definition of outcome at the time of last observation

The outcome at the time of last observation 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 in the CRF.

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

- Description (adverse event verbatim term).
- Start date and time.
- End date and 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 IMP when an adverse event occurs:

- Dose increased.
- Dose reduced.
- Drug interrupted.
- Drug withdrawn.
- Dose not changed.
- 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 (i.e., 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).

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 or 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 the competent authorities in all the member states concerned, and to the IEC, 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 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 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.

12.6.2 Vital signs

Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) will be measured in a supine position after resting for at least 5 minutes and recorded in the CRF. While resting, the subject should not receive anything to drink or eat.

12.6.3 Height and body weight

Height and body weight will be measured in light clothes and without shoes on and recorded in the CRF.

12.6.4 Twelve-lead electrocardiogram

Twelve-lead ECGs will be recorded in a supine position after resting for 5 minutes so that the ECG intervals (RR, PR, QRS, and QT) and heart rate can be measured. The ECG tracing must be printed and maintained as a source document by the investigator. Specific ECG procedures will be provided in a separate manual.

The investigator will review the ECG for clinically relevant abnormalities prior to dosing subjects. The investigator will only record clinically relevant abnormalities and their medical interpretation in the CRF.

Cardiologists at a central ECG laboratory will read all ECGs. The ECG report from the central ECG laboratory will be considered a source document.

If there are discrepancies between the central ECG analysis report and the assessment of the investigator, the investigator will document these on the ECG analysis report.

The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.

12.6.5 Safety laboratory

Serum chemistry and hematology

For each subject, non-fasting venous blood samples for clinical chemistry (2 mL) and for hematology (2 mL) will be drawn at the times specified in the schedule of events (Section 1.2). The

total blood volume per subject is given in Section 12.1. If possible, blood samples for pharmacokinetic and safety laboratory evaluations will be taken at the same time.

The check of the exclusion criteria will be based on the local laboratory values. Local laboratory parameters needed are: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine (the creatinine clearance will be calculated in the electronic CRF). The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.

The central laboratory will calculate the creatinine clearance using a formula that is appropriate for the respective age group.

Discontinuation criteria will be based on central laboratory values.

Trial sites will follow the instructions provided in the laboratory manual regarding the specific procedures for the handling and shipment of blood samples.

The investigator must review the laboratory report, document this review in the source documents, and record any clinically relevant changes in the opinion of the investigator during the trial in the source documents and as adverse events in the CRF.

The following tests will be performed:

Hematology panel	
Hemoglobin	Red blood cell (RBC) count
Hematocrit	Red blood cell morphology
Mean cell volume (MCV)	White blood cell (WBC) count
	White blood cell differential count
	White blood cell morphology
	Platelet count

Clinical chemistry panel	
Sodium	Lipase
Potassium	Triglycerides
Chloride	Total serum bilirubin
Blood urea nitrogen (BUN)	Alkaline phosphatase
Creatinine	Creatine phosphokinase
Uric acid	Lactic acid dehydrogenase (LDH)
Calcium	Alanine transaminase (ALT)
Phosphorus	Aspartate transaminase (AST)
Albumin	Gamma-glutamyltransferase (GGT)
Total protein	Glucose

Urinalysis

A urine sample for urinalysis will be taken at the times specified in the schedule of events (see Section 1.2). The assessment will be done locally with a dip stick. It must be documented clearly in source documents if and which abnormalities were observed. If no abnormalities were observed, then this needs to be documented in the source documents as well. If there are abnormalities, a urine sample will be sent to the central laboratory for sediment analysis. The decision not to send a sample to the central laboratory needs to be documented in the source documents.

The following tests will be performed:

Dipstick by the local laboratory [a]
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase

a) Including but not limited to.

12.6.6 Urine test for drugs of abuse

A urine sample will be collected to test for the following drugs, as a minimum, at the visits as described in the schedule of events (Section 1.2): cannabis, cocaine, opioids, methamphetamine, and amphetamines. The test may be positive in subjects who are receiving opioids or other medications for medical purposes (i.e., if prescribed). These subjects may participate even though the test is positive for these medications. A positive test that is not explained by prescribed medication will exclude the subject.

The assessment will be done locally, e.g., by the investigator, and documented in the CRF. Dip-stick test kits will be provided by the central laboratory.

12.6.7 Physical examination

During the physical examination, comprising but 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, 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 in the CRF.

12.6.8 Pregnancy test

A urine sample will be provided for testing by a pregnancy-test dip stick at the visits as described in the schedule of events (Section 1.2). The assessment will be done locally, e.g., by the investigator,

and documented in the CRF. Dip-stick pregnancy test kits will be provided by the central laboratory.

12.7 Appropriateness of measurements

During the trial, subject-reported pain assessments will be collected. The 2 pain scales used in this trial are the VAS and FPS-R. Pain intensity assessments with the FPS-R will be performed immediately after pain intensity measurements with the VAS (Bulloch and Tenenbein 2002). Both will be recorded in all subjects. These data will be used to gather information relevant to the measures to be included in future clinical trials.

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

The FPS-R has been established as a valid, paper-based self-reported measure of pain intensity in subjects aged 4 years to 15 years (Hicks et al. 2001, Miró and Huguet 2004).

The pain scales used have a wider validated age range than the defined age groups of the trial, so that the measurement of pain remains valid even if a subject moves into an older age group during the trial.

“Pain right now” was selected as the question to ask children and adolescents, as this is easier to report than, for example, average pain over the last 24 hours.

12.8 Compliance

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

Trial site compliance will be ensured by the implementation of a quality system and the performance of a combination of trial site visits, training, monitoring visits, and remote verification by the sponsor of appropriate use of electronic tools by the trial site and subjects. 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 or IRB. Acceptable time windows for CRF completion will be described in a separate document.

Subject compliance with regards to IMP intake will be confirmed by the investigator or delegated qualified personnel during trial site visits and phone contacts. Compliance will be checked during regular drug accountability as outlined in Section 10.7. Subjects are considered compliant if they have consumed a minimum of 80% and a maximum of 120% of the scheduled tablet consumption between 2 consecutive trial site visits.

Subject compliance with regards to diary entries will be checked by the investigator or qualified delegated personnel on a regular basis. If subjects do not complete the diary correctly, the investigator or qualified delegated personnel is to contact the subject, or parent(s) or legal guardian(s) to ensure diary completion. A subject is considered to be compliant if a minimum of 80% of all twice daily diary entries are available at the end of treatment.

Monitoring of CRF completion, diary compliance, and compliance with IMP intake by the sponsor will be described in a separate document.

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's representative (e.g., clinical research associate).

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 trial site and from other parties involved (e.g., data management staff) will have access to review all captured data during the trial via a secure internet connection.

After source data verification, the applicable 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 a re-signing by the investigator.

13.2 Subject reported outcomes

Diaries for each subject will be provided to the investigator by the sponsor in electronic format for Treatment Period of Part 1 to document the pain assessments (VAS and FPS-R) and intake of IMP and rescue medication, and for Tapentadol Period of Part 2 to document the intake of IMP. The other questionnaires will be reported on paper throughout the trial. An electronic version of the VAS will be used in the electronic diary (Part 1) and paper version of the VAS will be used in the CRF for the Tapentadol Period (Part 2). The electronic version and the paper version of the VAS are both validated.

Subjects will receive their diaries at the investigator's site and will be instructed on how to use it.

Due to the fact that this is a pediatric trial, the possibility for caregivers to enter data in the diaries is possible and will be recorded with a personal identification of the person who made the entry.

The data will be collected using an appropriately validated system. No queries will be issued to the investigator for these data, except for clarification of subject identifiers and any operational issues.

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 WHO Drug Dictionary (WHO-DD). Medical history terms and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). As required by the sponsor's standard operating procedures (SOPs), the versions 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, ECG data, and e-diary data) will be reconciled against CRF data (details of reconciliation will be specified separately but may include trial number, trial site number, subject 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 complete and clean data transfer.

Database lock

When all data have been received and entered into the trial database, all data checks and quality control checks have been performed, all queries are resolved, and the final statistical review has been held without resulting in new queries, the trial database will be considered clean and the data will be locked. For the main analysis (Part 1 and the first 12 weeks of Part 2), the detailed procedure will be described in the data management plan.

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, IEC/IRB review, and regulatory inspection.

All data captured in the CRF need to be justified by relevant source data. In certain circumstances, data may only be recorded in the trial-specific CRF and not in other documents. If this occurs, the CRF is considered to be the source document. Data expected to be only recorded in the CRF are: race/ethnic group.

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).

For subject reported outcomes captured directly via a diary, source data is defined as the data residing in the vendor's database.

During trial conduct, the vendor is responsible for data security.

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 after trial completion and finalization of data collection.

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 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

The statistical planning and analysis of the trial will be performed by sponsor personnel or by authorized sponsor delegates.

14.1 Sample size rationale

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

To show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning (1990) test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.1, 69 subjects are required in the FAS, assuming a 2:1 randomization of tapentadol PR:morphine PR.

A one-sided alpha of 0.1 is considered appropriate based on a method proposed by Hlavin et al. (2016). The approach makes use of prior knowledge and the concept of extrapolation from a larger population to a small target population (i.e., pediatric population), to reduce the burden of evidence in pediatrics by relaxing the Type I error, while controlling a certain posterior belief, i.e., confidence after successful pediatric trials, in effectiveness of the drug in children.

Further details for the application of the concept of Hlavin et al. (2016) in the context of this trial are provided in a separate document that is available upon request.

The reviews of the safety data during the trial by the DMC (Section 5.4) have no impact on the sample size.

14.2 Analysis of the trial – statistical analysis

The statistical analysis of this trial will be performed as described and as summarized here in the protocol and given in detail in the SAP.

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.

Main analysis of the trial

The main analysis of the trial will be performed after all subjects have completed the first 12 weeks (Visit TP3 or Visit OP3) of Part 2.

14.2.1 Analysis populations (analysis sets)

Enrolled population

The Enrolled Set includes all subjects with a signed (by subject, parent(s) or legal guardian(s) as appropriate) informed consent form and if required by local law an assent form.

Allocated Set

The Allocated Set includes all subjects who are allocated to treatment.

Safety Set

The Safety Set comprises all treated subjects, i.e., all subjects in whom IMP was administered (at least once).

Full Analysis Set

The FAS comprises all allocated and treated subjects, i.e., all allocated subjects who were administered any amount of IMP.

Per Protocol Set

The Per Protocol Set defines a subset of the subjects in the FAS without any major protocol deviation affecting the primary endpoint. The Per Protocol Set is only relevant for analyses during Part 1. No protocol deviation during Part 2 leads to exclusion from the Per Protocol Set.

Further details of the Per Protocol Set definitions will be specified in the SAP.

Pharmacokinetic Analysis Set

All subjects who have quantifiable serum concentrations during the Treatment Period will be included in the descriptive pharmacokinetic analysis.

Data from subjects who vomit within 6 hours of administration of IMP during the Treatment Period will be carefully assessed to decide if the data should be included in the pharmacokinetic analysis.

Subgroups

The primary endpoint will also be analyzed according to predefined age group and underlying pain condition. Further details, and also further subgroups, will be specified in the SAP.

14.2.2 General descriptive and graphical methods

Analyses will be performed within the specified subject populations as described in Section 14.2.1.

Separate analyses will be performed for Part 1 and Part 2. The analysis for Part 1 will take into consideration the Treatment Period of Part 1. The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2.

Part 1

For the Treatment Period, baseline measurements are defined as the last evaluation performed before starting IMP (i.e., Visit V1, Visit V2, or an unscheduled visit). For pain assessments, the baseline pain is defined as “pain right now” at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.

Part 2

For the Tapentadol Period, baseline measurements are defined as the last evaluation performed before or at Visit VE.

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

- Visit VE for subjects entering the Observation Period directly after Part 1.

- Visit ET for subjects switching from the Tapentadol Period to the Observation Period.

General

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. If applicable, changes from the baseline or predefined time points will be presented descriptively.

Data will also be listed and summarized using graphical displays, as appropriate.

Further analyses are outlined below.

14.2.3 Analysis of subject characteristics data

Subject characteristics data will be analyzed for the Safety Set as described in Section 14.2.2.

14.2.4 Analysis of subject disposition

Subject disposition data will be analyzed for the Safety Set as described in Section 14.2.2.

14.2.5 Analysis of pharmacokinetic data

As described in Section 14.2.2, descriptive statistics and graphical displays will be used to summarize the tapentadol and tapentadol-O-glucuronide serum concentration time data for each time interval specified during the Treatment Period for subjects in the pharmacokinetic analysis set.

The tapentadol and tapentadol-O-glucuronide data will also be subject to a population pharmacokinetic analysis described in a separate analysis plan (see Section 14.3).

14.2.6 Analysis of efficacy data

Unless otherwise stated, efficacy analyses will be performed on the FAS.

14.2.6.1 Primary endpoint (proportion of subjects classified as responders in Part 1)

The analysis of the primary endpoint will be performed on the data collected during the Treatment Period (Part 1). The FAS will be the primary analysis set and the Per Protocol Set will be used as a sensitivity analysis set.

Hypotheses

Null hypothesis: H_0: $p_T - p_C \leq -\delta$

"Treatment with tapentadol" is inferior to "treatment with morphine".

Alternative hypothesis: H_A: $p_T - p_C > -\delta$

"Treatment with tapentadol" is non-inferior to "treatment with morphine".

T = treatment with tapentadol; C = treatment with morphine; δ = non-inferiority margin; p_i = responder rate in investigational treatment (T) or active control (C).

As this endpoint is a binomial event rate, it will be summarized by descriptive statistics grouped by treatment group. The standard maximum likelihood estimators for the proportion of subjects classified as responders in each group will be the estimated proportions adjusted for the baseline

pain intensity, age group, and underlying pain condition. To obtain these estimators, a logistic regression model will be fitted to the response using the baseline pain intensity, age group, treatment, and underlying pain condition as explanatory variables. The Farrington-Manning (1990) test will then be applied and an 80% confidence interval calculated. The non-inferiority of tapentadol PR compared to morphine PR will be established if the lower limit of this 2-sided 80% confidence interval of the difference in the above estimated proportions is above the non-inferiority margin of -20%.

A sensitivity analysis will be carried out by fitting a Bayesian logistic regression model to compare the proportion of responders under tapentadol PR and morphine PR. Odds ratios will be calculated. Treatment response is the dependent variable and treatment group, age group at baseline (ageg), underlying pain condition (cancer/non-cancer-related pain), age group x baseline VAS, and age group x baseline FPS-R are possible (but not limited to) explanatory variables. The age group refers to a variable indicating whether, on the basis of the subject's age, to use the VAS pain assessment (for subjects aged 12 years to less than 18 years) in the model, or to use the FPS-R score (for subjects aged 6 years to less than 12 years).

Specifically, if X_i is the response indicator for subject i, then we will assume:

$X_i \sim \text{Bernoulli}(\lambda_i)$

$\log(\lambda_i /(1-\lambda_i)) = \beta_0 + \beta_1\ \text{ageg}_i + \beta_2\ \text{cancer}_i + \beta_3\ (\text{ageg*baseline VAS}) + \beta_4\ (1-\text{ageg})*\text{baseline FPS-R} + \beta_5\ \text{treatment}_i + \varepsilon_i$

Non-informative flat normal priors with zero mean and variance equal to 1000 will be assigned to the regression coefficients β_1 to β_4. The prior for the treatment effect β_5 (on the log-odds scale) will be a normal distribution with mean = 0.10 and standard deviation = 0.48; this prior distribution has been derived from the [redacted] trial (in subjects with moderate to severe chronic malignant tumor-related pain) using a down-weighting factor a = 0.4. The prior for the subject-specific random effects ε_i, will be normal $(0, \sigma^2)$. A non-informative Gamma (0.001, 0.001) prior will be assigned to the precision of the random effects $1/\sigma^2$.

The posterior distribution for the regression coefficients will not have an analytically closed form. Therefore, Markov chain Monte-Carlo methods will be used to obtain a sample from the posterior distribution for the difference between the response rates in tapentadol PR and morphine PR groups. This sample will be summarized by means of the posterior mean, median, standard deviation and 80% credibility interval. If the lower limit of the 80% credibility interval for the difference of the 2 response rates is >-0.2, then this would support non-inferiority by this sensitivity analysis.

Further sensitivity analyses are planned (but not limited to), e.g., keeping the criteria for response unchanged except for classifying subjects who stop treatment earlier than 14 days because of no further need for opioid treatment as responders rather than non-responders.

More details on the sensitivity analyses and strategies for handling missing data and discontinued subjects will be described in the SAP.

14.2.6.2 Pain scale assessed using a VAS and FPS-R

Descriptive statistics will be provided to evaluate the daily average pain (Part 1) or pain at each visit during the Tapentadol Period (Part 2) as well as changes to baseline for the different trial periods and respective treatment groups, as described in Section 14.2.2.

14.2.6.3 Rescue medication

The descriptive analyses of the use of rescue medication during the Treatment Period will focus on mean number of daily doses and the mean total daily dose (mg/kg). The morphine equivalent dose of tapentadol will be calculated so that a comparison of rescue medication with respect to the amount of IMP taken can be made. Comparisons will be made across time and also for subgroups of different ages.

14.2.6.4 Time to discontinuation

A survival analysis of the time to discontinuation of IMP overall, due to lack of efficacy, and due to TEAE will be performed for tapentadol PR and morphine PR for Part 1 (Treatment Period) and for tapentadol PR during the Tapentadol Period of Part 2 if at least 10% of the subjects per group discontinue.

14.2.7 Analysis of safety data

The analysis of safety data will be performed on the Safety Set.

Unless otherwise specified, separate analyses will be performed for the different trial periods and respective treatment groups.

14.2.7.1 Adverse events

The original terms used in the CRFs by investigators to identify adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) implemented by the sponsor.

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

Those TEAEs which started in Treatment Period and are carried over into Tapentadol Period will be considered as ongoing TEAEs. A worsening of a TEAE in Tapentadol Period in a subject previously treated with morphine PR in Treatment Period will be considered as a new TEAE.

The frequency and severity of adverse events will be analyzed descriptively as described in Section 14.2.2 both on a subject and event-based level.

All adverse events will be listed. Serious adverse events will be listed separately. Non-TEAEs will be listed separately.

Special attention will be given to those subjects who have discontinued treatment due to an adverse event or who experienced a severe or a serious adverse event. Such cases will be analyzed individually.

14.2.7.2 Safety laboratory tests

Safety laboratory data will be summarized by the type of safety laboratory test as described in Section 14.2.2. The safety laboratory analysis will be based on the data from the central laboratory.

Normal reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of safety laboratory data. Descriptive statistics will be calculated for each safety laboratory parameter at baseline (see Section 14.2.2) and at each scheduled time point. Changes from baseline will be presented descriptively as well as in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided.

14.2.7.3 Electrocardiogram

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

The ECG measurements will be summarized at each time point of measurement during the treatment period. The change from baseline will also be summarized. A categorical analysis for outliers will be performed as per the guidance “Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs” (ICH Topic E14).

All important abnormalities from the ECG readings, including changes in general and changes in T wave morphology, or the occurrence of U waves versus baseline recordings, will be reported.

14.2.7.4 Vital signs (pulse rate, systolic/diastolic blood pressure, and respiratory rate)

As described in Section 14.2.2, descriptive statistics as well as changes to baseline for the different trial periods will be presented. Frequency tabulations of abnormalities will be included.

14.2.7.5 Physical examination

Physical examination findings will be listed.

14.2.7.6 Height and weight

Height and weight will be analyzed as described in Section 14.2.2 for the different trial periods.

14.2.7.7 Constipation

Constipation, as assessed by the modified CAS will be descriptively analyzed per time point as described in Section 14.2.2 for the different trial periods. Further details concerning subgroups of interest e.g., subjects receiving treatment for constipation versus those who are not, will be specified in the SAP. Constipation will be assessed by changes from baseline (Visit V2) of total scores for the modified CAS.

14.2.7.8 Subjective opiate withdrawal scale

The SOWS questionnaire scores and changes from baseline (defined for the SOWS as the assessment made on the day of the last intake of IMP) will be descriptively analyzed per scheduled time point according to the last IMP taken. The total score of the full questionnaire (all 16 questions) will be used for a first analysis. Additionally the total score of the first 15 questions of the SOWS questionnaire will be analyzed in the same manner, being more appropriate for the studied population.

14.2.8 Acceptability and palatability

In order to assess acceptability and palatability, verbal rating responses will be tabulated per time point and changes from Visit V3 to Visit VE will be compared within treatment groups, as described in Section 14.2.2.

14.2.9 Final analysis

The main analysis of the trial will be performed after all subjects have completed Part 1 and the first 12 weeks (Visit TP3 or Visit OP3) of Part 2 of the trial.

The final analysis of Part 2 will be performed after all subjects have completed Part 2 of the trial and the final database has been locked.

Further details regarding the analyses will be provided in the SAP.

14.3 Population pharmacokinetic modeling and simulation

Pharmacokinetic data collected in this trial will be used to validate exposure predictions obtained with a pediatric tapentadol PR population pharmacokinetic model developed previously by the sponsor. The validation process will enable assessment of tapentadol accumulation in this pediatric population during administration of tapentadol PR. The model will be subsequently updated with the pharmacokinetic data collected in this trial. Population pharmacokinetic modeling and simulation will be performed using the non-linear mixed effect modeling approach as implemented in NONMEM® (version 7.2, ICON plc). These analyses will be planned, performed, and reported by sponsor personnel, or by authorized sponsor delegates in accordance with sponsor's SOPs.

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 contract 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 trial site and subject, 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 trial 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 visits 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 subjects/parents/legal guardians.

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.

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 applicable regulatory guidance (e.g., on ClinicalTrials.gov). 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 or 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 and reporting of the trial

An integrated clinical trial report, integrating clinical, pharmacokinetic, and statistical results of Part 1 (Treatment Period) and the first 12 weeks of Part 2 will be prepared by the sponsor once all subjects have completed the first 12 weeks (Visit TP3 or Visit OP3) of Part 2. A second report (optionally as an amendment) will be prepared once all subjects have completed Part 2.

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

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

All investigators will be provided with a summary of the final report.

The modeling and simulation analysis will be reported separately.

16.7 Approval

16.7.1 Sponsor

This protocol has been approved in accordance with sponsor SOPs.

16.7.2 International coordinating investigator

This protocol has been approved by the international coordinating investigator.

17 REFERENCES

Investigator's brochure for tapentadol, current edition.

Guidelines

EMEA ad hoc working party. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008.

ICH Topic E14.The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04). 2005.

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. World Health Organization 2012.

Publications

Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 2009; 24 (1): 25-36.

Benedetti MS, Whomsley R, Canning M. Drug metabolism in the paediatric population and in the elderly. Drug Discov Today 2007; 12 (15/16): 599-610.

Berde BC, Walco GA, Krane EJ, Anand KJS, Aranda JV, Kenneth D, et al. Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop. Pediatrics 2012; 129: 354-64.

Broomhead A, Kerr R, Tester W, O'Meara P, Maccarrone C, Bowles R, et al. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. J Pain Symptom Manage 1997; 14: 63-73.

Bulloch B, Tenenbein M. Validation of 2 Pain Scales for Use in the Pediatric Emergency Department. Pediatrics 2002; 110 (3): e33.

Czarnecki ML, Jandrisevits MD, Theiler SC, Huth MM, Weisman SJ. Controlled-release oxycodone for the management of pediatric postoperative pain. J Pain Symptom Manage 2004; 27: 379-86.

de Beer JdeV, Winemaker MJ, Donnelly GAE, Miceli PC, Reiz JL, Harsanyi Z, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. Can J Surg 2005; 48 (4): 277-83.

De Conno F, Kress HG. Opioids in palliative care: Differentiation and clinical relevance. Palliative Medicine 2006; 20: S1.

Edginton AN, Schmitt W, Voith B, Willmann S. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet 2006; 45 (7): 683-704.

Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of nonzero risk difference or non-unity relative risk. Stat Med 1990; 9: 1447-54.

Finkel JC, Finley A, Greco C, Weisman SJ, Zeltzer L. Transdermal fentanyl in the management of children with chronic severe pain: results from an international study. Cancer 2005; 104: 2847-57.

Goldman A, Bowman A. The role of oral controlled-release morphine in pain relief in children with cancer. Palliat Med 1990; 4: 279-85.

Guinard JX. Sensory and consumer testing with children. Trends in Food Science & Technology 2001; 11: 273-83.

Handelsman L, Cochrane KJ, Aronson M, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse 1987; 13 (3): 293-308.

Hayton WL. Maturation and growth of renal function: Dosing renally cleared drugs in children. AAPS Pharm Sci 2002; 2 (1) E3.

Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. Pain 2001; 93 (2): 173-83.

Hlavin G, Koenig F, Male C, Posch M, Bauer P. Evidence, eminence and extrapolation. Stat Med 2016; 35 (13): 2117-32.

Kadan-Lottick NS. Epidemiology of childhood and adolescent cancer. In Kliegman RM, Behrman RE, Jenson HB, Stanton BF, Eds. Kliegman: Nelson Textbook of Pediatrics. 18th ed. Philadelphia, Pa: WB Saunders Co; 2007: Chap 491; 2097-100.

Lasky T, Greenspan J, Ernst FR, Gonzalez L. Morphine use in hospitalized children in the United States: a descriptive analysis of data from pediatric hospitalizations in 2008. Clin Ther 2012; 34 (3): 720-7.

Martin-Herz SP, Patterson DR, Honari S, Gibbons J, Gibran N, Heimbach DM. Pediatric pain control practices of North American Burn Centers. J Burn Care Rehabil 2003; 24: 26-36.

McMillan SC, Williams FA. Validity and reliability of the Constipation Assessment Scale. Cancer Nurs 1989; 12: 183-8.

Miró J, Huguet A. Evaluation of reliability, validity, and preference for a pediatric pain intensity scale: the Catalan version of the faces pain scale – revised. Pain 2004; 111 (1-2): 59-64.

Rhodin M, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation; a quantitative description using weight and postmenstrual age. Pediatr Nephrol 2009; 24 (1): 67-76.

Scott J, Huskisson EC. Graphic representation of pain. Pain 1976; 2 (2): 175-84.

Scott PJ, Ansell BM, Huskisson EC. Measurement of pain in juvenile chronic polyarthritis. Ann Rheum Dis 1977; 36 (2): 186-7.

Woolery M, Carroll E, Fenn E, Wieland H, Jarosinski P, Corey B, et al. A constipation assessment scale for use in pediatric oncology. J Pediatr Oncol Nurs 2006; 23: 65-74.

18 PROTOCOL AMENDMENTS

18.1 Protocol amendment 01

Amendment rationale

Although there is no information on the excretion of tapentadol in human milk, there are pre-clinical data indicating that tapentadol is excreted in animal milk. Morphine is known to be excreted in breast milk, and may thus cause respiratory depression in the newborn. Therefore, an additional exclusion criterion was added to exclude female subjects who are breast-feeding a child.

In addition, a textual change has been made for consistency.

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 1.3.2: Exclusion criteria Section 9.2.2: Exclusion criteria	
The following will be checked at Visit V1 and Visit V2: [new exclusion criterion inserted, and subsequent numbering of criteria adjusted]	The following will be checked at Visit V1 and Visit V2: *13. Female subject breast-feeding a child. Safety.*
Section 8.5: Benefit/risk analysis	
Risks Lack of efficacy Tapentadol may not be as efficacious in children and adolescents as it is in adults, even if the exposure is comparable. However, this is considered to be unlikely. During the Treatment Period, rescue medication, in the form of morphine oral solution, will be available for use as rescue medication if pain relief is insufficient. Thereafter, subjects ~~will~~ receive rescue ~~medication as per standard of treatment~~.	Risks Lack of efficacy Tapentadol may not be as efficacious in children and adolescents as it is in adults, even if the exposure is comparable. However, this is considered to be unlikely. During the Treatment Period, rescue medication, in the form of morphine oral solution, will be available for use as rescue medication if pain relief is insufficient. Thereafter, subjects *may* receive *immediate release strong opioids for treatment of breakthrough pain and incidental pain.*

18.2 Protocol amendment 02

Amendment rationale

Protocol amendment 02 has been enacted to:

- Explicitly allow a home visit to take place instead of a site visit after a case-by-case approval by the sponsor.
- Allow more flexibility in selecting the supplier of the rescue medication by allowing both morphine sulfate and morphine hydrochloride to be used, and by using an interactive response technology system (voice and web based) to assign subjects to rescue medication.
- Allow the results of a non-protocol blood sample taken within 14 days of Visit 2 to be used for assessing the exclusion criteria and for baseline values without the need to repeat the sample at the Enrollment Visit. This was done to potentially reduce the volume of blood taken from the subject.
- Clarify and correct the definitions of the endpoints, populations, and statistical analyses.
- Clarify and correct the days on which the SOWS questionnaire is completed, and the questions to be assessed.
- Add the measurement of height for the calculation of the glomerular clearance at 3 monthly intervals in the tapentadol period of Part 2.
- Specify that if a subject turns 18 years old before Visit VE, an additional subject will be allocated to IMP.
- Specify that subjects who vomit after IMP intake must not take additional IMP until the time of their next scheduled IMP dose.
- Correct the labeling specification for the pharmacokinetic samples.

In addition, textual change has been made for consistency.

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: [redacted], ...	International coordinating investigator: [redacted], ...
Sponsor's medically qualified person: [redacted].	Sponsor's medically qualified person: [redacted], *Associate Principal Clinical Scientist.*
Sponsor's signatory: [redacted], Grünenthal GmbH.	Sponsor's signatory: [redacted], *Senior International Clinical Lead*, Grünenthal GmbH.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Definition of the primary endpoint Section 8.1.1: Primary endpoint definition	
Part 1 (primary analysis of the trial) The primary ~~efficacy~~ endpoint is ~~the proportion of subjects classified as~~ responder~~s. Responders are subjects who meet~~ both of the following criteria: ... Age groups are determined at Visit V2. Baseline pain is defined as "pain right now" at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.	Part 1 (primary analysis of the trial) The primary endpoint is *a binary variable "*responder*". A subject is defined as "responder" if* both of the following criteria *are met*: ... *The proportion of subjects classified as responders will be assessed and compared between the treatment groups.* Age groups are determined at Visit V2. Baseline pain is defined as "pain right now" at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.
Section 1: Protocol synopsis	
Definition of ~~the exploratory~~ endpoints.	Definition of *other* endpoints.
Section 8.1: Definition of endpoints	
8.1.3 ~~Exploratory~~ endpoints	8.1.3 *Other* endpoints
~~Exploratory~~ endpoints compared between treatment groups at each measurement time point are: ... Treatment Period endpoints (baseline is the value at Visit V2): ... • Palatability and acceptability as assessed by differences within treatment groups of the verbal rating score at Visit V3 and Visit VE (the End of Treatment Visit). ... Tapentadol Period endpoints (baseline is the value at Visit VE): ... Observation Period endpoints (baseline is the value at Visit VE or Visit ET [Early Termination Visit]): ... Part 1 or Part 2 ~~exploratory~~ endpoints:	*Other* endpoints compared between treatment groups at each measurement time point are: ... Part 1 - Treatment Period*, other* endpoints (baseline is the value at Visit V2): ... • Palatability and acceptability as assessed by differences within treatment groups of the *5-point hedonic faces scale with* the verbal rating score at Visit V3 and Visit VE (the End of Treatment Visit). ... *Part 2* - Tapentadol Period*, other* endpoints (baseline is the value at Visit VE): ... *Part 2* - Observation Period*, other* endpoints (baseline is the value at Visit VE or Visit ET [Early Termination Visit]): ... Part 1 or Part 2 - *other* endpoints:
Section 1: Protocol synopsis: Rescue medication	
During Part 1 only, morphine oral solution ~~(0.5% and 2%)~~ will be supplied by the sponsor as rescue medication for both treatment groups.	During Part 1 only, morphine oral solution will be supplied by the sponsor as rescue medication for both treatment groups.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Concomitant medications/therapies Section 10.5: Allowed and forbidden and prior/concomitant medications/therapies	
... Subjects suffering from cancer-related pain will be allowed to participate in trials of marketed therapeutic medications and therapies.	... Subjects suffering from cancer-related pain will be allowed to participate in trials of marketed therapeutic medications and therapies *(including trials of antibody therapies)*.
Section 1: Protocol synopsis: Statistical methods Section 14.2.2: General descriptive and graphical methods	
Separate analyses will be performed for Part 1 ~~(primary analysis of the trial)~~ and Part 2. The analysis for Part 2 will take into consideration the ~~different trial periods: Treatment Period of Part 1, and~~ Tapentadol Period and Observation Period of Part 2. **Part 1** For the Treatment Period, baseline measurements are defined as the last evaluation performed before starting IMP (i.e., Visit V1 ~~or~~ Visit V2). **Part 2** For the Tapentadol Period, baseline measurements are defined as ~~those taken~~ at Visit VE. For the Observation Period, baseline measurements are defined as ~~those taken~~ at Visit VE ~~or~~ Visit ET.	Separate analyses will be performed for Part 1 and Part 2. *The analysis for Part 1 will take into consideration the Treatment Period of Part 1.* The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2. **Part 1** For the Treatment Period, baseline measurements are defined as the last evaluation performed before starting IMP (i.e., Visit V1*,* Visit V2*, or an unscheduled visit*). *For pain assessments, the baseline pain is defined as "pain right now" at Visit V2, and will be assessed before any painful or unpleasant procedure, and before the first intake of IMP.* **Part 2** For the Tapentadol Period, baseline measurements are defined as *the last evaluation performed before or* at Visit VE. For the Observation Period, baseline measurements are defined as *the last evaluation performed before or* at*:* • Visit VE *for subjects entering the Observation Period directly after Part 1.* • Visit ET *for subjects switching from the Tapentadol Period to the Observation Period.*
Section 1.2: Schedule of events Section 1.2.4: Phone contacts Section 11.1.5: Phone contacts	
... Phone contacts can be made at any time, e.g., if the subject wants to report adverse events, or has questions regarding concomitant medication intake/therapies. ~~In case~~ no site visit takes place, phone contacts are mandatory if the subject would like to up or down titrate the IMP.	... Phone contacts can be made at any time, e.g., if the subject wants to report adverse events, or has questions regarding concomitant medication intake/therapies. *If* no *trial* site visit takes place, phone contacts are mandatory if the subject would like to up or down titrate the IMP. *A trial site visit may be performed as a home visit after prior approval by the sponsor.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.2.1: Part 1: Enrollment Visit and Treatment Period (Visit V1 to Visit VE)	
[Table] Obtain informed consent/assent ... Dispense IMP (the first dose of IMP will be taken ~~at the site~~) [Footnotes] a) Visit VE ~~should~~ also be performed if IMP is stopped during the Treatment Period. ... e) Local laboratory parameters needed are: ~~serum albumin,~~ total serum bilirubin, ~~total protein~~, and serum creatinine (the creatinine clearance will be calculated). ... m) Complete once daily ~~starting from visit with~~ the last intake of IMP ~~(normally Visit VE) until Visit F7D~~. At Visit VE, or earlier if applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires. ... [New footnote]	[Table] Obtain informed consent/assent [s] ... Dispense IMP (the first dose of IMP will be taken *during Visit V2, within 24 hours after randomization. Day 1 is the day of first IMP intake*) [Footnotes] a) Visit VE *must* also be performed *within 3 days of last IMP intake* if IMP is stopped during the Treatment Period. ... e) Local laboratory parameters needed are: total serum bilirubin, *serum albumin, aspartate transaminase, alanine transaminase*, and serum creatinine (the creatinine clearance will be calculated *in the electronic CRF*). *The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.* ... m) Complete once daily *until the seventh day after* the last intake of IMP. At Visit VE, or earlier if applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires. ... *s) The informed consent/assent may be obtained earlier than Day -14.*
Section 1.2.2: Part 2: Tapentadol Period	
[Table] Height [Footnote] g) Once daily ~~starting at the~~ ~~visit of~~ the last intake of IMP (normally Visit F12M or at Visit ET in case of early termination) ~~until Visit F7D.~~ At Visit F12M, or as applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires.	[Table] [measurements added at TP3, TP6, TP9, and TP12]. [Footnote] g) Once daily *until the seventh day after* the last intake of IMP (normally Visit F12M or at Visit ET in case of early termination). At Visit F12M, or as applicable, dispense the questionnaires. At Visit F7D, collect the completed questionnaires.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 3: Abbreviations and definition of terms: Definition of terms	
Treated subjects: ~~Allocated s~~subjects with at least 1 administration of IMP. Trial completers Part 2: Subjects who ~~have~~ completed the ~~12-month Extension Period,~~ either ~~with tapentadol treatment~~ ~~(~~Tapentadol Period~~)~~ or ~~without treatment~~ ~~(~~Observation Period~~)~~.	Treated subjects: *S*ubjects with at least 1 administration of IMP. Trial completers Part 2: Subjects who *fully* completed the *extension period, i.e.,* either *subjects completing the* Tapentadol Period *and the follow-up visit (F7D)* or *subjects completing the* Observation Period *(F12M) not earlier than 351 days after Visit VE).*
Section 8.4: Discussion of the trial design: Dosing	
... Based on the pharmacokinetic evidence described above for tapentadol, the sponsor considers it justified to move into an adolescent safety and efficacy trial without a prior pharmacokinetic trial in this age group using the prolonged release formulation. ~~However, a trial [redacted] that also assesses pharmacokinetic parameters in children and adolescents is ongoing with tapentadol oral solution (see Section 6.2).~~ An advisory committee meeting (in March 2012) initiated by the FDA to discuss "clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development" recommended, based on an FDA review of 22 products recently approved for adolescent use, that for dose confirmation in adolescents (12 years to less than 18 years), no pharmacokinetic trials are needed, but that doses can be derived using adult data.	... Based on the pharmacokinetic evidence described above for tapentadol, the sponsor considers it justified to move into an adolescent safety and efficacy trial without a prior pharmacokinetic trial in this age group using the prolonged release formulation. An advisory committee meeting (in March 2012) initiated by the FDA to discuss "clinical pharmacology aspects of pediatric clinical trial design and dosing to optimize pediatric drug development" recommended, based on an FDA review of 22 products recently approved for adolescent use, that for dose confirmation in adolescents (12 years to less than 18 years), no pharmacokinetic trials are needed, but that doses can be derived using adult data.
Section 8.5: Benefit/risk analysis: Risks	
~~*Independent statistical center*~~ ~~To allow for the conduct of the planned interim analysis, an independent statistical center will be established. The independent statistical center will re-assess the sample size after stage 1 of the trial. The independent statistical center will provide recommendations to the sponsor's steering committee as described in the independent statistical center charter.~~	[Paragraph deleted as not applicable]
Section 9.3.3: Procedure for the handling of prematurely discontinued subjects	
... ~~Treated~~ subjects will not be replaced. ~~Allocated subjects who were not treated with IMP will be replaced.~~ See Section 3 for a definition of allocated and treated subjects.	... *Subjects turning 18 years old before Visit VE may continue in the trial. However, an additional subject will then be enrolled and allocated to IMP. Otherwise treated* subjects will not be replaced. See Section 3 for a definition of allocated and treated subjects.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.2.1: Administration	
... The first dose of IMP will be taken at the site.	... The first dose of IMP will be taken *during visit V2 (Allocation Visit)*. *A dose must not be repeated if a subject vomits or regurgitates part or all of a dose. Vomiting and/or regurgitation of a dose must be recorded as an adverse event.*
Section 10.2.3.4: Titration	
The dose of IMP will be titrated within the given limits for dosing according to the body weight measured during the last visit ~~at the site~~ (...	The dose of IMP will be titrated within the given limits for dosing according to the body weight measured during the last visit (...
Section 10.6: Rescue medication	
During Part 1 (Treatment Period) only, morphine oral solution will be supplied by the sponsor as rescue medication for both treatment groups. ~~Subjects with a bodyweight <45.0 kg will receive morphine oral solution 0.5% and subjects with a body weight ≥45.0 kg will receive morphine oral solution 2% as rescue medication.~~ ... Substance name: Morphine sulfate ... Dose (strength): 0.5% and 2.0% ... [new paragraph]	During Part 1 (Treatment Period) only, morphine oral solution will be supplied by the sponsor as rescue medication for both treatment groups. *An interactive response technology system (voice and web based) will be used to assign subjects to rescue medication.* ... Substance name: Morphine sulfate *or morphine hydrochloride* ... Dose (strength): 0.5% and*/or* 2.0% ... *During Part 2, the use of immediate release strong opioids for treatment of breakthrough pain and incidental pain is allowed.*
Section 11: Trial procedures	
See Section 1.1 for a summary of the trial as a flow diagram and Section 1.2 for tabular schedules of events for each period.	See Section 1.1 for a summary of the trial as a flow diagram and Section 1.2 for tabular schedules of events for each period. *A trial site visit may be performed as a home visit after prior approval by the sponsor.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 11.1.1.1: Enrollment Visit (Visit V1; Day -14 to Day 1)	
... • Obtain informed consent and (if required by local law) assent (see Section 4.2 for the procedure). ... • Take blood for safety laboratory investigations (for both the central and local laboratories).	... • Obtain informed consent and (if required by local law) assent (see Section 4.2 for the procedure). *The informed consent/assent may be obtained earlier than Day -14.* ... • Take blood for safety laboratory investigations (for both the central and local laboratories). *The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.*
Section 11.1.1.2: Visit V2 (Allocation Visit; Day 1)	
... • Administer the first dose of IMP to the subject ~~at the investigator's site~~. Record administration in the diary.	... • Administer the first dose of IMP to the subject *(see Section 10.2.1). The first dose of IMP will be taken during this visit, within 24 hours after randomization. Day 1 is the day of first IMP intake.* Record administration in the diary.
Section 11.1.1.4: Visit VE (Day 15 ± 1, End of Treatment Visit)	
This visit is planned for Day 15 ± 1, but ~~should~~ also be performed if a subject discontinues IMP during the Treatment Period.	This visit is planned for Day 15 ± 1, but *must* also be performed *within 3 days of last IMP intake* if a subject discontinues IMP during the Treatment Period.
Section 11.1.1.4: Visit VE (Day 15 ± 1, End of Treatment Visit) Section 11.1.2.3: Visit ET (Early Termination Visit) Section 11.1.2.4: Visit F12M (at 12 months after Visit VE, range ± 14 days)	
... - Dispense SOWS questionnaire for completion at home if this is the visit of the last intake of IMP (only for subjects going in to the Observation Period). To be completed once daily until Visit F7D.	... - Dispense SOWS questionnaire for completion at home if this is the visit of the last intake of IMP (only for subjects going in to the Observation Period). To be completed once daily until *the seventh day after the last intake of IMP. To be collected at* Visit F7D.
Section 11.1.2.2: Visit TP1 to TP12 (every 28 days after Visit VE, range: ± 5 days)	
• Record body weight. • Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).	• Record body weight. • *Record height (only at Visit TP3, Visit TP6, Visit TP9, and Visit TP12).* • Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate).
Section 11.4: Subject trial cards	
Subjects/parent(s)/legal guardian(s), as applicable, will receive a "subject trial card". The trial card will list the following information:	Subjects/parent(s)/legal guardian(s), as applicable, will receive a "subject trial card". The trial card will list *at a minimum* the following information:

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.1: Overview of blood sampling in this trial	
If possible, blood samples for safety laboratory evaluations and serum pharmacokinetics should be taken at the same time. Sampling times are given in the schedule of events (Section 1.2).	If possible, blood samples for safety laboratory evaluations and serum pharmacokinetics should be taken at the same time. Sampling times are given in the schedule of events (Section 1.2). *The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.*
Section 12.2.3: Pain history	
The history, underlying pain condition (cancer/non-cancer-related pain), and treatments ~~for pain~~ in the last 30 days before enrollment will be recorded in the CRF.	The history, underlying pain condition (cancer/non-cancer-related pain), and treatments *given* in the last 30 days *for pain* before enrollment will be recorded in the CRF.
Section 12.4.1: Pain intensity	
... For the Tapentadol Period of Part 2, the investigator will document the pain that the subject has at each visit in the CRF ~~using a paper-based~~ VAS.	... For the Tapentadol Period of Part 2, the investigator will document the pain that the subject has at each visit in the CRF *based on the FPS-R and* VAS.
Section 12.5.3: Subjective opiate withdrawal scale	
... The 15 question SOWS questionnaire ~~is more~~ appropriate for the studied population. It takes less than 10 minutes to complete. The scale has been demonstrated to be a valid and reliable indicator of the severity of the opiate withdrawal syndrome over a wide range of common signs and symptoms. The SOWS questionnaire will be completed by the subjects at home daily ~~for 7 days~~ after ~~discontinuation~~ of IMP.	... The *first* 15 question*s of the 16-question* SOWS questionnaire *are* appropriate for the studied population. It takes less than 10 minutes to complete. The scale has been demonstrated to be a valid and reliable indicator of the severity of the opiate withdrawal syndrome over a wide range of common signs and symptoms. The SOWS questionnaire will be completed by the subjects at home daily *until the seventh day* after *the last intake* of IMP. *It will be collected at Visit F7D.*
Section 12.6.1: Adverse events: Special procedures for serious adverse events	
... If possible, after serious adverse events considered related to IMP (≥possible: see the section Classification of causation), a blood sample for the quantitation of systemic exposure of tapentadol ~~(or morphine),~~ and metabolites~~,~~ should be drawn in close temporal relationship to the serious adverse event.	... If possible, after serious adverse events considered related to IMP (≥possible: see the section Classification of causation), a blood sample for the quantitation of systemic exposure of tapentadol and metabolites should be drawn in close temporal relationship to the serious adverse event.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.6.5: Safety laboratory	
... The check of the exclusion criteria will be based on the local laboratory values. Local laboratory parameters needed are: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine (the creatinine clearance will be calculated in the electronic CRF). **Serum chemistry and hematology** ... The following tests will be performed: Red blood cell (RBC) count White blood cell (WBC) count ~~(if WBC abnormal, also differential count)~~ Platelet count **Urinalysis** … ~~Sediment by the central laboratory~~ ~~Red blood cells (RBC)~~ ~~White blood cells (WBC)~~ ~~Epithelial cells~~ ~~Crystals~~ ~~Casts~~ ~~Bacteria~~	... The check of the exclusion criteria will be based on the local laboratory values. Local laboratory parameters needed are: total serum bilirubin, serum albumin, aspartate transaminase, alanine transaminase, and serum creatinine (the creatinine clearance will be calculated in the electronic CRF). *The local laboratory sample does not need to be taken at the Enrollment Visit if suitable results from the same local laboratory are available from a blood sample obtained in the 14 days prior to Visit 2 for other reasons.* **Serum chemistry and hematology** ... The following tests will be performed: Red blood cell (RBC) count *Red blood cell morphology* White blood cell (WBC) count *White blood cell differential count* *White blood cell morphology* Platelet count

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2.1: Analysis populations (analysis sets)	
Enrolled population ~~A~~ll subjects ~~for whom an~~ informed consent form ~~was signed~~. **Safety Set** The Safety Set comprises all treated subjects. **Full Analysis Set** The FAS comprises all allocated and treated subjects. **Per Protocol Set** The Per Protocol Set ~~is~~ a subset of the FAS~~, excluding~~ subjects ~~with~~ protocol deviations~~ that may have an impact on the results of~~ the ~~efficacy~~ analyses.	**Enrolled population** *The Enrolled Set includes a*ll subjects *with a signed (by subject, parent(s) or legal guardian(s) as appropriate)* informed consent form *and if required by local law an assent form.* ***Allocated Set*** *The Allocated Set includes all subjects who are allocated to treatment*. **Safety Set** The Safety Set comprises all treated subjects*, i.e., all subjects in whom IMP was administered (at least once)*. **Full Analysis Set** The FAS comprises all allocated and treated subjects*, i.e., all allocated subjects who were administered any amount of IMP*. **Per Protocol Set** The Per Protocol Set *defines* a subset of the subjects *in the* FAS *without any major* protocol deviation *affecting* the *primary endpoint. The Per Protocol Set is only relevant for* analyses *during Part 1. No protocol deviation during Part 2 leads to exclusion from the Per Protocol Set*.
Section 14.2.6.1: Primary endpoint (proportion of subjects classified as responders in Part 1)	
... Further sensitivity analyses are planned (but not limited to), e.g., keeping the criteria for response unchanged~~,~~ except for classifying subjects who stop treatment earlier than 14 days ~~or use IMP intermittently~~ because of no further need for opioid treatment as responders rather than non-responders.	... Further sensitivity analyses are planned (but not limited to), e.g., keeping the criteria for response unchanged except for classifying subjects who stop treatment earlier than 14 days because of no further need for opioid treatment as responders rather than non-responders.
Section 14.2.6.2: Pain scale assessed using a VAS and FPS-R	
... Descriptive statistics will be provided to evaluate the ~~changes at each scheduled time point~~ as well as changes to baseline for the different trial periods and respective treatment groups, as described in Section 14.2.2.	... Descriptive statistics will be provided to evaluate the *daily average pain (Part 1) or pain at each visit during the Tapentadol Period (Part 2)* as well as changes to baseline for the different trial periods and respective treatment groups, as described in Section 14.2.2.
Section 14.2.6.3: Rescue medication	
... Comparisons will be made across time~~,~~ for subgroups of ~~body weight and for~~ different ages.	... Comparisons will be made across time *and also* for subgroups of different ages.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2.7.5: Physical examination	
~~Changes in~~ ~~p~~physical examination findings ~~compared to the previous assessment~~ will be listed ~~and summarized by body system. Further details concerning subgroups of interest will be specified in the SAP~~.	*P*hysical examination findings will be listed.
Section 14.2.7.8: Subjective opiate withdrawal scale	
The SOWS questionnaire score will be descriptively analyzed per scheduled time point according to the last IMP taken. ~~Changes to Visit ET will also be presented.~~	The SOWS questionnaire score*s and changes from baseline (defined for the SOWS as the assessment made on the day of the last intake of IMP)* will be descriptively analyzed per scheduled time point according to the last IMP taken. *The total score of the full questionnaire (all 16 questions) will be used for a first analysis. Additionally the total score of the first 15 questions of the SOWS questionnaire will be analyzed in the same manner, being more appropriate for the studied population.*
Section 14.2.9: Final analysis	
The final analysis of ~~both~~ Part 1 ~~and Part 2~~ of the trial will be performed after all subjects have completed Part 2~~. Further analysis details will be specified in the SAP~~.	The final analysis of Part 1 will *be performed after all subjects have completed Part 1* of the trial *and the data has been locked for analyses of Part 1.* *The final analysis of Part 2 will be performed after all subjects have completed Part 2 of the trial and the final data base has been locked.*
Section 19.9.1: Labeling	
The labels of the pharmacokinetic samples will be provided by the central laboratory and include at least the following information ~~(pre-printed, i.e., manual writing has to be avoided)~~: • Trial Number. • Unique Subject Identifier. • Visit Number. • ~~Sample time.~~	The labels of the pharmacokinetic samples will be provided by the central laboratory and include at least the following information: • Trial Number. • Unique Subject Identifier. • *Accession Number.* • Visit Number.

18.3 Protocol amendment 03

Amendment rationale

Protocol amendment 03 was been enacted to implement changes required by US authorities:

- Specify titration for subjects who were opioid naive at Visit V1.
- Add CSSRS, University of Michigan sedation score, and measurement of oxygen saturation (SpO_2).

The amendment was subsequently withdrawn.

18.4 Protocol amendment 04

Protocol amendment 04 is based on protocol amendment 02, and does not reflect changes introduced in protocol amendment 03 as this protocol amendment was withdrawn.

Amendment rationale

Protocol amendment 04 has been enacted to implement the following changes:

- The alpha for the primary endpoint analysis has been updated based on the methodology proposed by Hlavin et al. (2016). As a consequence of the alpha adjustment, the sample size has been reduced. Further details for the derivation of the adjusted alpha are provided in a separate document that is available upon request.
- A definition of long-term pain has been added.
- Specifications of the trial population have been modified, requiring the inclusion of fewer subjects in the lower age group. The expectation that at least 15 subjects will be treated with tapentadol PR for a minimum of 12 weeks has been introduced.
- The estimated dates of last subject out for Part 1 and Part 2 have been updated.
- The main analysis has been rescheduled such that it will be performed after all subjects have completed the first 12 weeks (Visit TP3 or Visit OP3) of Part 2.
- The interim analysis for sample size re-assessment has been removed due to the reduced sample size. The adaptive 2-stage design of the trial has been simplified to a fixed 1-stage design.
- Instructions pertaining to ECG-related discontinuation have been added.
- The timing of the Early Termination Visit has been explicitly defined.
- History of complex regional pain syndrome and history of a pain indication that is unlikely to respond to opioids have been added to the exclusion criteria.
- Safety experience from post-marketing data has been updated.
- Instructions for calculating the starting dose in Part 1 and Part 2 have been revised.
- Requirements for adverse event reporting during the Observation Period of Part 2 have been modified.

In addition, textual change has been made for consistency and, where necessary, to provide more detailed descriptions.

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 design	
Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring	Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring

Changes to this protocol include:	
Formerly read:	**Now reads:**
prolonged release opioid treatment. The target is to allocate ~~at least 12~~9 subjects ~~(with a maximum of 200 subjects)~~ in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily. ~~An interim analysis will be performed to check the sample size.~~	prolonged release opioid treatment. The target is to allocate *6*9 subjects in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily.
Section 1: Protocol synopsis: Trial population	
Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2 (Allocation Visit; Day 1), and who comply with the inclusion/exclusion criteria given in Section 1.3. The age groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined. At least ~~50~~% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years.	Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2 (Allocation Visit; Day 1), and who comply with the inclusion/exclusion criteria given in Section 1.3. *Long-term pain is defined as any pain condition that requires a minimum of 14 days of treatment with a strong oral opioid. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., spinal surgery), cancer-related pain (including pain caused by treatment) as well as chronic indications with moderate to severe pain.* The age groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined. At least *25*% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years. *At least 15 subjects must be treated with tapentadol PR for a minimum of 12 weeks.*
Section 1: Protocol synopsis: Concomitant medications/therapies	
All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed. Subjects ~~suffering from cancer related pain~~ will be allowed to participate in trials of marketed therapeutic medications and therapies (including trials of antibody therapies).	All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed. Subjects will be allowed to participate in trials of marketed therapeutic medications and therapies (including trials of antibody therapies) *at the same time as participating in this trial*.
Section 1: Protocol synopsis: Trial period Section 8: Trial design: Trial period	
Estimated date of first subject in: Oct 2014. Part 1, estimated date of last subject out: ~~Sep 2016~~. Part 2, estimated date of last subject out: ~~Sep 2017~~.	Estimated date of first subject in: Oct 2014. Part 1, estimated date of last subject out: *Sep 2018*. Part 2, estimated date of last subject out: *Sep 2019*.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Sample size rationale	
~~The design of the trial is an adaptive 2-stage design with possible sample size re-estimation after the first stage, with no early stopping for success or futility foreseen (see "Interim Analysis"). As a result of the interim analysis, the overall number of subjects in the FAS will be between N = 129 and an upper sample size limit of N_{max} = 200.~~ To show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.~~025~~, ~~12~~9 subjects are required in the FAS, assuming a 2:1 randomization of tapentadol PR:morphine PR. ~~Using the proposed method for sample size re-assessment, the final analysis does not have to be adjusted for the interim analysis.~~ ~~The operating characteristics of the trial design and the sample size was assessed in 2 steps. First, a sample size calculation was carried out using Adaptive Designs – Plans and Analyses software package ADDPLAN version 6.0.8 provided by Aptiv Solutions, for an adaptive 2-stage design without stopping at interim after 75% of data are available. The resulting total number of subjects (N = 129) was then implemented in a simulation process using the response rate as the primary endpoint and computing the empirical statistical power for several values of the overall sample size. These simulations were carried out using R version 2.12.2. The simulations were validated by an independent statistician.~~	To show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.*1*, *6*9 subjects are required in the *Full Analysis Set (*FAS*)*, assuming a 2:1 randomization of tapentadol PR morphine PR.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1: Protocol synopsis: Statistical methods	
The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2. ~~The primary analysis will be conducted after the end of stage 2 of the trial, meaning that all subjects have completed Part 1 of the trial.~~ ... ~~*Primary*~~ *analysis of the trial* The ~~primary~~ analysis of the trial will be performed after all subjects have completed ~~Part 1 (Treatment Period)~~. *Primary efficacy endpoint* ... The Farrington-Manning test will then be applied and a ~~95~~% confidence interval calculated. ... *Analysis of safety data* ... Adverse events will be tabulated separately for the treatment periods ~~and additionally by visit, as long as a sufficient number of subjects are available~~. ~~*Interim analysis*~~ ~~The trial will be conducted using an adaptive 2-stage design with possible sample-size re-estimation after the first stage, with no stopping for futility foreseen. The sample-size re-estimation will be done in an unblinded manner as the trial is open label. The interim analysis aims for verification of the assumptions for the sample size calculation by using a so called "promising zone" approach. This interim analysis is planned to be conducted after 75% of the initially proposed number of subjects in the FAS (i.e., 97 subjects) complete Part 1 of the trial.~~	The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2. ... *Main analysis of the trial* The *main* analysis of the trial will be performed after all subjects have completed *the first 12 weeks (Visit TP3 or Visit OP3) of Part 2*. *Primary efficacy endpoint* ... The Farrington-Manning test will then be applied and a*n 80*% confidence interval calculated. ... *Analysis of safety data* ... Adverse events will be tabulated separately for the treatment periods.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.2.1: Part 1: Enrollment Visit and Treatment Period (Visit V1 to Visit VE): footnotes	
a) Visit VE must also be performed within 3 days ~~of~~ last ~~IMP~~ intake if IMP is stopped during the Treatment Period. ... s) The informed consent/assent may be obtained earlier than Day -14.	a) Visit VE must also be performed within 3 days *after* last intake *of IMP* if IMP is stopped during the Treatment Period. ... s) The informed consent/assent may be obtained earlier than Day -14. *t) The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.*
Section 1.2.2: Part 2: Tapentadol Period: footnotes	
c) ~~The Early Termination Visit (~~Visit ET~~)~~ is ~~for subjects stopping IMP~~ before Visit F12M in Part 2.	c) Visit ET *must be performed within 3 days after last intake of IMP if IMP* is *stopped* before Visit F12M in Part 2.
Section 1.3.1: Inclusion criteria	
Subjects are eligible for the trial at Visit V1 if all the following apply: ... 3. Subject has an underlying long-term pain condition that is, according to the judgment of the investigator, expected to require a twice-daily prolonged release opioid treatment until at least the end of the 14-day Treatment Period (Visit VE).	Subjects are eligible for the trial at Visit V1 if all the following apply: ... 3. Subject has an underlying long-term pain condition *(e.g., cancer, chronic disease, planned or performed surgery)* that is, according to the judgment of the investigator, expected to require a twice-daily prolonged release opioid treatment until at least the end of the 14-day Treatment Period (Visit VE).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 1.3.2: Exclusion criteria	
The following will be checked at Visit V1: ... 4. 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). ... The following will be checked at Visit V2: ... 17. ~~If subject suffers from non-cancer related pain: participation in any interventional clinical trial within 30 days prior to Visit V2.~~	The following will be checked at Visit V1: ... 4. 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). • *Complex regional pain syndrome.* • *A pain indication with a strong psycho-somatic component that, in the judgment of the investigator, is unlikely to respond to opioids.* ... The following will be checked at Visit V2: ... 17. *[criteria deleted]*
Section 6.2: Relevant non-clinical and clinical data: Safety experience from post-marketing data	
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 [redacted]. 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 tapentadol 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. [redacted] Overall, the most frequently reported preferred terms for these events were (in descending order of frequency) nausea, drug ineffective, dizziness, *somnolence, vomiting, and* headache.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 8: Trial design	
Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring prolonged release opioid treatment. The target is to allocate ~~at least 12~~9 subjects ~~(with a maximum of 200 subjects)~~ in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily. ... **Trial population** Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from severe long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2, and who comply with the inclusion/exclusion criteria given in Section ~~9.2~~. ~~Age~~ groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined. At least ~~50~~% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years.	Part 1 is a 14-day (Treatment Period) Phase II/III, randomized, multi-site, open-label, active-controlled, parallel group trial in subjects aged 6 years to less than 18 years, suffering from long-term pain requiring prolonged release opioid treatment. The target is to allocate *69* subjects in a ratio of 2:1 to treatment with tapentadol PR or morphine PR twice daily. ... **Trial population** Subjects will be enrolled who are aged 6 years to less than 18 years (for the duration of Part 1 of the trial) and suffer from severe long-term pain requiring prolonged release opioid treatment for at least 14 days after Visit V2 *(Allocation Visit; Day 1),* and who comply with the inclusion/exclusion criteria given in Section *1.3*. *Long-term pain is defined as any pain condition that requires a minimum of 14 days of treatment with a strong oral opioid. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., spinal surgery), cancer-related pain (including pain caused by treatment) as well as chronic indications with moderate to severe pain.* *The age* groups of 6 years to less than 12 years and 12 years to less than 18 years are predefined. At least *25*% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years. *At least 15 subjects must be treated with tapentadol PR for a minimum of 12 weeks.*
Section 8.4: Discussion of the trial design	
Choice of population and trial sites Tapentadol PR has shown to be an efficacious and safe drug for the treatment of different chronic pain indications that are common in the adult population, such as low back pain, osteoarthritis and cancer-related pain. ... Chronic daily pain can occur in children in the context of chronic daily headaches, neurodegenerative disorders,	**Choice of population and trial sites** *The trial includes children with different indications requiring treatment with an oral strong opioid for at least 14 days. Subjects that could be considered for the trial include, but not exclusively, those with expected long-term post-surgical pain (e.g., orthopedic surgery), cancer-related pain (including pain caused by treatment), as well as chronic indications with moderate to severe pain.* Tapentadol PR has shown to be an efficacious and safe drug for the treatment of different chronic pain indications that are common in the adult population, such as low back pain, osteoarthritis and cancer-related pain. ... Chronic daily pain can occur in children in the context of chronic daily headaches, neurodegenerative disorders,

Changes to this protocol include:	
Formerly read:	**Now reads:**
inflammatory disorders, post-traumatic neuropathic pain conditions ~~(including complex regional pain syndromes),~~ and in children with advanced cancer and other life-limiting diseases. ... Multiple trial sites, e.g., specialized in pediatric oncology and hematology, burns and orthopedics, in multiple countries will be required for the recruitment of ~~at least 12~~9 subjects in the specified time. ... ~~**Interim analysis**~~ ~~The trial will include 1 interim analysis, to decide on the adequacy of the chosen sample size. The interim analysis is planned to be conducted after 75% of the initially planned number of subjects in the FAS (i.e., 97 subjects) complete Part 1 of the trial (Section 14.2.10). The rationale for the interim analysis is that information about the primary endpoint and the treatment effect measured in the population under investigation is limited. Therefore, assumptions needed for an appropriate sample size calculation to achieve a specified power in a fixed sample design are subjected to uncertainty. An adaptive design allows for sample size re-assessment at the interim analysis under control of the overall Type I error rate.~~ ~~To ensure the integrity and validity of the trial results, an independent statistician will conduct the sample size re-assessment at the interim analysis. The rules for the sample size re-assessment and final analysis are pre-specified, see Section 14.2.10.~~ ... **Stratification** ... The predefined age groups are 6 years to less than 12 years, and 12 years to less than 18 years, and subjects will be stratified so that at least ~~50~~% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years. ... **Dosing** ... Based on these results, a starting dose of ~1.25 mg/kg to 1.5 mg/kg every 12 hours, with a maximum dose of ~4.5 mg/kg every 12 hours, were chosen in this trial. As the IMP used in this trial is only available as tapentadol PR 25 mg and tapentadol PR 100 mg tablets, the doses in the age sub-groups (Table 2) are chosen to be as close as possible to the estimated doses. ~~In subjects previously taking an opioid, a conversion~~	inflammatory disorders, post-traumatic neuropathic pain conditions*,* and in children with advanced cancer and other life-limiting diseases. ... Multiple trial sites, e.g., specialized in pediatric oncology and hematology, burns and orthopedics, in multiple countries will be required for the recruitment of *6*9 subjects in the specified time. ... **Stratification** ... The predefined age groups are 6 years to less than 12 years, and 12 years to less than 18 years, and subjects will be stratified so that at least *25*% of the subjects will be allocated to IMP at Visit V2 in the age group of 6 years to less than 12 years. ... **Dosing** ... Based on these results, a starting dose of ~1.25 mg/kg to 1.5 mg/kg every 12 hours, with a maximum dose of ~4.5 mg/kg every 12 hours, were chosen in this trial. As the IMP used in this trial is only available as tapentadol PR 25 mg and tapentadol PR 100 mg tablets, the doses in the age subgroups (Table 2) are chosen to be as close as possible to the estimated doses.

Changes to this protocol include:	
Formerly read:	**Now reads:**
~~factor will be used to calculate the starting dose (Section 19.8).~~	
Section 9.2: Inclusion/exclusion criteria	
[Inclusion and exclusion criteria deleted from section.] [Links set to Section 1.3.]	
Section 9.3: Trial discontinuation and treatment not completed	
Subjects may, however, also discontinue participation in the trial completely.	Subjects may, however, also discontinue participation in the trial completely *(trial not completed)*.
Section 10.2.3.2 Starting doses in Part 1 for subjects with previous opioid treatment	
Subjects ~~with~~ previous opioid treatment will start at 70% of the equi-analgesic dose of their previous treatment or lower; depending on the available dose, but using at least the minimum dose according to weight group (see Table 2 for tapentadol PR and Table 3 for morphine PR). Subjects pre-treated with morphine can continue on their previous dose or next lower dose according to Table 3 if the dose does not match a dose given on the dosing table. ~~A conversion table to calculate equi-analgesic doses of common opioids to tapentadol PR and morphine PR is provided in Section 19.8.~~	Subjects *taking* previous opioid treatment will start at 70% of the equi-analgesic dose of their previous treatment or lower; depending on the available dose, but using at least the minimum dose according to weight group (see Table 2 for tapentadol PR and Table 3 for morphine PR). Subjects pre-treated with morphine can continue on their previous dose or next lower dose according to Table 2 if the dose does not match a dose given on the dosing table*, if randomized to morphine*. *Conversion from other opioids to morphine should be done according to clinical routine. To calculate the dose of prolonged release opioids per intake, it is recommended to calculate the total daily dose of the immediate release opioid and divide the result by 2. To rotate subjects from other opioids to tapentadol PR, the morphine-equivalent dose should be calculated first followed by the calculation of the final tapentadol PR dose (1 mg morphine PR is equivalent to 2.5 mg tapentadol PR).*
Section 10.2.3.3: Starting dose of tapentadol PR in Part 2	
Subjects converting from morphine PR (Treatment Period of Part 1) to tapentadol PR (Tapentadol Period of Part 2) will start tapentadol PR ~~with~~ 70% of the current morphine equivalent dose or lower, depending on the available dose, but using at least the minimum dose according to their weight group (Table 2). ~~As tapentadol PR 2.5 mg is equivalent to morphine PR 1 mg, the suggested starting total daily dose of tapentadol PR in mg is 1.75 x total daily dose of morphine PR in mg.~~	Subjects converting from morphine PR (Treatment Period of Part 1) to tapentadol PR (Tapentadol Period of Part 2) will start tapentadol PR *at* 70% of the current morphine equivalent dose or lower, depending on the available dose, but using at least the minimum dose according to their weight group (Table 2).
Section 10.3.1: Part 1	
Subjects will be stratified using the interactive response technology system by age group (6 years to less than 12 years and 12 years to less than 18 years, at Visit V2 [Allocation Visit]) so that at least ~~50~~% of the subjects are in the younger age group, and by underlying pain condition (cancer/non-cancer-related pain).	Subjects will be stratified using the interactive response technology system by age group (6 years to less than 12 years and 12 years to less than 18 years, at Visit V2 [Allocation Visit]) so that at least *25*% of the subjects are in the younger age group, and by underlying pain condition (cancer/non-cancer-related pain).

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 10.5: Allowed and forbidden and prior/concomitant medications/therapies	
... All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed. ~~Subjects suffering from cancer-related pain will be allowed to participate in trials of marketed therapeutic medications and therapies (including trials of antibody therapies).~~	... All medications/therapies that are not explicitly mentioned under allowed or forbidden treatments are also considered to be allowed.
Section 11.1.1.1: Enrollment Visit (Visit V1; Day -14 to Day 1)	
... • Record a 12-lead ECG.	... • Record a 12-lead ECG. *The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.*
Section 11.1.1.4: Visit VE (Day 15 ± 1, End of Treatment Visit)	
This visit is planned for Day 15 ± 1, but must also be performed within 3 days ~~of~~ last ~~IMP~~ intake if a subject discontinues IMP during the Treatment Period.	This visit is planned for Day 15 ± 1, but must also be performed within 3 days *after* last intake *of IMP* if a subject discontinues IMP during the Treatment Period.
Section 11.1.2.3: Visit ET (Early Termination Visit)	
~~The Early Termination Visit (~~Visit ET~~) is for subjects stopping~~ IMP before Visit F12M in Part 2. If Visit F12M and Visit ET are performed on the same day, assessments scheduled for both visits will not be repeated at Visit F12M.	Visit ET *must be performed within 3 days after last intake of IMP if* IMP *is stopped* before Visit F12M in Part 2. If Visit F12M and Visit ET are performed on the same day, assessments scheduled for both visits will not be repeated at Visit F12M.

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 12.6.1: 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). ... **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.	*During Part 1 and during the Tapentadol Period of Part 2 and until Visit OP3 of the Observational Period* 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). *After Visit OP3 of the Observation Period of Part 2, only adverse events and serious adverse events that, in the judgment of the investigator, are at least possibly related to IMP will be reported.* ... **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*, with the following exception: after Visit OP3 of the Observation Period of Part 2, only adverse events and serious adverse events that, in the judgment of the investigator, are at least possibly related to IMP will be reported.*
Section 12.6.2: Vital signs	
Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) will be measured in a supine position after resting for 5 minutes and recorded in the CRF. While resting, the subject should not receive anything to drink or eat.	Vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate) will be measured in a supine position after resting for *at least* 5 minutes and recorded in the CRF. While resting, the subject should not receive anything to drink or eat.
Section 12.6.4: Twelve-lead electrocardiogram	
... Cardiologists at a central ECG laboratory will read all ECGs. The ECG report from the central ECG laboratory will be considered a source document.	... Cardiologists at a central ECG laboratory will read all ECGs. The ECG report from the central ECG laboratory will be considered a source document. *If there are discrepancies between the central ECG analysis report and the assessment of the investigator, the investigator will document these on the ECG analysis report.* *The inclusion as well as discontinuation of a subject will be based on the judgment of the investigator. If the subject has been included but fulfills any of the discontinuation criteria based on the ECG analysis report of the central ECG laboratory, the ECG must be repeated within 1 week of receiving the central ECG report and the subject must be discontinued if any of the discontinuation criteria is confirmed by the investigator.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 13.3: Data management	
Database lock ~~For each defined reporting time point, w~~hen all data have been received and entered, all data checks and quality control checks have been performed, all queries are resolved, and ~~a~~ final ~~data~~ review ~~meeting~~ has been held without resulting in new queries, the trial database will be considered clean and ~~can be frozen~~. For the ~~primary~~ analysis ~~after~~ Part 1, the ~~database~~ will be ~~frozen after every subject has completed Part 1 or has terminated early~~.	**Database lock** *W*hen all data have been received and entered *into the trial database*, all data checks and quality control checks have been performed, all queries are resolved, and *the* final *statistical* review has been held without resulting in new queries, the trial database will be considered clean and *the data will be locked*. For the *main* analysis *(*Part 1 *and the first 12 weeks of Part 2),* the *detailed procedure* will be *described in the data management plan*.
Section 14.1: Sample size rationale	
~~The design of the trial is an adaptive 2-stage design with possible sample size re-estimation after the first stage, with no early stopping for success or futility foreseen. This interim analysis aims for verification of the assumptions for the sample size calculation by using a so called "promising zone" approach (see Section 14.2.10), stopping for any reason is not foreseen based in the results of the interim analysis. As a result of the interim analysis, the overall number of subjects in the FAS will be between N = 129 and an upper sample size limit of N_{max} = 200.~~ To show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning (1990) test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.~~025~~, ~~12~~9 subjects are required in the FAS, assuming a 2:1 randomization of tapentadol PR:morphine PR. ~~Using the proposed method for sample size re-assessment, the final analysis does not have to be adjusted for the interim analysis.~~ ~~The operating characteristics of the trial design and the sample size was assessed in 2 steps. First, a sample size calculation was carried out using Adaptive Designs – Plans and Analyses software package ADDPLAN version 6.0.8 provided by Aptiv Solutions, for an adaptive 2-stage design without stopping at the interim analysis after 75% of data are available. The resulting total number of subjects (N = 129) was then implemented in a simulation process using the response rate as the primary endpoint and computing the empirical statistical power for several values of the overall sample size. These simulations were carried out using R version 2.12.2. The simulations were validated by an independent statistician.~~ ~~A detailed description of the process can be found the sponsor's trial master files.~~	To show the non-inferiority of tapentadol PR compared to morphine PR using a Farrington-Manning (1990) test by a non-inferiority margin of 20% with at least 80% power and a 1-sided significance level of alpha = 0.*1*, *6*9 subjects are required in the FAS, assuming a 2:1 randomization of tapentadol PR:morphine PR. *A one-sided alpha of 0.1 is considered appropriate based on a method proposed by Hlavin et al. (2016). The approach makes use of prior knowledge and the concept of extrapolation from a larger population to a small target population, (i.e., pediatric population), to reduce the burden of evidence in pediatrics by relaxing the Type I error, while controlling a certain posterior belief, i.e., confidence after successful pediatric trials, in effectiveness of the drug in children.* *Further details for the application of the concept of Hlavin et al. (2016) in the context of this trial are provided in a separate document that is available upon request.*

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 14.2: Analysis of the trial – statistical analysis	
~~**Primary**~~ **analysis of the trial** The ~~primary~~ analysis of the trial will be performed after all subjects have completed ~~Part 1 (Treatment Period), i.e., after the end of stage 2 of the trial (see Section 14.2.10)~~.	***Main*** **analysis of the trial** The *main* analysis of the trial will be performed after all subjects have completed *the first 12 weeks (Visit TP3 or Visit OP3) of Part 2*.
Section 14.2.6.1: Primary endpoint (proportion of subjects classified as responders in Part 1): Hypotheses	
... The Farrington-Manning (1990) test will then be applied and a ~~95~~% confidence interval calculated. The non-inferiority of tapentadol PR compared to morphine PR will be established if the lower limit of this 2-sided ~~95~~% confidence interval of the difference in the above estimated proportions is above the non-inferiority margin of -20%. ~~The method chosen for sample size re-assessment allows for an unchanged test statistic to be used for final analysis.~~ ... This sample will be summarized by means of the posterior mean, median, standard deviation and ~~95~~% credibility interval. If the lower limit of the ~~95~~% credibility interval for the difference of the 2 response rates is >-0.2, then this would support non-inferiority by this sensitivity analysis.	... The Farrington-Manning (1990) test will then be applied and a*n 80*% confidence interval calculated. The non-inferiority of tapentadol PR compared to morphine PR will be established if the lower limit of this 2-sided *80*% confidence interval of the difference in the above estimated proportions is above the non-inferiority margin of -20%. ... This sample will be summarized by means of the posterior mean, median, standard deviation and *80*% credibility interval. If the lower limit of the *80*% credibility interval for the difference of the 2 response rates is >-0.2, then this would support non-inferiority by this sensitivity analysis.
Section 14.2.7.1: Adverse events	
Adverse events will be tabulated separately for the treatment periods ~~and additionally by visit, as long as a sufficient number of subjects are available~~.	Adverse events will be tabulated separately for the treatment periods.
Section 14.2.7.4: Vital signs (pulse rate, systolic/diastolic blood pressure, and respiratory rate)	
As described in Section 14.2.2, descriptive statistics as well as ~~for~~ changes to baseline for the different trial periods will be presented. Frequency tabulations of abnormalities will be included.	As described in Section 14.2.2, descriptive statistics as well as changes to baseline for the different trial periods will be presented. Frequency tabulations of abnormalities will be included.
Section 14.2.9: Final analysis	
The ~~final~~ analysis of ~~Part 1~~ will be performed after all subjects have completed Part 1 of the trial ~~and the data has been locked for analyses of Part 1~~. The final analysis of Part 2 will be performed after all subjects have completed Part 2 of the trial and the final data base has been locked.	The *main* analysis *of the trial* will be performed after all subjects have completed Part 1 *and the first 12 weeks (Visit TP3 or Visit OP3) of Part 2* of the trial. The final analysis of Part 2 will be performed after all subjects have completed Part 2 of the trial and the final database has been locked. *Further details regarding the analyses will be provided in the SAP.*
Section 14.2.10: ~~Interim analysis~~	Section 14.2.10: [deleted]

Changes to this protocol include:	
Formerly read:	**Now reads:**
Section 16.6: Final report and reporting of the trial	
An integrated clinical trial report, integrating clinical, pharmacokinetic, and statistical results of Part 1 (Treatment Period) will be prepared by the sponsor once all subjects have completed ~~Part 1~~.	An integrated clinical trial report, integrating clinical, pharmacokinetic, and statistical results of Part 1(Treatment Period) *and the first 12 weeks of Part 2* will be prepared by the sponsor once all subjects have completed *the first 12 weeks (Visit TP3 or Visit OP3) of Part 2*.
Section 17: References: Publications	
... ~~Mehta CR, Pocock, SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statistics in Medicine 2011; 30(28): 3267-84.~~	*Hlavin G, Koenig F, Male C, Posch M, Bauer P. Evidence, eminence and extrapolation. Stat Med 2016; 35(13): 2117-32.* ...
Section 19: Appendix	
Section 19.8: ~~Conversion factors for opioids~~	Section 19.8: [deleted]
Section 19.10: ~~Interim analysis using the promising zone approach~~	Section 19.11: [deleted]

18.5 Protocol amendment 05

Protocol amendment 05 is implemented to reverse a change introduced in amendment 04 relating to the recording of adverse events after Visit OP3.

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 12.6.1: Adverse events	
~~During Part 1 and during the Tapentadol Period of Part 2 and until Visit OP3 of the Observational Period 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). ~~After Visit OP3 of the Observation Period of Part 2, only adverse events and serious adverse events that, in the judgment of the investigator, are at least possibly related to IMP will be reported.~~	*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). ...

Changes to this protocol include:	
Formerly read:	**Now reads:**
... **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~~, with the following exception: after Visit OP3 of the Observation Period of Part 2, only adverse events and serious adverse events that, in the judgment of the investigator, are at least possibly related to IMP will be reported~~.	**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.

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 disorders		
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	illeus
intestinal ischaemia	intestinal perforation	melaena
mesenteric occlusion	mesenteric vein thrombosis	pancreatitis
peritonitis		
General disorders and administration site conditions		
malignant hyperthermia		

Hepatobiliary 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’s 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 heamorrhage	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	

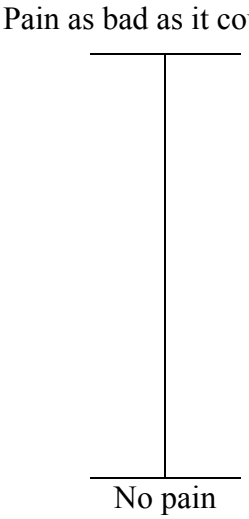
CTC = Common Toxicity Criteria also referred to as the Common Terminology Criteria for Adverse Events (CTCAE).
Source: [redacted].

19.2 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"



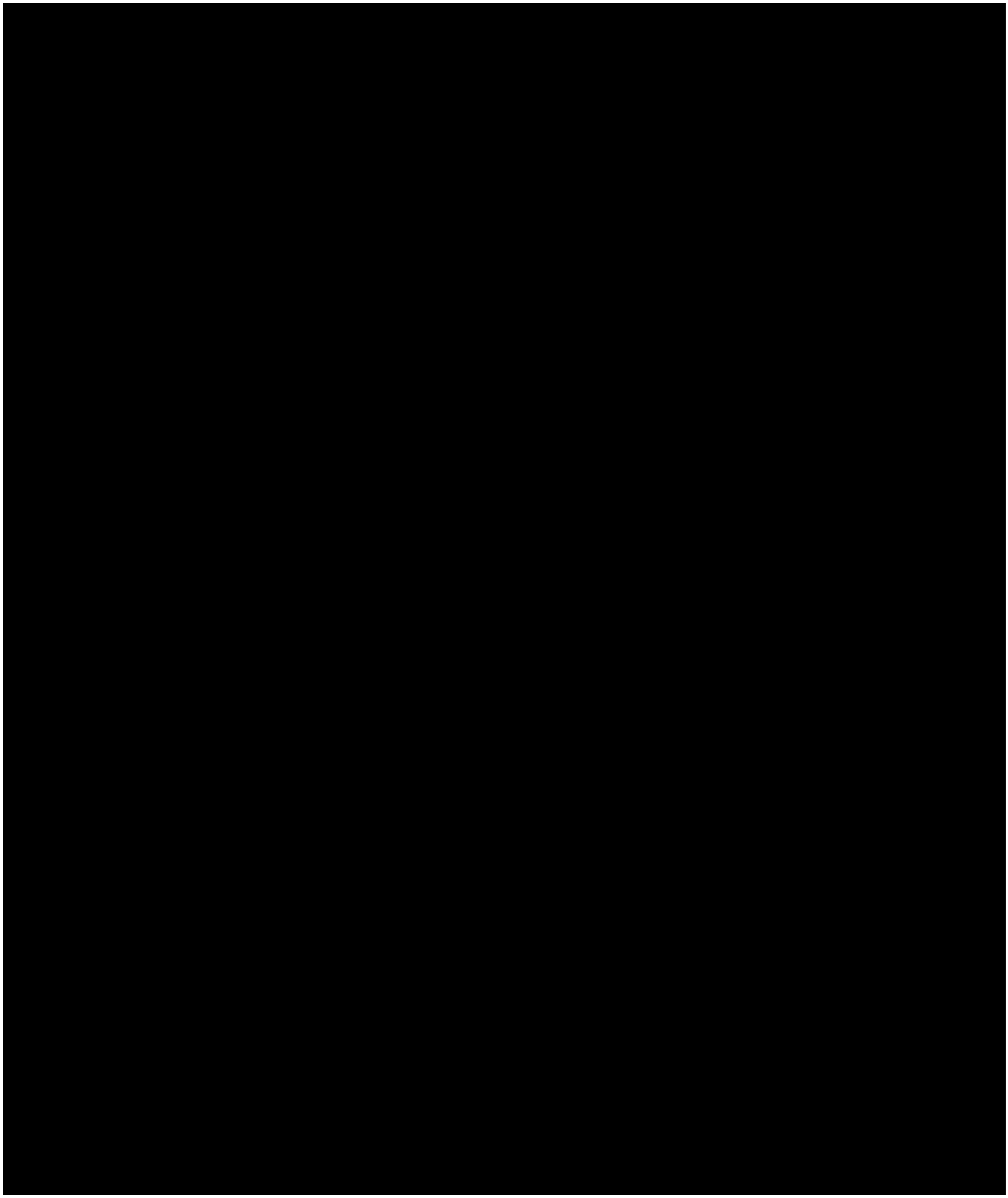
Pain intensity will be scored such that a score of 0 is equivalent to "no pain" and a score of 100 is equivalent to "pain as bad as it could be".

An electronic version of the VAS will be used in the electronic diary (Part 1) and paper version of the VAS will be used in the CRF for the Tapentadol Period (Part 2). The electronic version and the paper version of the VAS are both validated.

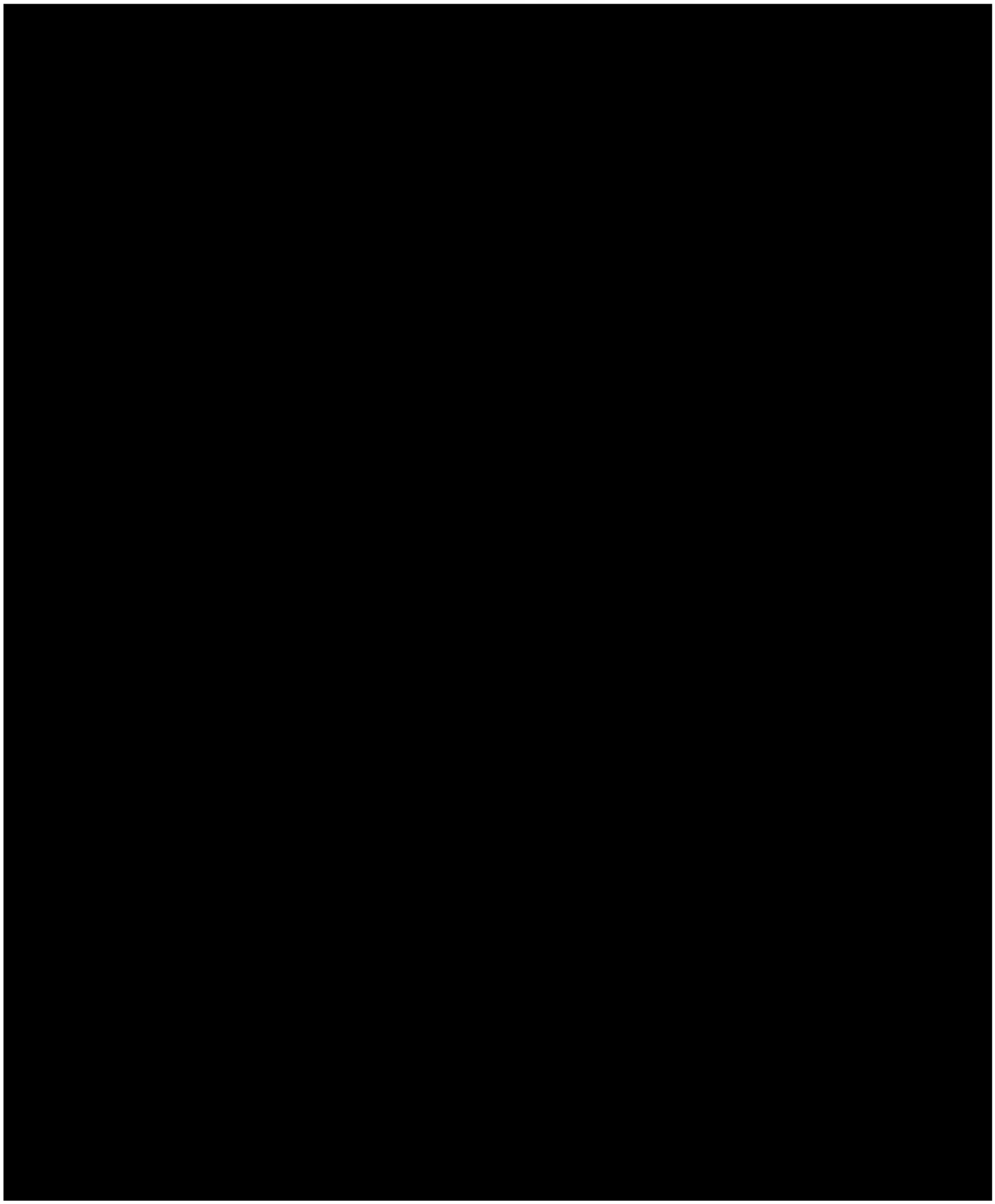
The subject will be instructed to make a mark on the line to indicate the pain intensity.

For the paper version, the line will be 100 mm in length. 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 millimeters from the bottom of the scale to the subject's mark using a standard ruler. This value will be recorded in the CRF.

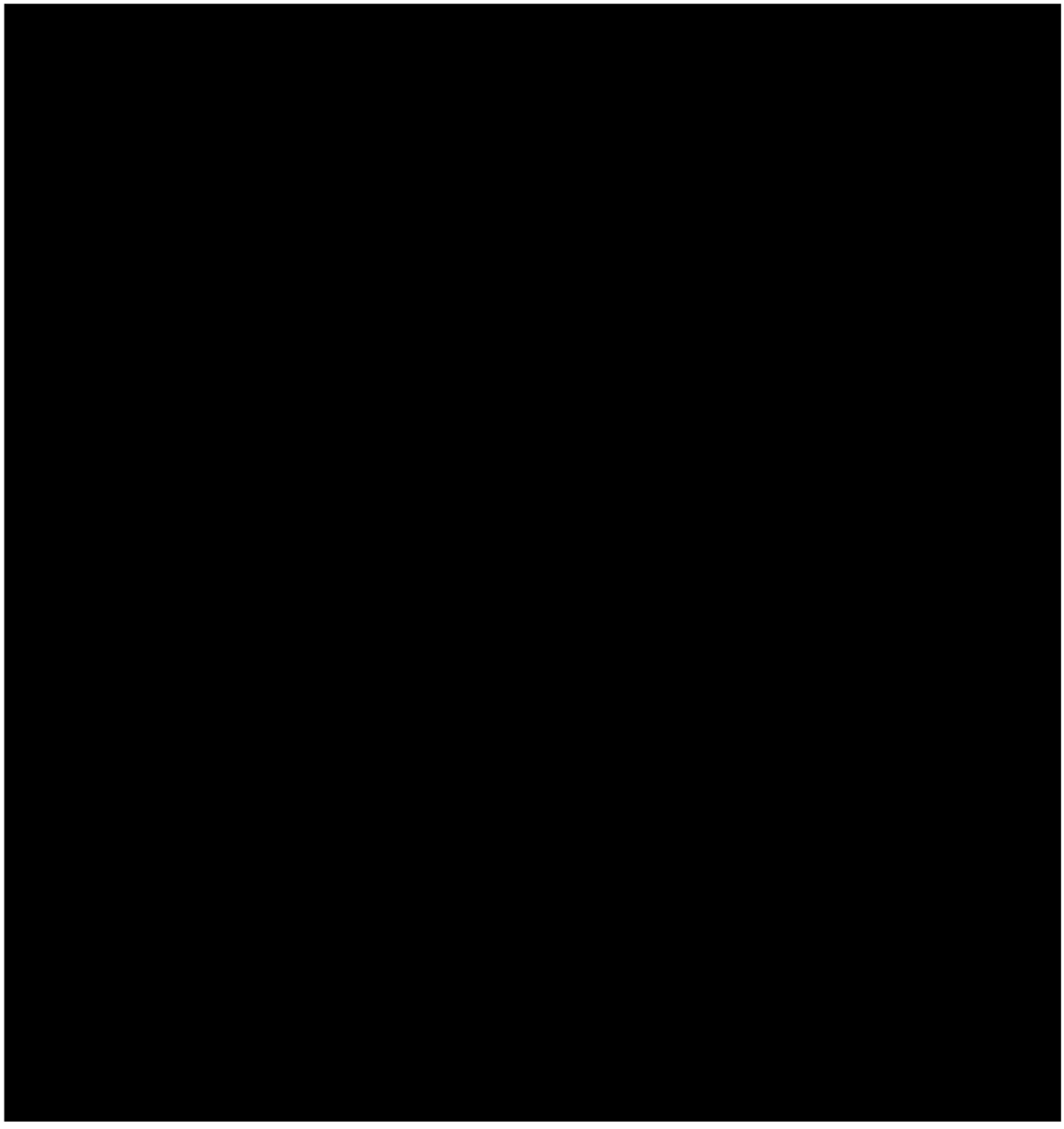
19.3 Faces Pain Scale – Revised



19.4 Modified constipation assessment scale



19.5 Subjective opiate withdrawal scale



19.6 Palatability and acceptability

Questions on palatability and acceptability

- How does the medication taste

really bad	bad	a bit bad/ a bit good	good	really good

- Swallowing the medication is

really difficult	difficult	a bit difficult/ a bit easy	easy	really easy

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

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

The detection of potential severe cases of drug-induced liver injury will be based on laboratory data from the central laboratory.

Check laboratory values at the times specified in the trial protocol for increases of alanine transaminase, aspartate transaminase, and total serum 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 serum 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 serum 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 laboratory tests as listed in Table 6.

Table 6: 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
Hemochromatosis	Ferritin or optionally genetic testing (e.g., in unclear cases)
Hepatocellular cancer	α –fetoprotein

IG = immune globulin; HB = hemoglobin; AG = antigen; RNA = ribonucleic acid; PCR = polymerase chain reaction; V = virus; ANA = anti-nuclear antibody; SMA = smooth muscle antibody; VCA = viral capsid antigen.

19.8 Collecting, handling, and shipment of pharmacokinetic serum samples

19.8.1 Labeling

The labels of the pharmacokinetic samples will be provided by the central laboratory and include at least the following information:

- Trial Number.
- Unique Subject Identifier.
- Accession Number.
- Visit Number.

19.8.2 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.

19.8.3 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 3 hours.
- 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.

19.8.4 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 (the address will be supplied in a separate document). 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.