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SDR-SAP-TRIAL-02

STATISTICAL ANALYSIS PLAN

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
Development phase:	Phase II/III
Investigational medicinal products:	Tapentadol prolonged release (PR) tablets Morphine PR tablets

Version	Date	DMS version number
Original	23 Oct 2014	1.0
Amendment 01	30 Aug 2017	2.0
Amendment 02	13 Feb 2018	3.0

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Trial Biostatistician

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2 ABBREVIATIONS

Abbreviation	Explanation
ADaM	Analysis Data Model
AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CIR	(Crude) Incidence rate
CL_{CR}	Creatinine clearance
DMS	Document management system
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EAIR	Exposure adjusted incidence rate
eCRF	Electronic case report form
FAS	Full Analysis Set
FPS-R	Faces Pain Scale–revised
IMP	Investigational medicinal product
ICTR	Integrated clinical trial report
IVRS/IWRS	Integrated voice/web response system
LLOQ	Lower limit of quantification
MAR	Missing at random
mCAS	Modified constipation assessment scale
MCMC	Markov chain Monte-Carlo
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Potentially clinically important
PPS	Per Protocol Set
PR	Prolonged release
PT	Preferred Term
SAF	Safety Set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOWS	Subject opiate withdrawal scale
SOC	System Organ Class

Abbreviation	Explanation
ULN	Upper limit normal
TEAE	Treatment emergent adverse event
VAS	Visual analog scale
WHO-DD	World Health Organization Drug Dictionary

Système International d'Unités units, vital signs and laboratory parameters are not included in this list.

3 INTRODUCTION

This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the trial KF5503-66 in accordance with the protocol Amendment 05 dated 27 July 2017. The analysis will be performed by a contract research organization in accordance with this SAP.

KF5503-66 consists of two parts, a 14-day Treatment Period comparing tapentadol Prolonged Release (PR) to morphine PR (Part 1), and a 12-month follow-up period to obtain the long-term safety profile with and without treatment of tapentadol PR (Part 2). The analyses of both parts of the trial are covered by this SAP.

4 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 investigational medicinal product (IMP).

5 TRIAL DESIGN

5.1 Overall trial design and plan

Only a brief synopsis of the trial design is presented here; full details can be found in the trial protocol.

Part 1

Part 1 starts with an Enrollment Visit (Visit V1; Day -14 to Day 1), followed by the 14-day Treatment Period. The Treatment Period will include the following visits:

- Visit V2 (Allocation Visit; Day 1).
- Visit V3 (Day 8 ± 1).
- Visit VE (Day 15 ± 1, End of Treatment Visit).

Subjects completing the Treatment Period with tapentadol PR or morphine PR and who have need for continued opioid treatment can enter the Tapentadol Period of Part 2.

Subjects not completing the Treatment Period, those who complete the Treatment Period but do not want to continue with tapentadol PR and subjects who discontinue the Tapentadol Period will enter the Observation Period of Part 2.

Part 2

Tapentadol Period

Subjects on morphine during Part 1, start tapentdol PR at 70% of the equivalent morphine dose. These subjects have 2 additional visits (M1, M2) at the beginning of the Tapentadol Period.

For all subjects in the Tapentadol Period, visits TP1-TP12 and F12M are performed, unless subjects switch to the Observation Period, in which case they perform Visit ET (Early Termination Visit).

Observation Period

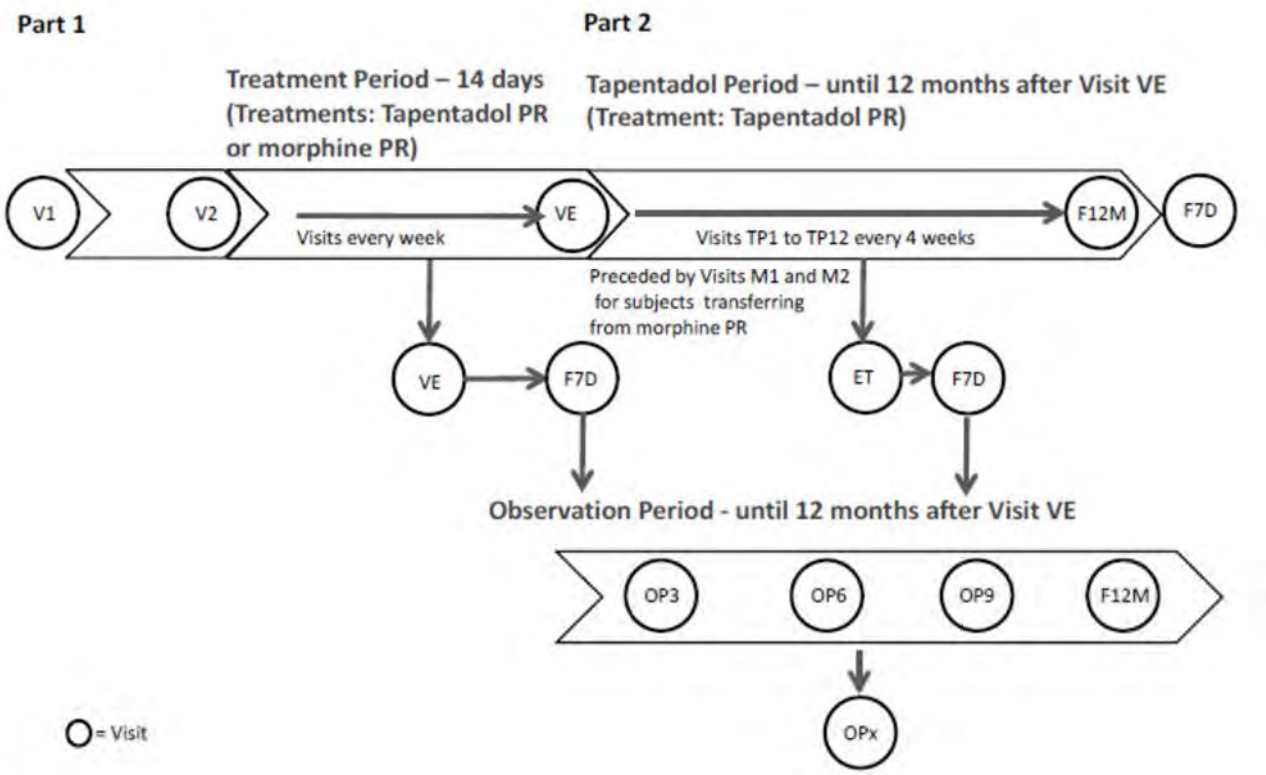
Scheduled visits in the Observation Period are every 3 months (OP3, OP6, OP9 and F12M), unless subjects stop participation in the trial at Visit OPx (unscheduled final visit).

Final post treatment visit

All subjects, who have received at least 1 dose of IMP will have a final post treatment visit (Visit F7D) 1 week after stopping IMP.

Details of the assessments performed during the Treatment, Observation and Tapentadol Period can be found in Section 11 of the trial protocol and schedules of events are given in Table 1, Table 2 and Table 3, respectively.

For a summary of the trial as a flow diagram, see Figure 1.



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.

Figure 1: Flow diagram of the trial

Table 1: Schedule of events – Treatment Period

Period	**Enrollment**	**Treatment Period**			
Visit	**V1**	**V2**	**V3**	**VE**	**F7D**
Day (range)	-14 to 1	1	8 (±1)	15 (±1)	
Obtain informed consent/assent	X				
Record demographic data	X				
Record age	X	X		X	
Record medical history	X				
Record pain history	X				
Record prior medication intake/therapies	X				
Record concomitant medication intake/therapies	X	X	X	X	X
Perform physical examination	X	X		X	X
Record height	X			X	
Record body weight	X	X	X	X	
Record vital signs	X	X	X	X	X
Record 12-lead ECG	X			X	
Take blood for central laboratory	X			X	
Take blood for local laboratory	X				
Perform urine pregnancy test		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	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) until Visit VE.					
2. To record intake of IMP and rescue medication, including time of administration.		X	X	X	
Check diary compliance			X	X	
Collect diary				X	
Record pain assessment in diary (VAS, FPS-R)		X			
Record “pain right now” in eCRF (VAS, FPS-R)				X	
Complete questionnaires					
- Modified constipation assessment scale		X	X	X	
- Subjective opiate withdrawal scale				X [a]	X [a]
- Acceptability and palatability of IMP			X	X	
Allocate subjects		X			
Collect returned IMP and rescue medication			X	X	
Perform drug accountability			X	X	

Period	Enrollment	Treatment Period			
Visit	**V1**	**V2**	**V3**	**VE**	**F7D**
Day (range)	-14 to 1	1	8 (±1)	15 (±1)	
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)		X	X	X	
Dispense rescue medication		X	X		
Discuss IMP titration/dose adjustment		X	X	X	
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	
Take blood sample for serum pharmacokinetics		X	X	X	
Dispense subject trial card	X				
Assess/record adverse events	X	X	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	
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

a) 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.

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

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.

Table 2: Schedule of Events - Observation Period

Period	**Observation Period**				
Visit	**OP3**	**OP6**	**OP9**	**OPx**	**F12M**
Month (range: ± 14 days)	3	6	9	(unscheduled)	12
Record concomitant medication intake/therapies	X	X	X	X	X
Perform physical examination				X	X
Record height				X	X
Record body weight				X	X
Record vital signs (respiratory rate, systolic and diastolic blood pressure, and pulse rate)				X	X
Complete modified constipation assessment scale questionnaire				X	X
Take blood for central laboratory (hematology, clinical chemistry)				X	X
Collect urine/perform dip stick urinalysis				X	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.

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.

Table 3: Schedule of Events - Tapentadol Period

Period			**Tapentadol Period**													
Visit	M1	M2	TP1	TP2	TP3	TP4	TP5	TP6	TP7	TP8	TP9	TP10	TP11	TP12	ET	F12 M	F7D
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	X	X
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																	
- Modified constipation assessment scale															X	X	
- Subjective opiate withdrawal scale															X	X	X
Record “pain right now” in eCRF (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					X			X			X			X	X	X	

Period			**Tapentadol Period**														
Visit	M1	M2	TP1	TP2	TP3	TP4	TP5	TP6	TP7	TP8	TP9	TP10	TP11	TP12	ET	F12 M	F7D
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)	
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			
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	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.

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.

5.2 Sample size

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 arms 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 (i.e., responder rate, see Section 13.1).

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 periodic reviews of the Data Monitoring Committee (DMC) (see Section 6.3) during the trial address only safety and no efficacy data and thus have no impact on the sample size.

5.3 Randomization

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

Randomization will be outsourced to a Central Randomization Center that will develop an Interactive Voice/Web Response System (IVRS/IWRS). The IVRS/IWRS will be used to assign a subject number at the Enrollment Visit as well as a randomization number and medication kit number at randomization.

Eligible subjects will be allocated in the ratio of 2:1 (tapentadol PR:morphine PR) 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 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.

6 OVERVIEW OF PLANNED ANALYSES

6.1 Final analyses

Final analysis Part 1

The final analysis of Part 1 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 (if not discontinued before),
- And all data of Part 1 and Part 2 up to Visit TP3/OP3 is cleaned.

Together with this final analysis of Part 1, an interim analysis of Part 2 will be conducted. This interim analysis will be based on all data of Part 2 (also including information after TP3/OP3) available in the database at the time point of completion of the cleaning for Part 1 and Part 2 up to Visit TP3/OP3.

For the final analysis of Part 1 and the interim analysis of Part 2, all data available in the database will be fixed in a snapshot. Individual subjects that have completed the entire trial and are clean will be locked.

The final analysis of Part 1 will encompass all analyses of Part 1 as described in this SAP. The interim analysis of Part 2 will encompass all Part 2 analyses planned according to this SAP.

An integrated clinical trial report, integrating clinical, pharmacokinetic, and statistical results of the final analysis of Part 1 and the interim analysis of Part 2 will be prepared by the sponsor.

Final analysis Part 2

The final analysis of Part 2 will be performed once all subjects have completed Part 2 of the trial and the final data base has been hard locked.

The final analysis of Part 2 will encompass all Part 2 analyses as described in this SAP.

A second integrated clinical trial report (optionally as an amendment) will be prepared including the final results of Part 2.

6.2 Interim analyses

As described in the previous section, an interim analysis of Part 2 will be performed.

6.3 Data Monitoring committee analyses

An independent DMC is overseeing and evaluating data from selected pediatric trials with tapentadol administration performed by Grünenthal, including KF5503-66. The purpose of the DMC is to perform an independent and objective review of generated safety data on a regular basis, and to provide recommendations about continuing or terminating the trials or modifying trial protocols or trial conduct. The members of the DMC are independent of Grünenthal and the contract research organization conducting the trial.

Details and operational aspects of the oversight by the DMC were given in a charter. DMS Version 1.0 of this charter was issued on the 06 May 2014 and thus before the first subject-in in this trial.

7 DOCUMENT AND CHANGE HISTORY

7.1 Changes in analysis compared to the trial protocol

Not applicable.

7.2 SAP amendment rationale

7.2.1 Amendment 02

Amendment 02 to the final SAP was prepared to add a few additional analyses and refine some definitions and programming specifications:

1. Additional analyses:
   - Analysis for the time to discontinuation from treatment due to "no more need for opioid treatment" during the Tapentadol Period was added, as this is one of the main reasons for discontinuation of treatment of Part 2.
   - Summary statistics for the underlying diagnosis/reason for the pain leading to enrollment of the subjects in the trial.
   - For all subjects, irrespective of age, one analysis of the primary endpoint based on VAS and one analysis based on FPS-R.
   - Subgroup analyses of the primary endpoint for subjects with and without a neuropathic pain component to assess the effect of treatment depending on the type of the underlying pain.
   - Overview of the individual response criteria to get a complete picture of reasons for subjects being responder or non-responder.
2. Programming specifications:
   - Additional specifications to handle missing data were added:
     - If the time of the first IMP intake is missing, it will be imputed (by 0:00 in case of morning intake or 12:00 in case of evening intake) to derive the time from first IMP intake to first rescue medication intake.
     - In case of a missing intermediate visit during the Tapentadol Period, the visit date will be imputed to derive the average daily dose for the time frame between two scheduled consecutive visits.
     - In case of missing baseline pain intensity for the Tapentadol Period in the eCRF, the last available pain intensity value from the Treatment Period provided in the eDiary will be used as baseline.
     - Missing baseline pain intensities for the Treatment Period will be imputed using the multiple imputation that is used to impute the missing pain intensity values during the last 3 days of treatment.
   - Consideration of deviations from the protocol with respect to the time point of visits in relation to IMP intakes:

  - Protocol Amendment 02 specifies that subjects should receive their first IMP intake within 24 hours after randomization and that Day 1 is defined as the day of first IMP intake. Therefore, the definition of Day 1 of the trial in the SAP was updated accordingly to ensure clarity and consistency in the specification of Day 1. For the definition of the treatment completers, this redefined Day 1 of the trial will be considered.
  - As time to discontinuation refers to discontinuation from *treatment*, it was specified that the dates of first and last IMP intakes should be used for the respective calculations rather than the dates of the scheduled visits.
  - The protocol specifies that subjects should have taken their last IMP of the Treatment Period on the day of VE or the evening before. In reality; this intake might have occurred earlier, in particular for subjects that discontinued treatment. For the derivation of the primary endpoint, it was therefore specified that the last 3 days of treatment should be considered for pain assessment rather than the last 3 days prior to VE.
- The options of the multiple imputation were specified more clearly, covering how the imputation by treatment group should be done, which variables to be included in the model and how to handle the different pain scales and the ranges of their respective scores.
- The prior distribution for the precision of the random effects used in the Bayesian analysis of the primary endpoint was redefined based on the expert recommendation provided in the literature (Gelman 2016).
- The factor for the morphine PR equivalent of tapentadol PR that has to be used for some calculations was added.
- A specification of days to be considered for the SOWS (Day 0 = day of last IMP) was added, as deviating from trial day definition.
- For the Z-score related to *weight* and *height*, a rule to derive the age in months based on the available information in years was provided as required for the calculation.

7.2.2 Amendment 01

Amendment 01 to the final SAP was prepared to cover the following topics:

- Changes arising from protocol Amendment 02 dated 23 June 2015 and protocol Amendment 04 dated 23 May 2017 were implemented, including the following major changes:
  - The update of the alpha for the primary endpoint analysis based on the methodology proposed by Hlavin et al. (2016) with the consequence of sample size reduction and use of 80% confidence interval for the primary endpoint analysis.
  - The deletion of the interim analysis for the sample size reassessment due to the sample size reduction. The adaptive 2-stage design of the trial has been simplified to a fixed 1-stage design.
  - The rescheduling of the final analysis of Part 1 such that it will be performed after all subjects have completed the first 12 weeks (Visit TP3 or Visit OP3) of Part 2 and the introduction of an interim analysis of Part 2 at this time point as required by PDCO.
- Further analyses required for public disclosure were added.

- Analyses of the time to trial discontinuation were removed due to the specific trial design. Subjects who discontinue treatment can continue the trial in the Observation Period, which led to a much lower number of trial discontinuations. The time to treatment discontinuation will be investigated.
- Applicable contentwise adaptions according to the actual standard SAP template (SDR-SAP-TRIAL-07) were implemented. Major adaptions are:
  - Type of information to be provided for time to event variables has been updated.
  - Concomitant medication and therapy taken during IMP administration will be flagged and summarized rather than those started after last dose of IMP.
  - Implementation of additional general programming specifications.
  - Use of category "high and low" for laboratory, vital signs and ECG parameters instead of "worst" for overall post-baseline assessment.
- Subgroup analyses prespecified in the previous SAP but not in the protocol were deleted due to the reduced overall sample size.
- Some definitions were further specified to avoid room for interpretation and to cover special cases. Those cover in particular:
  - On-treatment-period for Part 1 and Part 2.
  - Treatment completers and trial completers.
  - Determination of modal dose of IMP.
  - Clearer specification of pain intensity values during the last 3 days of the Treatment Period.
  - Specification of the dose level of IMP during the last 3 days of the Treatment Period.
  - Specification of categories to be used to summarized rescue medication.
  - Specification of the type of graphical displays to be produced for concentration data of tapentadol and tapentadol-O-glucuronide.
  - Specification of "daily average" pain values.
  - Specification of first and last IMP intake.
- Interpretation of the "baseline pain intensity" definition has been broadened based on the change in protocol Amendment 02 that the "first dose of IMP will be taken during Visit V2, within 24 hours after randomization". Due to this update, the first IMP intake does not necessarily take place on the same calendar day as the randomization (day of V2), but might be the day thereafter. Furthermore, although baseline pain ideally should be assessed before the medication is started, in practice, the first eDiary might be completed only after the first IMP was taken. Therefore:
  1. The last pain intensity value recorded in the eDiary before starting IMP will be considered as baseline pain, which can also be part of an eDiary after the day of V2.
  2. If the first available eDiary entry corresponds to the time point (day and time of the day [morning/evening]) of the first IMP intake, but states that the IMP was already taken, this pain intensity value will nevertheless be used as baseline pain intensity.

The latter is acceptable, as this can be considered as a conservative approach as baseline values will more likely decrease rather than increase after first IMP intake and therefore changes from baseline will more likely become smaller.

- Sensitivity analyses of the primary endpoint were added:
  - Excluding CRPS patients: This additional analysis was planned based on concerns of the DMC chairperson that CRPS patients do not have an appropriate medical indication for inclusion in the trial, as chronic opiate therapy in patients with CRPS is controversial and might be contraindicated.
  - Discarding baseline pain intensity as an explanatory variable in the logistic regression model: As the prerequisites for the measured baseline pain intensity values are highly different between the subjects due to the allowed intake of weak and strong opioid until the day of allocation to IMP (including) and due to the possibility of the first IMP intake before the baseline pain intensity assessment, the robustness of the primary endpoint results without consideration of baseline pain in the model will be evaluated.
  - Adding dose level of IMP during the last 3 days of the Treatment Period as an explanatory variable in the logistic regression model: As a flexible dosing of subjects within different pre-specified weight-depending dose levels is possible, the robustness of the primary endpoint results with consideration of the individual dose level in the model will be evaluated.
- Analysis of exposure adjusted incidence rates was limited to TEAEs of the Tapentadol Period:
  - Due to the short treatment duration of 14-days only and very low rate of discontinuations during the Treatment Period
  - And as AEs assigned to the Observation Period are not considered treatment-emergent.

  Furthermore, the presentation of confidence intervals for the difference in incidence rates was discarded due to the reduced sample size and the following limited value of information.
- A summary of the height Z-Scores was added to Part 2. Converting heights to Z-score allows for a comparison of heights across ages and sexes and therefore better evaluation over time.
- Description of the multiple imputation approach was improved to provide clearer programming instructions.

Some further minor adaptations (e.g. adding further details or clarifications to individual analyses, rewordings) and minor editorial changes (e.g., the correction of typing errors or format changes) are not specified here.

8 ANALYSIS CONVENTIONS

8.1 General principles

Analysis structure

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. For Part 1, all presentations will be done per treatment arm, i.e., comparing the tapentadol arm to the morphine arm.

The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2. Given that the different periods, i.e., Tapentadol Period and Observation Period, are not comparable, due to the heterogeneity of the populations (see Section 18.1.3 for additional information), all analyses of Part 2 will be illustrated separately for the Tapentadol and Observation Period as detailed below, if not specified differently.

For the Tapentadol Period, all statistical analyses will be presented by the following arms:

- Subjects in the Tapentadol Period pretreated with morphine during Part 1.
- Subjects in the Tapentadol Period pretreated with tapentadol during Part 1.
- All subjects in the Tapentadol Period.

For the Observation Period, all statistical analyses will be presented by the following arms:

- Subjects pretreated with morphine during Part 1 and continuing the trial in the Observation Period directly after Part 1.
- Subjects pretreated with tapentadol during Part 1 and continuing the trial in the Observation Period directly after Part 1.
- All subjects continuing the trial in the Observation Period directly after Part 1.
- Subjects discontinuing the Tapentadol Period before F12M and continuing the trial in the Observation Period.

Unless otherwise specified, descriptive summaries will be provided for each time point and for the change from baseline (defined in Section 8.2.2) to each time point. Additionally, for Part 2, the last assessment (defined in Section 8.2.2) and change from baseline to the last assessment will be summarized.

Data presented in subject data listings will be sorted by treatment if not specified differently.

Unscheduled measurements of laboratory parameters, vital signs and electrocardiogram will be presented in the subject data listing. In general, unscheduled measurements will not be included in the analysis. However, they will be considered in the derivation of the overall post-baseline value (see Section 18.1.12.1) that is used in the shift and alert frequency analyses.

Details on the programmatic derivation of the trial periods can be found in Section 18.1.2.10.

Summary statistics

Data collected in this trial will be summarized according to their nature as follows:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation (SD), minimum and maximum values, median and quartiles. If there are less than 5 observations descriptive statistics will be presented based on the rules specified in Section 18.1.2.2.
- Categorical variables: absolute and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects in the trial at the respective time point in the analyzed population.

- Time-to-event variables: Kaplan-Meier estimates together with the 95% confidence intervals (CI) will be provided with the respective number at risk and the number censored at the relevant time points. In addition, the median time-to-event and its 95% confidence interval for all arms will be presented. For calculating the survival estimate CI bounds, the log-log transformed estimate of CI bounds will be used. Censoring mechanisms depend on the specific endpoint and will be described in the respective section.

Details on rounding and presentation in case of missing data can be found in Section 18.1.2.

Coding of eCRF-entries

All Medication and additional therapies/treatments will be coded using the World Health Organization Drug Dictionary (WHO-DD) or in case of non-medicinal therapies via Medical Dictionary for Regulatory Activities (MedDRA). The versions of these reference documents will be specified on the appropriate statistical outputs.

All investigator-reported terms for medical history in the electronic case report form (eCRF) and all original terms used by the investigators in the eCRFs to identify adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For the final analyses, the latest version of the WHO-DD/MedDRA at the time of coding for final evaluations will be used. These might be different for the final analyses of Part 1 and the final analysis of Part 2. Coding for the DMC analyses is addressed in the DMC SAP.

8.2 Definitions

8.2.1 Definition of subgroup

For some parameters, statistical analyses will also be presented for the following subgroups:

- Age groups:
  - 6 years to less than 12 years.
  - 12 years to less than 18 years.

  Age groups are determined using the age assessment at Visit V2 for both parts. In case of discrepancies between the IVRS/IWRS recording and the eCRF for age, the entry in the eCRF will be used for all analyses unless explicitly stated otherwise.
- Underlying pain condition (based on information from the eCRF at Visit V1)
  - Cancer related pain.
  - Non-cancer related pain.

Table 4: Subgroup analysis

	Age group	**Underlying pain condition**
Subject disposition	Enrolled Set	Enrolled Set
Demographics + other baseline characteristics (excluding medical history and prior and concomitant medication)	SAF	SAF
Descriptive statistics of primary efficacy endpoint	FAS	FAS
Exploratory statistical analysis and forest plots of primary efficacy endpoint as described in Section 13.1.3	FAS	FAS
Pain assessments	FAS	FAS
Acceptability and palatability questionnaire	FAS	-
Rescue medication	FAS	-
Serum concentrations of tapentadol and tapentadol-O-glucuronide	PK-Set	PK-Set
Incidence of TEAEs by SOC and PT (selected analyses)	SAF	SAF

8.2.2 Further definitions

Term	Part/Period	Definition
Pre-treatment-period	-	Before first IMP administration (excluded)
Therapeutic reach	-	The therapeutic reach is the time after the last IMP intake that a subject is still considered to be potentially affected by a study drug. For tapentadol PR and morphine PR, the therapeutic reach is defined as 72 hours after (last) IMP intake.
On-treatment-period	Part 1	• Subjects continuing in the Tapentadol Period after the Treatment Period: a. Start: First IMP administration of Part 1 (included) b. End: i. If the last administration of IMP during Part 1 is more than 3 days before Visit VE: Last administration of IMP during Part 1 + 72 hours (included, therapeutic reach) ii. If the last administration of IMP during Part 1 is less than 3 days before Visit VE: Visit VE (included) • Subjects not continuing in the Tapentadol Period after the Treatment Period: c. Start: First IMP administration (included) d. End: Last administration of IMP during Part 1 + 72 hours (included)
	Part 2	Tapentadol Period only: a. Start: Visit VE (excluded in case VE is included in the on-treatment period of Part 1; included in case VE is not included in the on-treatment period of Part 1) b. End: Last administration of IMP during the Tapentadol Period + 72 hours (included)
Post-treatment-period	-	After last IMP administration drug intake + 72 hours (excluded)
Enrolled subjects	-	Informed consent form signed. If required by local law an assent form signed.
Treated subjects	-	Subjects with at least 1 administration of IMP.
Treatment completers	Part 1	Subjects who have completed the 14-day Treatment Period. Completion of the 14-day Treatment Period means that a subject performs the End of Treatment Visit (Visit VE) in the allowed window of 15 ± 1 days, i.e., at or later than Day 14, and has the last IMP intake of part 1 no earlier than Day 13 in the evening.
	Part 2	Subjects who have completed the 12-month Tapentadol Period. Completion of the 12-month Tapentadol Period means that a subject. performs the 12-month follow-up visit (F12M) in the window of 365 ± 14 days, i.e., at or later than 351 days after Visit VE, as part of the Tapentadol Period.
Trial completers	Part 1	Subjects who have completed the 14-day Treatment Period and who performed Visit F7D or entered the Tapentadol Period of Part 2.
	Part 2	Subjects who fully completed the extension period, i.e., either subjects completing the Tapentadol Period and the follow-up visit (F12M and F7D) or subjects completing the Observation Period (F12M) not earlier than 351 days

Term	Part/Period	Definition
		after Visit VE.
Baseline values	Treatment Period	• Baseline measurements are defined as the last evaluation performed before starting IMP (i.e., Visit V1, Visit V2 or unscheduled visit). • For pain assessment, 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. Details on the programming aspects regarding the baseline pain intensity can be found in Section 18.1.5.3.
	Tapentadol Period:	Baseline measurements are defined as the last evaluation performed before or at Visit VE
	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
Last assessment	Treatment Period	Assessment at Visit VE. Performed for all subjects completing Part 1 or discontinuing IMP early.
	Tapentadol Period	• Assessment at Visit F12M for subjects completing the Tapentadol Period. • Assessment at Visit ET for subjects discontinuing the Tapentadol Period prior to 12 months after Visit VE.
	Observation Period	• Assessment at Visit F12M for subjects completing the Observation Period 12 month after Visit VE. • Assessment at Visit OPx for subjects discontinuing the Observation Period prior to 12 month after Visit VE.

9 SUBJECT POPULATIONS

9.1 Enrolled Set

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.

9.2 Allocated Set

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

Analysis of the Allocated Set will be conducted according to the allocated treatment.

9.3 Safety Set

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

The analysis on the SAF will be conducted on the actual treatment received.

9.4 Full Analysis Set

The Full Analysis Set includes all allocated and treated subjects, i.e., all allocated subjects who were administered any amount of IMP.

The FAS is the primary analysis set, i.e., the analysis set used for the conduct of the primary analysis of this trial.

The analysis on the FAS will be conducted according to the allocated treatment.

9.5 Per Protocol Set

The Per Protocol Set defines a subset of the subjects in the Full Analysis Set without any major protocol deviation affecting the primary endpoint. As the Per Protocol Set is only relevant for analyses during Part 1, no protocol deviation during Part 2 yields to exclusion from the Per Protocol Set.

The impact of a deviation on the efficacy assessment will be assessed by the sponsor during clinical review on a case by case basis prior to database lock. The decision will be documented in the final statistical review.

The analysis on the PPS will be conducted according to the allocated treatment.

9.6 Pharmacokinetic Analysis Set (PK-Set)

All subjects who have quantifiable serum concentrations (i.e., serum concentrations above the lower limit of quantification) 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.

9.7 Application of analysis sets

Table 5 shows the use of analysis sets in different analyses.

As SAF and FAS are expected to be identical, the analysis of demographics and baseline characteristics, including medical history and prior and concomitant medication, will only be presented for the SAF. In case of differences resulting in a need for an additional presentation for the FAS, the analysis will be provided as an additional analysis.

Demographics and other baseline characteristics are planned for SAF in PK Set. In case these two analysis sets coincide, presentations will only be prepared for the SAF.

Table 5: Use of analysis sets

	Enrolled Set	Allocated Set	SAF	FAS	PPS	PK Set
Subject disposition	X	X	X	X	X	X
Subject discontinuations			X			
Protocol deviations			X			
Demographics	X		X			X
Other baseline characteristics			X			X
Subject medical history			X			
Previous and concomitant medication			X			
Exposure			X			
Compliance				X		
Serum concentrations and pharmacokinetics						X
Primary endpoint				X	X	
Other efficacy endpoints				X		
Secondary safety endpoints			X			
Other safety parameter			X			

10 DISPOSITION

Details on the programming aspects regarding disposition can be found in Section 18.1.4.

10.1 Subject disposition

All presentations for subject disposition will be as described in Section 8.1. For all Periods, descriptive summaries will also be presented overall.

For describing the subject disposition, the following populations will be summarized for each of the three different trial periods if applicable:

- Subjects enrolled (only overall for Treatment Period).
- Subjects enrolled but not allocated and reason for non-allocation (only overall for Treatment Period).
- Subjects allocated (Treatment Period only).
- Subjects allocated but not treated and reason for not being treated (Treatment Period only).
- SAF.
- FAS.
- PPS (Treatment Period only).
- PK-Set (Treatment Period only).
- Trial completers.
- Treatment completers (not applicable for Observation Period).

- Subjects allocated and discontinued the trial.
- Subjects allocated and discontinued IMP (not applicable for Observation Period).
- Subjects who discontinued Tapentadol Period and entered Observation Period (Tapentadol Period only).

For subjects enrolled, subjects enrolled but not allocated and for the reasons for not being allocated, the percentage denominator will be the number of enrolled subjects. For all other calculations, the percentage denominator will be the number of allocated subjects.

For the Tapentadol and Observation Period, the information will be presented based on the subjects in the SAF entering these periods. The percentage denominator will be the corresponding number of subjects in the SAF.

In addition, subject disposition will be presented for the subgroups as specified in Table 4.

Furthermore, an overview table will be prepared presenting the number of subjects enrolled, allocated, allocated and treated, in the SAF, in the FAS and the PK-Set per country. Percentage calculation will be done in 2 ways:

- Denominator will be the number of all allocated subjects.
- Denominator will be the number of allocated subjects in the respective country.

Reasons for exclusion from the analysis populations will be summarized. The percentage denominator will be the number of subjects allocated.

10.2 Subject discontinuations

Part 1

Discontinuations from the trial and from IMP will be presented for the SAF overall, per country and per site.

Reasons for discontinuations from the trial and from IMP will be presented for

- Subjects discontinued from the trial.
- Subjects discontinued from IMP.

Percentage denominator will be the number of subjects discontinuing in the respective arm.

Part 2

Discontinuations from the trial will be shown for all subjects entering part 2. Discontinuation from IMP will be presented for all subjects entering the Tapentadol Period. Presentation will be done overall, per country and per site.

Reasons for discontinuations from the trial and from IMP will be presented for:

- Subjects entering Part 2 and discontinued the trial.
- Subjects entering the tapentadol period of Part 2 and discontinued IMP.

Percentage denominator will be the number of subjects discontinuing in the respective arm.

Part 1 and Part 2

The details for “other reasons” will be presented in a listing sorted by site and treatment, if applicable.

If more than 10% of subjects in the SAF per treatment group of Part 1 discontinue the IMP in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period respectively, the distribution of the time to discontinuation from IMP will be summarized using time-to-event methods. Time will be in days until discontinuation for Part 1 and in weeks until discontinuation for the Tapentadol Period. For the Tapentadol Period, a graphical display using Kaplan-Meier methods displaying subjects at risk per time-point will also be produced.

The calculation of time to IMP discontinuation and the censoring algorithm are described in Section 18.1.4.1.

If more than 10% of subjects in the SAF per treatment group of Part 1 discontinue the IMP in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period due to lack of efficacy, the time to discontinuation due to lack of efficacy will be calculated and evaluated as described above only for subjects who discontinued due to lack of efficacy. Additionally to the censoring algorithm described in Section 18.1.4.1, subjects who discontinue IMP for reasons other than lack of efficacy will be censored at the time of discontinuation.

If more than 10% of the subjects in the SAF per treatment group of Part 1 discontinue IMP in the Treatment Period or if more than 10% of the subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period due to an adverse event (AE), time to discontinuation due to AEs will be calculated and evaluated as described above only for subjects who discontinued due to AEs. Additionally to the censoring algorithm described in Section 18.1.4.1, subjects who discontinue the IMP for reasons other than AE will be censored at the time of discontinuation.

If more than 10% of subjects in the SAF per treatment group of Part 1 discontinue IMP in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period due to no more need for opioid treatment, the time to discontinuation due to no more need for opioid treatment will be calculated and evaluated as described above. Additionally to the censoring algorithm described in Section 18.1.4.1, subjects who discontinue IMP for other reasons will be censored at the time of discontinuation.

All discontinuation data will be presented in a subject data listing sorted by site and treatment.

10.3 Protocol deviations

Major protocol deviations will be summarized, overall and by site, based on the SAF and will be grouped into different categories such as:

- Violation of inclusion/exclusion criteria.
- Time schedule deviations.
- Non-compliance regarding intake of IMP/rescue medication.
- Inappropriate intake of concomitant medication.
- Missing essential data.
- Subject not discontinued as per protocol.
- Other non-compliance.

Major protocol deviations will be presented in a subject data listing sorted by site and treatment.

11 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

No statistical tests for comparison of demographic and baseline data between treatment arms will be performed.

Subject demographics and baseline characteristics will be summarized descriptively as described in Section 8.1. For Part 1 and Observation Period Part 2, in addition to the presentation by the arms as specified in Section 8.1, descriptive summaries will also be presented overall.

Subject demographics will also be presented for the enrolled set (Part 1); presentation will be without treatment group but only for overall.

Furthermore, the subgroups as given in Table 4 will be displayed for subject demographics and other baseline characteristics, excluding medical history and prior and concomitant medication.Details on the programming aspects regarding demographics and other baseline characteristics can be found in Section 18.1.4.

11.1 Subject demographics

Subjects demographics are age [years], body mass index (BMI) [kg/m²], sex, race, ethnicity and age group. Age groups will be 6-<12 years and 12-<18 years.

Weight and height will be collected several times during the trial and will be analyzed separately as safety parameters. The assessments of height and weight at the Enrollment Visit (Visit 1) will be used for the calculation of the BMI. For completeness, baseline values of height and weight are tabulated with subject demographics as well.

Age will be collected at visit V1, V2 and VE.

- Age at Visit V2 will be used for subject demographics of both parts.

Date of signing the informed consent/assent form will be included in the subject data listings only.

11.2 Other baseline characteristics

For parameters collected on more than one occasion during the trial including baseline, the assessment at Baseline Visit will be presented with assessments collected later on and earlier in the trial and not separately for baseline. These parameters are

- 12-lead Electrocardiogram (ECG).
- Laboratory parameters.
- Vital signs.
- Dip stick urinalysis.
- Modified constipation assessment scale (mCAS).
- Physical examination.

As a parameter of special interest, baseline pain will be reported together with the assessments collected later on and earlier and in addition as baseline characteristics.

Further baseline characteristics to be presented are:

- Pain cause (cancer-related pain, non-cancer-related pain)

- Type of pain (neuropathic, nociceptive/somatic, nociceptive/visceral and all possible combinations)
- Baseline pain intensity, pain cause and type of pain will be summarized descriptively.

The results of urine test for drugs of abuse, will be included in the subject data listings only.

11.3 Subject medical history

The assessment of a disease as prior or concomitant is done by the investigator and will be evaluated as documented on the relevant medical history page of the eCRF.

Medical history will be summarized and sorted alphabetically, separately for prior and concomitant diseases, by primary System Organ Class and Preferred Term coded via MedDRA. The number and percentage of subjects with at least one disease will be displayed for each System Organ Class and Preferred Term.

The underlying diagnosis/reason for the pain leading to enrollment of subjects in the trial will be summarized descriptively by primary System Organ Class and Preferred Term in a separate presentation, coded via MedDRA and sorted alphabetically.

11.4 Prior and concomitant medication or therapy

Therapies will only be displayed in the subject data listings.

Prior and concomitant medication is collected in the eCRF as per enrollment. For the analysis, the following algorithms will be used to define prior and concomitant medication:

Part 1

- Prior is all medication stopped prior to the first dose of IMP, regardless of its start date.
- Concomitant is any medication not stopped before the first dose of IMP, but with start date not after the End of Treatment Visit of the Treatment Period (Visit VE).
- Medication starting after the End of Treatment Visit of the Treatment Period (Visit VE) will not be assigned to Part 1, but Part 2.

Part 2

For all presentations, except displaying prior and concomitant medication for subjects in the Observation Period that have switched from the Tapentadol Period to the Observation Period:

- Prior is all medication stopped prior to or at the End of Treatment Visit of the Treatment Period (Visit VE), regardless of its start date.
- Concomitant is any medication not stopped before or at the End of Treatment Visit of the Treatment Period (Visit VE) and, for subjects discontinuing treatment early in the Tapentadol Period, with start date not after Visit ET.

For presenting prior and concomitant medication for subjects in the Observation Period that have switched from the Tapentadol Period to the Observation Period:

- Prior is all medication stopped prior to or at the Early Termination Visit (Visit ET) regardless of its start date.
- Concomitant is any medication not stopped before or at Visit ET, regardless of its start date.

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup). For each medication the number of subjects will be displayed. In addition the number of subjects with medication taken during IMP administration for the Treatment and Tapentadol Period (flag definition see Section 18.1.5.5) will be displayed.

Medication or therapy taken during IMP administration for the Treatment Period of Part 1 as well as medication or therapy taken during IMP administration for the Tapentadol Period of Part 2 will be flagged in the subject data listing.

Handling incomplete dates is described in Section 18.1.5.5.

12 EXPOSURE AND COMPLIANCE

12.1 Exposure

IMP intake is assessed in the eDiary as well as the drug accountability page of the eCRF. Unless specified differently, analyses described below will be based on data collected in the eDiary.

Part 1

The daily doses of IMP per kg body weight will be determined for each subject and summarized descriptively for each calendar day of the Treatment Period.

A graphical illustration will illustrate the means and 95% confidence intervals of the daily doses of IMP per kg body weight (Tapentadol equivalents; 1 mg morphine PR is equivalent to 2.5 mg tapentadol PR) of each day separately for the two treatment arms.

The duration of exposure will be summarized descriptively. Duration of exposure of Part 1 is defined as:

Date of last IMP administration in Part 1 – Date of first IMP intake +1

Furthermore, the overall average daily dose per kg body weight will be determined for each subject and summarized descriptively. This analysis will be based on data assessed via drug accountability collected in the eCRF.

Part 2

Exposure to IMP is only assessed during the Tapentadol Period and analyses of exposure of Part 2 will only be presented for the Tapentadol Period.

The average daily doses and modal (i.e., most frequent) doses of IMP per kg body weight will be determined for each four-week interval between two visits (excluding visits M1 and M2) and summarized descriptively per interval. In case of more than one modal dose value for an interval, the average of those will be considered.

For a detailed definition of the time intervals and how to handle subjects terminating the Tapentadol Period in between two scheduled visits, see Section 18.1.6.

A graphical illustration will illustrate the means and 95% confidence intervals of the average daily doses of IMP of each interval for the two arms of differently pretreated subjects.

The duration of exposure will be summarized descriptively. Duration of exposure of Part 2 is defined as

Date of last IMP administration in Part 2 – Date of first IMP intake in Part 2 +1

Furthermore the overall average daily dose per kg body weight will be determined for each subject between visit VE and visit ET/F12M and summarized descriptively. This analysis will be based on data assessed via drug accountability collected in the eCRF.

12.2 Compliance

Compliance to the IMP dose regimen (%) is defined as the amount of IMP actually taken by a subject divided by the expected IMP amount the subject should have taken in the respective period and multiplied by 100. The information will be taken from the drug accountability pages and the "Initial Dose/Dose Adjustment"-pages of the eCRF. An algorithm for the calculation of actual and expected IMP amount is given in Section 18.1.7.

Compliance will be presented for both parts separately using the following categories: <80%, 80-<95%, 95-105%, >105-120%, >120%.

For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be presented overall. For Part 2, compliance will only be presented for the Tapentadol Period.

13 EFFICACY ANALYSES

13.1 Primary endpoint

The primary efficacy endpoint and its analyses only involve Part 1 of the trial.

The primary efficacy 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. A definition is given in Section 8.2.2.
- One of the following calculated from the scheduled pain assessments ("pain right now") is documented during the last 3 days of treatment in 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.

Pain assessments during the last 3 days of treatment in the Treatment Period means the last six scheduled pain assessments up to the time point of last IMP intake of the Treatment Period whether these fall across 3 (morning assessment 2 days before last IMP intake until evening assessment at the day of last IMP intake given last IMP taken in the evening) or 4 calendar days (evening assessment 3 days before last IMP intake until morning assessment at the day of last IMP intake given last IMP taken in the morning).

Summary statistics for the primary efficacy endpoint for the FAS and PPS will be provided.

13.1.1 Main analysis

The FAS will be the primary analysis set.

Let p_T, p_C be defined as

p_T : expected value of the responder rate in the tapentadol arm

p_C : expected value of the responder rate in the morphine arm

Let the non-inferiority margin be $\delta = 0.2$.

The primary null hypothesis to be tested in this trial is that treatment with tapentadol is inferior to treatment with morphine, i.e.,

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

The alternative hypothesis is that treatment with tapentadol is non-inferior to treatment with morphine, i.e.,

$$H_1: p_T - p_C > -\delta$$

Maximum-Likelihood estimates $\hat{p}_T$, $\hat{p}_C$ for p_T, p_C will be obtained fitting a logistic regression model to the response using baseline pain intensity, age group, treatment and underlying pain condition as explanatory variables.

The method introduced by Farrington and Manning (1990) will be used to determine the variance estimator $\hat{v}_0$.

Based on $\hat{p}_T, \hat{p}_C$ and the Farrington-Manning variance estimate $\hat{v}_0$, the p-value of the Farrington-Manning test regarding non-inferiority and the 80% -confidence interval (CI) of the difference in responder rates will be determined.

Non-inferiority of tapentadol versus morphine will be assigned if the lower bound of the CI exceeds the negative non-inferiority margin $-\delta = -0.2$.

For details on the methods and formulas used, see Section 18.1.8.

Handling missing data

The primary efficacy endpoint consists of two parts. Information on the first part, *Completion of the 14-day Treatment Period,* will always be available. However information on the pain assessments during the last 3 days of treatment in the Treatment Period might only be partially available. In this case Multiple Imputation will be used to impute missing values. A detailed description of this method can be found in Section 18.1.8.

13.1.2 Sensitivity analysis

The sensitivity analyses will only be performed at the final analysis of Part 1.

1. Different analysis set:

   To assess the robustness of the results with respect to heterogeneous compliance to the protocol and protocol violation, the analysis of the primary endpoint will be repeated for the Per Protocol Set.

2. Different completer definition:

To assess the robustness of the results with respect to the definition of the primary efficacy endpoint, the analysis of the primary endpoint will be repeated using the following modifications in the definition of a responder:

- Subjects stopping treatment earlier than 14 days because of no further need for opioid treatment (according to reason for discontinuation given in eCRF) will be classified as treatment responders instead of non-responders.

3. Different imputation method:

   To assess the impact of the missing imputation method on the results, the analysis of the primary endpoint will be repeated without imputing missing pain assessments. The average of the available pain assessments will be calculated and used to assign responder status. If no pain value during the last 3 days of treatment in the Treatment Period is present for a subject, that subject will be assigned a non-responder.

4. Different adjustment factors:

   To assess the robustness of the results with respect to different explanatory variables in the logistic regression model, the analysis of the primary endpoint will be repeated

   - Once discarding baseline pain intensity.
   - And once including the IMP dose level during the last 3 days of the Treatment Period as specified in Section 18.1.6.1.

5. Bayesian analysis:

   A further 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. The Bayesian Framework allows incorporating prior information gathered on tapentadol in earlier trials in the analysis. Prior information that was obtained from trials in adults will be incorporated into the analysis using a conditional power prior approach (see e.g., Neelon and O'Malley 2010), which allows to down-weight the prior information in the final analysis. A detailed description of this analysis can be found in Section 18.1.8.3.

   For this sensitivity analysis, the responder status as derived based on the alternative imputation method described in sensitivity analysis 3. above will be used.

6. Exclusion of CRPS patients:

   The main analysis of the primary endpoint will be repeated excluding subjects with CRPS as underlying diagnosis/reason for pain as provided in the eCRF.

13.1.3 Other analysis

Summary statistics for the primary endpoint will be provided for each level of the subgroups defined in Table 4 and for subgroups of subjects with and without a neuropathic pain component (based on information from the Pain Condition page of the eCRF at Visit V1).

Furthermore, as exploratory analyses, for subgroup levels that include at least 5 subjects in each of the two treatment groups, the differences in Maximum Likelihood-estimators between morphine and tapentadol and their 80% confidence intervals obtained by the Farrington Manning method will be provided and illustrated together in one forest plot.

In addition, summary statistics for the primary endpoint per IMP dose level during the last 3 days of treatment in the Treatment Period will be presented.

Based on observed, non-imputed data, the individual criteria considered for the response assessment for the FAS will be summarized descriptively. The following categories will be presented:

- Completion of the 14-day Treatment Period (yes/no).
- Average pain during the last 3 days of treatment in the Treatment Period <50 (VAS) or <5 (FPS-R) (yes/no).
- Average pain reduction for the last 3 days of treatment during the Treatment Period from baseline of ≥20 (VAS) or ≥2 (FPS-R) (yes/no).
- Completion of the 14-day Treatment Period and average pain during the last 3 days of treatment in the Treatment Period <50 (VAS) or <5 (FPS-R).
- Completion of the 14-day Treatment Period and average pain reduction for the last 3 days of treatment during the Treatment Period from baseline of ≥20 (VAS) or ≥2 (FPS-R).
- Completion of the 14-day Treatment Period, but average pain during the last 3 days of treatment in the Treatment Period ≥50 mm (VAS) or ≥5 (FPS-R) and average pain reduction for the last 3 days of treatment during the Treatment Period from baseline <20 mm (VAS) or <2 (FPS-R).

The pain related criteria will be presented using VAS for all subjects, using FPS-R for all subjects and using VAS for subjects 12-<18 years or FPS-R for subjects 6-<12 years.

The analysis of the primary endpoint will also be repeated using the following modifications in the definition of a responder:

- Using VAS for all subjects 6-<18 years old to assess the pain related response criteria (average pain <50 or average reduction from baseline pain ≥20 on a VAS).
- Using FPS-R for all subjects 6-<18 years old to assess the pain related response criteria (average pain <5 or average reduction from baseline pain ≥2 on a FPS-R).

13.2 Secondary endpoint

There is no secondary efficacy endpoint in this trial. For secondary safety endpoints, please see Section 15.1.

13.3 Other endpoints

13.3.1 Pain assessed using a VAS and FPS-R scale

Part 1

The diary values are used for statistical analysis.

Daily average pain values will be calculated for each subject as described in Section 18.1.9. For each day during the Treatment Period these averages and their changes from baseline will be summarized descriptively. In addition, these summary tables will be presented for the subgroups as specified in Table 4.

Graphical presentations over time of the Treatment Period for the determined averages and changes from baseline will be provided (mean and 95% confidence interval), including numbers at the bottom of the plot representing the number of subjects by treatment arm and day.

Additionally, the average change from baseline to the last 3 days of treatment in the Treatment Period (last six scheduled assessments) will be summarized descriptively.

Part 2

For the Tapentadol Period of Part 2, the investigator will document the pain that the subject has at each visit in the eCRF using a paper-based VAS and FPS-R. These eCRF values are used for statistical analysis.

Changes in the VAS and FPS-R at each scheduled time point (including Visit F12M) from baseline and the change from baseline to the last assessed pain value, i.e., the value assessed at either Visit F12M or Visit ET, will be summarized descriptively for the Tapentadol Period of Part 2. In case no baseline pain value from the eCRF is available, the last available pain values from the eDiary of the Treatment Period will be used as baseline. In addition, these summary tables will be presented for the subgroups as specified in Table 4.

13.3.2 Rescue medication

The analyses of rescue medication address only Part 1. Rescue medication is assessed in the eDiary and assessed in the drug accountability page of the eCRF.

Analyses based on eDiary-data:

For each day of the Treatment Period (day 1 until day 16) the two endpoints

- Number of daily doses.
- Total daily dose (mg/kg).

will be summarized descriptively and compared to the mean amount of IMP (morphine equivalent) within the treatment arms of that day. The individual daily amount of IMP will be compared over time to the two endpoints with Pearson's and Spearman's correlation coefficients (see Section 18.1.9 for details).

In addition, descriptive statistics will be presented for the subgroups as specified in Table 4.

The time from first IMP to first rescue medication intake will be summarized using time-to-event methods. The calculation of time to first rescue medication and the censoring algorithm are described in Section 18.1.9.

The percentage of days with rescue medication intake will be summarized descriptively as a categorical variable using the following percentage categories: 0, (0-10), [10-20), [20-30),…, [90-100), 100. The percentages will be calculated considering the day of the first IMP intake up to the day of the last IMP intake of Part 1 (both included).

Analyses based on eCRF-data:

Based on information in the drug accountability page of the eCRF, the average mean daily dose for each subject, i.e., the cumulative volume difference between Visit V2 and Visit VE divided by the number of days between Visit V2 and Visit VE (both days included), will be analyzed descriptively.

13.4 Acceptability and palatability

The acceptability and palatability questionnaire consists of two dimensions (taste/swallowing). The response to each dimension is measured on an ordinal, five-category scale.

For each of the two visits (Visit V3 and VE) and each of the two dimensions, responses will be summarized with descriptive statistics. The change between the two visits will be displayed for each dimension in a shift table.

In addition, descriptive statistics will be presented for the subgroups as specified in Table 4.

14 ANALYSIS OF PHARMACOKINETIC AND PHARMACODYNAMICS PARAMETERS

Blood samples for serum pharmacokinetics are only taken from the tapentadol arm during Part 1 of the trial. Thus all subsequent elaborations only refer to the tapentadol arm of the Treatment Period of Part 1.

Descriptive statistics of the observed concentrations of tapentadol and tapentadol-O-glucuronide at the respective time points will be presented for all subjects and for subgroups as specified in Table 4. The concentrations will be descriptively summarized by

- N>LLOQ (lower limit of quantification).
- Arithmetic mean, standard deviation and coefficient of variation.
- Geometric mean, standard deviation and coefficient of variation.

In addition, the data will be graphically displayed:

- Boxplots of plasma concentrations of tapentadol and tapentadol-O-glucuronide (on linear scale) by subgroups as specified in Table 4.
- Mean plasma concentration and 95% confidence interval of tapentadol and tapentadol-O-glucuronide (on linear scale) by subgroups as specified in Table 4.

The bioanalytical methods for the determination of individual serum concentrations of tapentadol and tapentadol-O-glucuronide will be reported together with the serum concentration results in separate bioanalytical reports. These bioanalytical reports will be appended to the ICTR.

A population pharmacokinetic/pharmacodynamic analysis will be performed using a non-linear mixed-effect modeling approach to investigate the pharmacokinetic properties, the correlation between drug exposure and therapeutic effect, concerned tolerability and safety aspects of the tapentadol and tapentadol-O-glucuronide. A pharmacometric analysis plan will be written before data base lock, and the pharmacokinetic/pharmacodynamic results will be reported separately from the ICTR. Therefore, the population pharmacokinetic/pharmacodynamic analysis is not subjects of this SAP.

15 SAFETY ANALYSES

No statistical tests for comparison of safety data between treatment arms will be performed.

Safety data will be summarized descriptively as described in Section 8.1.

All safety data will be presented for the SAF unless otherwise specified.

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

15.1 Secondary endpoint

The main secondary endpoints are:

Part 1

Constipation as assessed by changes from baseline of total scores for the modified constipation assessment scale (mCAS).

Part 1 and Part 2

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

15.1.1 Constipation assessed by the modified constipation assessment scale

The assessment of constipation is considered a secondary endpoint for Part 1. For Part 2 it is considered an exploratory endpoint and its analysis is addressed in Section 15.2.6.

Descriptive summaries of each time point and summaries of the changes from baseline to Visit V3 and from baseline to Visit VE will be provided for the total score as well as each item.

15.1.2 Adverse events

Definition of non-treatment emergent adverse events (non-TEAE)

- All adverse events occurring during the pre-treatment Period (defined in Section 8.2.2) are defined as pre-treatment non-TEAEs.
- All adverse events occurring during the post-Treatment Period (defined in Section 8.2.2) are defined as post-treatment non-TEAEs.

Definition of treatment emergent adverse events (TEAE)

- All adverse events occurring or worsening on-treatment in one of the trial periods (defined in Section 8.2.2) are defined as TEAEs of this period. Due to the consideration of the therapeutic reach in the definition of the on-treatment period, a TEAE that occurred during the on-treatment period of the Treatment or Tapentadol Period will be assigned to this trial period, although it actually might have started during the Observation Period.

The assessment whether an AE is a TEAE or a non-TEAE will be based on the start time of the AE recorded on the Adverse Event page of the eCRF. In case of partial dates or times, this assessment is done after imputation of missing date/time information; an AE will be considered treatment emergent unless the information available will clearly exclude it. For details on the imputation of missing date/time and programming aspects of adverse events in general, see Section 18.1.11.

15.1.2.1 Analyses of adverse events

The following overview tables of TEAEs will be generated as described in Section 8.1 for Part 1 and the Tapentadol Period of Part 2. For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be presented overall.

1. Summary of the number and percentage of subjects with at least one:
   - TEAE.
   - Serious TEAE.
   - Non-serious TEAE.
   - Unexpected TEAE.
   - Related TEAE.
   - Related serious TEAE.
   - TEAE leading to discontinuation from IMP.
   - TEAE leading to discontinuation from the trial.
   - Deaths.

For Part 1 in addition:

- TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2.
- TEAE of Part 1, that are ongoing during the Observation Period of Part 2.
- TEAE of Part 1, that actually started during the Observation Period of Part 2 (within the therapeutic reach of the last IMP intake of the Treatment Period).

For Tapendatol Period of Part 2 in addition:

- TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2
- TEAE of Tapentadol Period of Part 2, that actually started during the Observation Period of Part 2 (within the therapeutic reach of the last IMP intake of the Tapentadol Period)
- TEAE of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2

2. Summary presenting the number of TEAEs per subject categorized as 0, 1, 2, 3, 4, 5, and >5.
3. Summary of the number and percentage of TEAEs for:
   - TEAEs.
   - Serious TEAEs.
   - Non-serious TEAEs.
   - Unexpected TEAE.
   - Related TEAEs.
   - Related serious TEAEs.
   - TEAE leading to discontinuation from IMP.
   - TEAE leading to discontinuation from the trial.

For Part 1 in addition:

- TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2.
- TEAE of Part 1, that are ongoing during the Observation Period of Part 2.
- TEAE of Part 1, that actually started during the Observation Period of Part 2.

For Tapendatol Period of Part 2 in addition:

- TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2.

- TEAE of Tapentadol Period of Part 2, that actually started during the Observation Period of Part 2.
- TEAE of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2.

The percentage denominator will be the total number of TEAEs.

In addition, these overview tables will be presented for subgroups as specified in Table 4.

15.1.2.2 Incidence, Incidence Rates and number of events

The incidence of an AE is defined as the number of subjects with occurrence of this AE during the period of interest (pre-treatment, on-treatment or post-treatment).

The incidence rate (CIR for crude incidence rate) of an AE is defined as the number of subjects with occurrence of this AE during the period of interest divided by the total number of subjects n in the respective arm (defined in Section 8.1).

Analysis by Preferred Term

For Part 1 and the Tapentadol Period of Part 2, for TEAEs with an incidence rate of ≥ 5 % in at least one of the arm displayed, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by Preferred Term (PT), sorted by decreasing incidence rate in the arm of subjects randomized to tapentadol.

Percentages will be calculated related to the total number of subjects/events presented in the table, i.e., the number of subjects with TEAEs and the total number TEAEs for the respective trial Period.

Analysis by System Organ Class and Preferred Term

For Part 1 and the Tapentadol Period of Part 2, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by System Organ Class (SOC) and PT (sorted alphabetically) for each

- TEAEs.
- Serious TEAEs.
- Non-serious TEAEs.
- Related TEAEs.

In addition, for TEAEs, the incidence, incidence rate, the number of events and the percentage of events will be summarized by SOC and PT for the subgroups as specified in Table 4.

For serious TEAEs, the incidence, incidence rate, the number of events and the percentage of events will also be presented for serious related TEAEs, serious fatal TEAEs and serious fatal related TEAEs.

Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of SOC and PT for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.

For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.

The incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each

- Pre-treatment (Part 1 only, all enrolled subjects, by treatment arm and overall)
  - Non-TEAE.
  - Serious non-TEAE.
- Post-treatment (all trial Periods together, SAF, presenting the arms of the Observation Period)
  - Non-TEAE.
  - Serious non-TEAE.

Percentages will be calculated related to the total number of subjects/events presented in the respective table as outlined above for the TEAE tables by SOC and PT.

Analysis by System Organ Class, Preferred Term and descriptors

For Part 1 and the Tapentadol Period of Part 2, the number and percentage of events will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors. Presentations will be for TEAEs only.

- Intensity: mild, moderate, severe.
- Causal relationship to the IMP: related (with subcategories: possible, probable/likely, certain), not related (with subcategories: not related, unlikely), unknown (with subcategories: conditional/unclassified, assessable/unclassifiable, causal relationship missing).
- Outcome: recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown.
- Non IMP related countermeasures: none, newly started medication, trial discontinuation, others.
- Action taken with IMP: dose increased, dose reduced, drug interrupted, drug withdrawn, dose not changed, not applicable, unknown.
- Measures of location and variation will be calculated for:
- Duration of TEAEs: Duration will be analyzed in days with measures of dispersion and variation.
- Time to onset of TEAE will be analyzed in days with measures of dispersion and variation.

Denominator for percentage calculation will be the number of all TEAEs for presentation over all SOCs, and the number of TEAEs per SOC or PT respectively for the presentation per SOC and PT, respectively.

The number and percentage of all post-treatment non-TEAEs (all Periods together) will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors:

- Intensity.
- Time to onset of post-treament non-TEAEs after last IMP administration will be summarized with measures of dispersion and variation.

Listings

The following listings will be produced for all enrolled subjects:

- Deaths.
- Serious adverse events other than death.
- AEs leading to discontinuation from the trial.
- AEs leading to discontinuation from IMP.
- AEs leading to IMP dose decrease or interruption of IMP.
- AEs starting on the day of Visit VE (including the last IMP intake of Part 1 and first IMP intake of Part 2 [eDiary and dispense information]).

15.1.2.3 Exposure adjusted incidence rate

To overcome the difficulties of interpreting the incidence rate in the presence of subjects who prematurely discontinue in the Tapentadol Period of the trial, the exposure-adjusted incidence rate (EAIR) will be used (Siddiqui 2009) in addition to the CIR.

The EAIR is defined as the number of subjects x with a specific TEAE during the period of interest divided by the total exposure time T (in years) in the respective trial group. The exposure time of a subject is the period the subject is at risk to experience the respective TEAE for the first time. It starts at the time-point of first intake of IMP and lasts until occurrence of the first event in the period of interest or is censored at the end of the period of interest of the subject in case of no event. The total exposure time T is defined as the sum of exposure times over all subjects in the respective treatment arm.

The EAIR is interpreted as the number of events occurring per unit time, i.e., subject years in this trial.

For TEAEs of the Tapentadol Period with a CIR of at least 5% in either arm defined in Section 8.1, the point estimates of the EAIR and CIR will be presented for each arm. Sorting will be by PT.

15.2 Other endpoints

15.2.1 Laboratory parameters

The following laboratory parameters will be analyzed as continuous variables:

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 morphology	White blood cell differential count
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

Urine dipstick by the local laboratory	
pH	Specific gravity

The following categorical laboratory parameters will be summarized:

Urine dipstick by the local laboratory	
Glucose	Bilirubin
Protein	Urobilinogen
Blood	Nitrite
Ketones	Leukocyte esterase

Parameters of the Hematology and clinical chemistry panel are assessed by a central laboratory and for a subset of parameters additionally at baseline of Part 1 by a local laboratory. For summary statistics and for the classification of values based on the reference and alert ranges, only values obtained from the central laboratory will be used. The creatinine clearance (CL_{CR}) will be calculated in the eCRF using a central laboratory standard age appropriate formula and will also be analyzed. Dipstick urinalysis will be performed locally and will be used for summary statistics. Only in case of abnormalities, a urine sample will be sent to the central laboratory for sediment analysis. These results will only be included in the subject data listings.

Laboratory data will be descriptively summarized by type of laboratory test and by visit. Change from Baseline to each visit will be presented for all laboratory parameters.

Shift tables from baseline for the different visits and overall post-baseline (see Section 18.1.12.1) will be generated for each laboratory parameter for categories low, normal and high, based on the reference ranges of the central laboratory.

Furthermore, a summary by type of laboratory test, by visit and overall post-baseline will be provided on the number and percentage of subjects with a value outside the sponsor defined alert ranges (potentially clinically important (PCI) values, Section 18.2). See Section 18.1.12 for details regarding the analysis.

For the Tapentadol Period of Part 2, graphical presentations over time of the trial for the observed data will be provided (mean and 95% confidence interval), including numbers on the top and the bottom of the plot representing the number of subjects and the frequency of subjects with a PCI value by visit for the two arms of differently pretreated subjects.

These graphs will be provided for the continuous laboratory parameters given in Table 6.

Table 6: Laboratory parameters presented in graphical illustrations

Lactic acid dehydrogenase (LDH)	Alanine transaminase (ALT)	Aspartate transaminase (AST)
Gamma glutamyltransferase (GGT)	Alkaline phosphatase	Total serum bilirubin

A listing of subjects with PCI values will be provided. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Subjects potentially qualifying for Hy´s law criteria (FDA 2009), i.e., subjects showing confirmed (repeated) post-randomization (including unscheduled visits) values of ALT or AST of >3x ULN and total bilirubin of >2x ULN, will be given in a separate listing.

All laboratory values will be presented in the subject data listing of the respective part. Values out of reference ranges will be flagged as H (above the reference range) or L (below the reference range) in the listing. If a value classified as high or low is in addition also out of alert ranges, it will be flagged as H* or L* in the listing.

15.2.2 Electrocardiogram

Twelve-lead electrocardiogram parameters are RR interval, PR interval, QRS interval, QT interval and heart rate and are assessed during Part 1 only. Furthermore, the QTcF interval will be calculated using Fridericia ($QTcF = QT/(RR)^{1/3}$) correction. The investigator will record clinically relevant abnormalities and their medical interpretation in the eCRF. Cardiologists at a central ECG laboratory will read all ECGs. The ECG report from the central ECG laboratory will be considered a source document.

Electrocardiogram parameters will be summarized by visit. Changes from baseline to Visit VE will be presented descriptively.

Shift tables from baseline to Visit VE and overall (worst value on treatment, see Section 18.1.12.1 for definition of worst) will be generated for each ECG parameter for categories low, normal and high, based on the reference ranges provided in Table 7 and for categories normal, prolonged regarding the QTcF based on reference ranges provided in Table 8.Furthermore for the overall interpretation on ECG findings (‘normal’, ‘abnormal, clinically not relevant’ and ‘abnormal, clinically relevant’) assessed by the investigator, a summary by visit and overall post-baseline will be provided. See Section 18.1.12.1 for details regarding the analysis. A subject data listing of all abnormal, clinically relevant findings as documented by the investigator in the eCRF will be created.

All ECG values will be presented in the subject data listing. Values out of reference ranges (based on Table 7 and Table 8) will be flagged as H (above the reference range) or L (below the reference range) in the listing.

In case of the occurrence of a clear technical problem, the non-reliable measurements will be ignored during the analysis but will be shown in the subject data listings.

Table 7: Classification of abnormal ECG parameters

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	6 - < 12 years	<100	>180
	12 - <18 years	<100	>200
QRS (msec)	6 - <12 years	<50	>89
	12 - <18 years	<60	>99
QT (msec)	6 - <18 years	<320	>450
RR (msec)	6 - <18 years	<600	>1200

The ECG parameters are based on standard criteria of the ECG provider ERT.

Table 8: Classification of abnormal QTcF values

Parameter (unit)	Classification	Criterion
QTcF_MN (msec)	Normal	≤450
	Prolonged	>450

The QTcF_MN (_MN: mean of all beats) values are based on standard criteria of the ECG provider ERT.

15.2.3 Vital signs

Vital signs measured in the trial are respiratory rate, systolic and diastolic blood pressure and pulse rate.

For each parameter of the vital signs, observed values will be summarized by visit. In addition changes from baseline for all post-baseline visits will be summarized.

Shift tables from baseline for the different visits and overall (worst value on treatment, see Section 18.1.12.1 for definition of worst) will be generated for each vital sign parameter for categories low, normal and high, based on the reference ranges, defined by the sponsor, in Table 9.

Furthermore, a summary by visit and overall post-baseline will be provided on the number and percentage of subjects with alert value results. Alert values are abnormally low or abnormally high measurements regarded as potentially clinically important values defined by the sponsor (Table 10). See Section 18.1.12.1 for details regarding the analysis.

For Part 1, graphical presentations over time of the trial for the observed data will be provided (mean and 95% confidence interval), including numbers on the top and the bottom of the plot representing the number of subjects and the frequency of subjects with abnormally high/low values (based on Table 10) by treatment arm and visit.

For the Tapentadol Period, graphical presentations over time of the trial for the observed data will be provided (mean and 95% confidence interval), including numbers on the top and the bottom of the plot representing the number of subjects and the frequency of subjects with abnormally high/low values (based on Table 10) by visit and the two arms of differently pretreated subjects.

A listing of subjects with vital sign results outside the sponsor defined alert ranges will be provided (Table 10).

All vital signs values will be presented in the subject data listing of the respective part. Values out of normal ranges (Table 9) will be flagged as H (above the normal range) or L (below the normal range) in the listing. If a value classified as high or low is in addition also out of alert ranges, it will be flagged as H* or L* in the listing.

Table 9: Normal ranges of vital signs

	Age class			
Parameter (unit)	**6 - <9 years**	**9 - <12 years**	**12 - <16 years**	**16 - <18 years**
Diastolic BP (mmHg)	57-71	60-75	64-78	65-81
Systolic BP (mmHg)	95-110	101-116	108-121	109-127
Heart rate HR (bpm)	74-111	67-103	62-96	58-92
Respiration rate	18-24	16-22	15-21	13-19

The ranges of vital signs are based on Fleming et al. 2011 and NIH pediatric blood pressure charts.

Table 10: Potentially clinically important values for vital signs

Parameter (unit)		**Age class**			
		6 - < 9 years	**9 - <12 years**	**12 - <16 years**	**16 - <18 years**
Diastolic BP (mmHg)	abnormally low	< 42	<45	<49	<50
	abnormally high	>86	>89	>93	>95
Systolic BP (mmHg)	abnormally low	<80	<86	<93	<95
	abnormally high	>125	>130	>135	>140
Heart rate HR (bpm)	abnormally low	<74	<67	<62	<58
	abnormally high	>111	>103	>96	>92
Respiration rate	abnormally low	<12	<12	<12	<12
	abnormally high	>24	>24	>24	>24

15.2.4 Urine pregnancy test

In female subjects who are post-menarchal or older than 12 years at the time of the scheduled visit, a urine pregnancy test will be performed during Part 1 and the Tapentadol Period of Part 2. No urine pregnancy test will be performed during the Observation Period.

Results of all urine pregnancy tests will be presented in a subject data listing, including all information collected on the respective eCRF-page.

15.2.5 Physical examination

Results of all physical examinations will be presented in a subject data listing, including the descriptions of abnormalities.

15.2.6 Constipation assessed by the modified constipation assessment scale

Part 1

Analyses of the mCAS of Part 1 are described in Section 15.1.1 as the mCAS of Part 1 is a secondary endpoint.

Part 2

Assessments and changes from baseline will be summarized descriptively for the total score and each item.

15.2.7 Height

Part 1

Assessments of height and changes from baseline will be summarized descriptively by age subgroups for each visit. In addition to the presentation by treatment arm, descriptive summaries will also be presented overall.

Part 2

Assessments of height and changes from baseline will be summarized descriptively by age subgroups. The patient's height will be transformed into an age and sex adjusted Z-score. The Z-score and change from baseline in Z-score will be summarized by visit, by treatment arm and overall.

Details on the programming aspects regarding the height Z-Score can be found in Section 18.1.5.2.

15.2.8 Weight

Assessments and changes from baseline will be summarized descriptively for each visit.

Additionally the number and percentage of subjects in the following weight groups will be illustrated for each visit:

- Below 17.5 kg
- 17.5 kg to <22.5 kg
- 22.5 kg to <27.5 kg
- 27.5 kg to <32.5 kg
- 32.5 kg to <40.0 kg
- 40.0 kg to <45.0 kg
- 45.0 kg to <50.0 kg
- 50.0 kg to <55.0 kg
- 55.0 kg to <60.0 kg
- Above 60.0 kg

For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be presented overall.

15.2.9 Subjective opiate withdrawal scale (SOWS)

The SOWS questionnaire is a self-administered scale for grading opioid withdrawal symptoms. The version of the questionnaire used in this study includes questions to 16 symptoms whose intensity the subject rates on a scale of 0 (not at all) to 4 (extremely).

The SOWS questionnaire will be completed once daily starting from

- Part 1: the day after Visit VE (baseline) until the seventh day after the last intake of IMP for subjects not entering the Tapentadol Period.

- Part 2: the day after Visit ET/F12M of the Tapentadol Period (baseline) until the seventh day after the last intake of IMP for subjects entering the Tapentadol Period.

The total score of the SOWS questionnaire and the change from baseline will be descriptively analyzed per day after last IMP intake up to Day 7 (Day 0 = day of last IMP intake, Day 1 = day after last IMP intake,…, Day 7 = 7 days after last IMP intake). For subjects stopping IMP intake prior to Visit VE/ET/F12M, the information of the last IMP intake (End of Trial page of eCRF) will be used to determine the day after last IMP intake.

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.

Analyses of Part 2 will be presented for the Tapentadol Period only.

Details on the programming aspects regarding the SOWS can be found in Section 18.1.13.

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17 SAP AMENDMENTS

17.1 Amendment 02

Amendment rationale

Please refer to Section 7.2 for a description of the amendment rationale.

Detailed description of changes

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

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

Changes include:

Formerly read:	**Now reads:**
Section 10.1: Subject disposition	
• Subjects ~~switched from~~ Tapentadol ~~to~~ Observation Period (Tapentadol Period only).	• Subjects *who discontinued* Tapentadol *Period and entered* Observation Period (Tapentadol Period only).
Section 10.2: Subject discontinuations	
	If more than 10% of subjects in the SAF per treatment group of Part 1 discontinue IMP in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period due to no more need for opioid treatment, the time to discontinuation due to no more need for opioid treatment will be calculated and evaluated as described above. Additionally to the censoring algorithm described in Section 18.1.4.1, subjects who discontinue IMP for other reasons will be censored at the time of discontinuation.
Section 11.2: Other baseline characteristics	
The ~~underlying diagnosis/reason for pain which qualified the subject for inclusion, as well as the~~ results of urine test for drugs of abuse, will be included in the subject data listings only.	The results of urine test for drugs of abuse, will be included in the subject data listings only.
Section 11.3: Subject medical history	
	The underlying diagnosis/reason for the pain leading to enrollment of subjects in the trial will be summarized descriptively by primary System Organ Class and Preferred Term in a separate presentation, coded via MedDRA and sorted alphabetically.

Formerly read:	**Now reads:**
Section 12.1: Exposure	
A graphical illustration will illustrate the means and 95% confidence intervals of the daily doses of IMP per kg body weight (Tapentadol equivalents) of each day separately for the two treatment arms.	A graphical illustration will illustrate the means and 95% confidence intervals of the daily doses of IMP per kg body weight (Tapentadol equivalents*; 1 mg morphine PR is equivalent to 2.5 mg tapentadol PR*) of each day separately for the two treatment arms.
Section 13.1: Primary endpoint	
The primary efficacy 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. A definition is given in Section 8.2.2. • One of the following calculated from the scheduled pain assessments ("pain right now") documented during the last 3 days of the Treatment Period: – … Pain assessments during the last 3 days of the Treatment Period means the last six scheduled pain assessments ~~before Visit VE~~ whether these fall across 3 (morning assessment ~~3~~ days before ~~VE~~ until evening assessment ~~1 day before VE~~) or 4 calendar days (evening assessment 3 days before ~~VE~~ until morning assessment at day of ~~VE~~). ~~The information which pain assessments should be considered can be obtained from the eDiary: If the morning diary of VE is available and assigned to the Treatment Period, this pain assessment will be included; if the morning diary of VE is not available or not assigned to the Treatment Period, the assessments of the 3 calendar days before will be used.~~	The primary efficacy 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. A definition is given in Section 8.2.2. • One of the following calculated from the scheduled pain assessments ("pain right now") documented during the last 3 days of *treatment in* the Treatment Period: – … Pain assessments during the last 3 days of *treatment in* the Treatment Period means the last six scheduled pain assessments *up to the time point of last IMP intake of the Treatment Period* whether these fall across 3 (morning assessment *2* days before *last IMP intake* until evening assessment *at the day of last IMP intake given last IMP taken in the evening*) or 4 calendar days (evening assessment 3 days before *last IMP intake* until morning assessment at *the* day of *last IMP intake given last IMP taken in the morning*).
Section 13.1.1: Main analysis	
The primary efficacy endpoint consists of two parts. Information on the first part, *Completion of the 14-day Treatment Period,* will always be available. However information on the pain assessments during the last 3 days of the Treatment Period might only be partially available.	The primary efficacy endpoint consists of two parts. Information on the first part, *Completion of the 14-day Treatment Period,* will always be available. However information on the pain assessments during the last 3 days of *treatment in* the Treatment Period might only be partially available.
Section 13.1.2: Sensitivity analysis	
2. Different imputation method: … If no pain value during the last 3 days ~~before Visit VE~~ is present for a subject, that subject will be assigned a non-responder.	2. Different imputation method: … If no pain value during the last 3 days *of treatment in the Treatment Period* is present for a subject, that subject will be assigned a non-responder.
Section 13.1.3: Other analysis	
Summary statistics for the primary endpoint will be provided for each level of the subgroups defined in Table 4.	Summary statistics for the primary endpoint will be provided for each level of the subgroups defined in Table 4 *and for subgroups of subjects with and without a*

Formerly read:	**Now reads:**
…	*neuropathic pain component (based on information from the Pain Condition page of the eCRF at Visit V1).*
In addition, summary statistics for the primary endpoint per IMP dose level during the last 3 days of the Treatment Period will be presented.	…
	In addition, summary statistics for the primary endpoint per IMP dose level during the last 3 days of *treatment in* the Treatment Period will be presented.
	Based on observed, non-imputed data, the individual criteria considered for the response assessment for the FAS will be summarized descriptively. The following categories will be presented:
	• *Completion of the 14-day Treatment Period (yes/no).*
	• *Average pain during the last 3 days of treatment in the Treatment Period <50 (VAS) or <5 (FPS-R) (yes/no).*
	• *Average pain reduction for the last 3 days of treatment during the Treatment Period from baseline of ≥20 (VAS) or ≥2 (FPS-R) (yes/no).*
	• *Completion of the 14-day Treatment Period and average pain during the last 3 days of treatment in the Treatment Period <50 (VAS) or <5 (FPS-R).*
	• *Completion of the 14-day Treatment Period and average pain reduction for the last 3 days of treatment during the Treatment Period from baseline of ≥20 (VAS) or ≥2 (FPS-R).*
	• *Completion of the 14-day Treatment Period, but average pain during the last 3 days of treatment in the Treatment Period ≥50 mm (VAS) or ≥5 (FPS-R) and average pain reduction for the last 3 days of treatment during the Treatment Period from baseline <20 mm (VAS) or <2 (FPS-R).*
	The pain related criteria will be presented using VAS for all subjects, using FPS-R for all subjects and using VAS for subjects 12-<18 years or FPS-R for subjects 6-<12 years.
	The analysis of the primary endpoint will also be repeated using the following modifications in the definition of a responder:
	• *Using VAS for all subjects 6-<18 years old to assess the pain related response criteria (average pain <50 or average reduction from baseline pain ≥20 on a VAS).*
	• *Using FPS-R for all subjects 6-<18 years old to assess the pain related response criteria (average pain <5 or average reduction from baseline pain ≥2 on a FPS-R).*

Formerly read:	**Now reads:**
Section 13.3.1: Pain assessed using a VAS and FPS-R scale	
Part 1 … Additionally, the average change from baseline to the last six scheduled assessments ~~before performing Visit VE (either scheduled at day 14±1 or earlier when the Treatment Period is terminated early)~~ will be summarized descriptively. **Part 2** … Changes in the VAS and FPS-R at each scheduled time point (including Visit F12M) from baseline and the change from baseline to the last assessed pain value, i.e., the value assessed at either Visit F12M or Visit ET, will be summarized descriptively for the Tapentadol Period of Part 2. In addition, these summary tables will be presented for the subgroups as specified in Table 4.	**Part 1** … Additionally, the average change from baseline to the *last 3 days of treatment in the Treatment Period (*last six scheduled assessments*)* will be summarized descriptively. **Part 2** … Changes in the VAS and FPS-R at each scheduled time point (including Visit F12M) from baseline and the change from baseline to the last assessed pain value, i.e., the value assessed at either Visit F12M or Visit ET, will be summarized descriptively for the Tapentadol Period of Part 2. *In case no baseline pain value from the eCRF is available, the last available pain values from the eDiary of the Treatment Period will be used as baseline.* In addition, these summary tables will be presented for the subgroups as specified in Table 4.
Section 15.2.9: Subjective opiate withdrawal scale (SOWS)	
The total score of the SOWS questionnaire and the change from baseline will be descriptively analyzed per day after last IMP intake.	The total score of the SOWS questionnaire and the change from baseline will be descriptively analyzed per day after last IMP intake *up to Day 7 (Day 0 = day of last IMP intake, Day 1 = day after last IMP intake,…, Day 7 = 7 days after last IMP intake).*
Section 16: References	
	Chen F, Brown G, Stokes M. Fitting your favorite mixed models with PROC MCMC. Paper SAS 5601-2016: 1-27. *Gelman A. Prior distributions for variance parameters in hierarchical models. Bayesian Analysis 2006; 1 (3): 515-533.* *Hlavin G, Koenig F, Male C, Posch M, Bauer P. Evidence, eminence and extrapolation. Stat Med 2016; 35 (13): 2117-32.*
Section 18.1.2.4: Trial day count	
The day of ~~allocation/baseline visit/~~first IMP is defined as trial Day 1.	The day of first IMP *intake* is defined as trial Day 1.
Section 18.1.2.10: Trial phases and periods	
Observation Period • For subjects ~~switching from~~ the Tapentadol Period ~~to~~ the Observation Period during Part 2, the Observation Period start date is the date assessed on the *End of Period* page in the eCRF at the end of the Tapentadol Period.	*Observation Period* • For subjects *who discontinue* the Tapentadol Period *and enter* the Observation Period during Part 2, the Observation Period start date is the date assessed on the *End of Period* page in the eCRF at the end of the Tapentadol Period.

Formerly read:	**Now reads:**
Section 18.1.4.1: Subject discontinuation	
Completion status Treatment completer: • Part 1: – If (End of Treatment Visit date – ~~Randomization date~~) ≥ 13 and either (Last IMP intake of the Treatment Period – ~~Randomization date~~) ≥ 13 or (Last IMP intake of the Treatment Period- ~~Randomization date~~ = 12 with last IMP intake of the Treatment Period in the evening • Part 2, Tapentadol Period only: – If $(F12M\ date - End\ of\ Treatment\ Visit\ date) \geq 351$ ... **Time to discontinuation** Time to treatment discontinuation will be calculated in days for Part 1 as: Date of Last IMP intake of the Treatment Period – ~~Randomization~~ date + 1 Time to treatment discontinuation will be calculated in weeks for Part 2 as: (date of Last IMP intake of the Tapentadol Period – date of ~~Visit VE~~ + 1)/7 **Censoring algorithm** Censoring algorithm is defined as follows: • Time to IMP discontinuation: – Part 1: time will be censored at the ~~End of Treatment Visit (VE)~~ for treatment completers Part 1 – Part 2, Tapentadol Period: time will be censored at the ~~visit 12 month after Visit VE (F12M)~~ for treatment completers Part 2	**Completion status** Treatment completer: • Part 1: – If (End of Treatment Visit date – *First IMP intake of the Treatment Period date*) ≥ 13 and either (Last IMP intake of the Treatment Period – *First IMP intake of the Treatment Period date*) ≥ 13 or (Last IMP intake of the Treatment Period – *First IMP intake of the Treatment Period date)* = 12 with last IMP intake of the Treatment Period in the evening. • Part 2, Tapentadol Period only: – If $(F12M\ date - End\ of\ Treatment\ Visit\ date) \geq 351$ *with F12M completed as part of Tapentadol Period.* ... **Time to discontinuation** Time to treatment discontinuation will be calculated in days for Part 1 as: Date of Last IMP intake of the Treatment Period – *date of First IMP intake of the Treatment Period* + 1 Time to treatment discontinuation will be calculated in weeks for Part 2 as: (date of Last IMP intake of the Tapentadol Period – *date of First IMP intake of the Tapentadol Period* + 1)/7 **Censoring algorithm** Censoring algorithm is defined as follows: • Time to IMP discontinuation: – Part 1: time will be censored at the *date of last IMP intake of the Treatment Period* for treatment completers Part 1. – Part 2, Tapentadol Period: time will be censored at the *date of last IMP intake of the Tapentadol Period* for treatment completers Part 2.
Section 18.1.5.2: Other baseline characteristics	
Derivation of height Z-Scores The height Z-Scores will be calculated using the WHO Child Growth Standards. …	**Derivation of height Z-Scores** The height Z-Scores will be calculated using the WHO Child Growth Standards. … *As age in months is required for this calculation, it will be derived by multiplying the recorded age in years by*

Formerly read:	Now reads:
	12 and adding 6 months.
Section 18.1.6.1: Dose level for the sensitivity analysis of the primary endpoint	
The IMP dose level during the last 3 days of the Treatment Period will be specified based on the information from the *Initial Dose/Dose Adjustment*-page of the eCRF. Therefore, the last six scheduled IMP intakes of the Treatment Period, i.e., the last IMP of Part 1 and the 5 predecessing intakes, will be considered~~.~~ ~~For subjects completing the Treatment Period, these should be the last six scheduled IMP intakes before VE and should fall across 3 (morning intake 3 days before VE until evening intake 1 day before VE in case the last IMP intake is the one in the evening of the day before VE) or 4 calendar days (evening intake 3 days before VE until morning intake at day of VE in case the last IMP intake is the one in the morning of the day of Visit VE)~~, analogous to the pain intensity assessments considered for the primary endpoint assessment.~~ For subjects discontinuing the Treatment Period, these will be the last six scheduled IMP intakes before the Treatment is discontinued.~~ For each of the six considered IMP intakes, the dose level (1 to 5) of the dose as given in the eCRF will be determined based on the tapentadol PR and morphine PR dosing tables provided in the trial protocol. The most frequent dose level will then be used as IMP dose level during the last 3 days of the Treatment Period. In case several different dose levels occur equally often among these 6 time points, the highest dose level of these will be used.	The IMP dose level during the last 3 days of *treatment in* the Treatment Period will be specified based on the information from the *Initial Dose/Dose Adjustment*-page of the eCRF. Therefore, the last six scheduled IMP intakes of the Treatment Period, i.e., the last IMP of Part 1 and the 5 predecessing intakes, will be considered, analogous to the pain intensity assessments considered for the primary endpoint assessment. For each of the six considered IMP intakes, the dose level (1 to 5) of the dose as given in the eCRF will be determined based on the tapentadol PR and morphine PR dosing tables provided in the trial protocol. The most frequent dose level will then be used as IMP dose level during the last 3 days of *treatment in* the Treatment Period. In case several different dose levels occur equally often among these 6 time points, the highest dose level of these will be used.
Section 18.1.6.2: Average daily doses during the Tapentadol Period	
	In case of a missing intermediate visit, it will be artificially introduced for this analysis by dividing the available surrounding visit interval to two equally sized subintervals. Hence, if the i-th visit for a subject j is missing ($Date\ of\ TP_{i,j}$), this visit will be estimated as the midpoint of the surrounding visit interval $(Date\ of\ TP_{i-1,j}, Date\ of\ TP_{i+1,j}]$ *and the two newly introduced timeframes* $\left(Date\ of\ TP_{i-1,j}, Date\ of\ TP_{i,j}\right]$ *and* $(Date\ of\ TP_{i,j}, Date\ of\ TP_{i+1,j}]$ *will be used for further calculations. In case the length of the available visit interval is not a multiple of 2, it will be splitted such that the first time interval is 1 day longer than the second one.*

Formerly read:	**Now reads:**
Section 18.1.8.1: Missing baseline pain intensity for the Treatment Period	
For the primary endpoint analysis (main analysis and sensitivity analyses if applicable), including baseline pain intensity as a ~~a factor~~ in the analysis model, missing values will be imputed by ~~the average baseline pain intensity of the respective age group.~~	For the primary endpoint analysis (main analysis and sensitivity analyses if applicable), including baseline pain intensity as a*n explanatory variable* in the analysis model, missing values will be imputed by *the values resulting from the multiple imputation for the missing pain values during the 3 last days of treatment in the Treatment Period as explained in the "Handling missing data" paragraph of the following section. For those analyses based on primary endpoint data from multiple imputation, the corresponding imputed baseline values of the respective dataset will be used. For those analyses of the primary endpoint based on observed data, the average of the baseline values for the 200 multiple imputation datasets for a subject will be used for imputation of this missing baseline value.*
Section 18.1.8.2: Primary analysis	
Handling missing data ... Information on the pain assessments during the last 3 days of the Treatment Period might only be partially available. In this case *Multiple Imputation* will be used to impute missing values: 1. For each treatment group, a multivariate normal distribution for the vector of the last 6 scheduled pain measurements during the Treatment Period, denoted by $(Y_1, \dots, Y_6)$, is assumed $(Y_1, \dots, Y_6) \sim MVN(\mu, \Sigma)$. Missing observations are assumed to depend on the observed values of the subjects in the same treatment group. Therefore, in both treatment arms, missing pain assessments will be imputed using information from an imputation model that is only based on the subjects in the respective arm~~, with baseline pain intensity, age group and underlying pain condition as explanatory variables~~. The multiple imputations will be done via SAS PROC MI. The imputation model will be based on the default Markov chain Monte Carlo (MCMC) method for general patterns of missingness (Dmitrienko et al. 2005). For the sake of reproducibility of the results, the seed for pseudo-random number generation will be set to 550366 ~~for each of both treatment arms~~. The number *K* of imputed data sets will be set to 200, resulting in 200 complete data sets: • Number of imputed data sets: $K = 200$	**Handling missing data** … Information on the pain assessments during the last 3 days of *treatment in* the Treatment Period might only be partially available. In this case *Multiple Imputation* will be used to impute missing values: 1. For each treatment group, a multivariate normal distribution for the vector of the age group (AGE), underlying pain condition (PAIN) and baseline pain intensity (BASE) as well as the last 6 scheduled pain measurements during *treatment of* the Treatment Period, denoted by $(Y_1, \dots, Y_6)$, is assumed $(AGE, PAIN, BASE, Y_1, \dots, Y_6) \sim MVN(\mu, \Sigma)$. Missing observations are assumed to depend on the observed values of the subjects in the same treatment group. Therefore, in both treatment arms, missing pain assessments will be imputed using information from an imputation model that is only based on the subjects in the respective arm. *The multiple imputation will be performed once for all subjects using VAS, and once for all subjects using FPS-R. To ensure that the imputed values are within the range of the respective pain scale (0-10 for FPS-R and 0-100 for VAS), minimum and maximum values for the variable to be imputed should be specified.* The multiple imputations will be done via SAS PROC MI. The imputation model will be based on the default Markov chain Monte Carlo (MCMC) method for general patterns of missingness (Dmitrienko et al. 2005). *A BY statement will be*

Formerly read:	**Now reads:**
	used to implement the imputation by treatment group. The variables will be given the following order: age group, pain condition, baseline pain, last 6 scheduled pain assessments starting with the earliest one. For the sake of reproducibility of the results, the seed for pseudo-random number generation will be set to 550366. The number *K* of imputed data sets will be set to 200, resulting in 200 complete data sets: • Number of imputed data sets: $K = 200$ *Imputed values for missing baseline pain intensities, to be used as explanatory variable in the logistic regression model, will also be obtained from the multiple imputation.*
Section 18.1.8.3: Bayesian analysis - details	
~~A non-informative Gamma (0.001, rate=0.001) prior will be assigned to the precision of the random effects $1/\sigma^2$.~~ … One MCMC chain of length 110,000 will be run, discarding the first 10,000 and keeping every 5th. The resulting thinned sample of size 2,000 will be summarized for each model parameter by means of the posterior mean, median, standard deviation and 80% credibility interval. … Then compute the difference p_T-p_C. At the end of the MCMC run, the posterior sample of size 2,000 for p_T-p_C will be also summarized together with the model parameters.	*A half-t distribution (delta=0, var=10, df=3) will be used as prior for the precision of the random effects σ. The half-t distribution is defined as the absolute value of a Student-t distribution centered at zero and is recommended as a prior distribution for the hierarchical standard deviation when the number of groups is small (see Gelman 2016 and Chen et al. 2016).* … One MCMC chain of length 1*,*1*0*0,000 will be run, discarding the first 10*0*,000 and keeping every 5*0*th. The resulting thinned sample of size 2*0*,000 will be summarized for each model parameter by means of the posterior mean, median, standard deviation and 80% credibility interval. … Then compute the difference p_T-p_C. At the end of the MCMC run, the posterior sample of size 2*0*,000 for p_T-p_C will be also summarized together with the model parameters.
Section 18.1.10: Rescue medication	
The summary table for the number of daily doses and total daily dose per day of the Treatment Period include the mean amount of IMP (morphine equivalents). … **Time to first rescue medication intake** Censoring algorithm is defined as follows: • Time to first rescue medication intake will be censored at the End-of-Treatment Visit (VE)	The summary table for the number of daily doses and total daily dose per day of the Treatment Period include the mean amount of IMP (morphine equivalents*; 1 mg morphine PR is equivalent to 2.5 mg tapentadol PR*). … **Time to first rescue medication intake** *If the time of the first IMP intake is missing, 0:00 will be used if the first IMP intake was in the morning and 12:00 will be used if the first IMP was taken in the evening.*

Formerly read:	Now reads:
regardless of whether subjects complete part 1 or perform Visit VE prior to day 14.	Censoring algorithm is defined as follows: • Time to first rescue medication intake will be censored at the End-of-Treatment Visit (VE) regardless of whether subjects complete part 1 or perform Visit VE prior to day 14. *The time to be considered for the censoring will be set to 23:59, or the time of first IMP intake of the Tapentadol Period if available.*

17.2 Amendment 01

Amendment rationale

Refer to Section 7.2 for a description of the amendment rationale.

Detailed description of changes

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

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

Changes include:

Formerly read:	Now reads:
Section 2: Abbreviations	
~~CP Conditional power~~ ~~LLN Lower limit normal~~ SAS Statistical~~analysis software~~	SAS Statistical *Analysis System*
Section 3: Introduction	
This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the trial KF5503-66~~.~~ The analysis will be performed ~~in the Department of Biostatistics at~~ a contract research organization in accordance with this SAP. ~~This SAP corresponds to the Trial Protocol of KF5503-66 Document Management System (DMS) Version 5.0.~~	This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the trial KF5503-66 *in accordance with the protocol Amendment 05 dated 27 July 2017.* The analysis will be performed *by* a contract research organization in accordance with this SAP. … *The analyses of both parts of the trial are covered by this SAP.*
Section 5.1: Overall trial design and plan	
Part 1 ~~Part 1 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 Section 17 for details).~~ The Treatment Period will include the following visits: • ~~Enrollment Visit (Visit V1; Day -14 to Day 1)~~ • Visit V2 (Allocation Visit; Day 1)	*Only a brief synopsis of the trial design is presented here; full details can be found in the trial protocol.* **Part 1** *Part 1 starts with an Enrolment Visit (Visit V1; Day -14 to Day 1), followed by the 14-day Treatment Period.* The Treatment Period will include the following visits: • Visit V2 (Allocation Visit; Day 1)

Formerly read:	**Now reads:**
Section 5.1 Overall trial design and plan, Figure 1 footnotes	
	Footnotes were added, based on the corresponding footnotes in the trial protocol.
Section 5.1 Overall trial design and plan, Table 1	
Lines: Subjective opiate withdrawal scale ~~<————>~~ Dispense IMP (the first dose of IMP will be taken ~~at~~ the ~~site~~)	Lines: Subjective opiate withdrawal scale X^a X^a 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 were added, based on the corresponding footnotes in the trial protocol.
Section 5.1 Overall trial design and plan, Table 2	
	Footnotes were added, based on the corresponding footnotes in the trial protocol.
Section 5.1 Overall trial design and plan, Table 3	
Lines: Record height at ET and F12M	Lines: Record height at *TP2, TP6, TP9, TP12,* ET and F12M Footnotes were added, based on the corresponding footnotes in the trial protocol.
Section 5.2: Sample size	
~~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. Stopping for any reason is not foreseen based on the results of the interim analysis. As a result of the interim analysis, the overall number of subjects in the Full Analysis Set (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, 129~~ 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~~	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.*

Formerly read:	**Now reads:**
~~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 in the sponsor's trial master files.~~	
Section 5.3: Randomization	
Randomization will be outsourced to a Central Randomization Center ~~(Almac Clinical Technologies)~~ that will develop an Interactive Voice/Web Response System (IVRS/IWRS).	Randomization will be outsourced to a Central Randomization Center that will develop an Interactive Voice/Web Response System (IVRS/IWRS).
Section 6.1: Final analyses	
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. ~~Two separate integrated clinical trial reports (ICTRs) will be written, one after Part 1, another after Part 2. The results of the final analyses of the relevant parts will be the basis for the ICTRs. For details on the final analyses please refer to Section 13 and Section 15.~~	***Final analysis Part 1*** The final analysis of Part 1 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 *(if not discontinued before),* • And *all* data *of Part 1 and Part 2 up to Visit TP3/OP3 is cleaned.* *Together with this final analysis of Part 1, an interim analysis of Part 2 will be conducted. This interim analysis will be based on all data of Part 2 (also including information after TP3/OP3) available in the database at the time point of completion of the cleaning for Part 1 and Part 2 up to Visit TP3/OP3.* *For the final analysis of Part 1 and the interim analysis of Part 2, all data available in the database will be fixed in a snapshot. Individual subjects that have completed the entire trial and are clean will be* locked. *The final analysis of Part 1 will encompass all* analyses of Part 1 *as described in this SAP. The interim analysis of Part 2 will encompass all Part 2 analyses planned according to this SAP.* *An integrated clinical trial report, integrating clinical, pharmacokinetic, and statistical results of the final analysis of Part 1 and the interim analysis of Part 2 will be prepared by the sponsor.* ***Final analysis Part 2*** The final analysis of Part 2 will be performed *once* all subjects have completed Part 2 of the trial and the final data base has been *hard* locked. *The final analysis of Part 2 will encompass all Part 2 analyses as described in this SAP.* *A second integrated clinical trial report (optionally as an amendment) will be prepared including the final results of Part 2.*

Formerly read:	**Now reads:**
Section 6.2: 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 any reason foreseen (Mehta and Pocock 2011). 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. Interim data will be defined, cleaned and locked for interim analysis. The sample-size re-estimation will be done in an unblinded manner as the trial itself is open label. The feasibility threshold (= upper sample size limit), to which the sample size might be increased in this trial is N_{max} = 200.~~ ~~For details on the interim analysis, please refer to Section 17.~~	*As described in the previous section, an interim analysis of Part 2 will be performed.*
Section 7.1: Changes in analysis compared to the trial protocol	
As changes were addressed in the protocol amendments, all changes were deleted.	*Not applicable.*
Section 7.2: SAP amendment rationale	
	SAP amendment rationale for Amendment 01 was added. Please see section for further details.
Section 8.1: General principles	
Analysis structure ~~If 2 or more of the population sets as defined in the SAP coincide, presentations will only be prepared for 1 population.~~ For Part 1, all presentations will be done per treatment arm, i.e., comparing the tapentadol arm to the morphine arm. ~~For Part 2,~~ the different periods, i.e., Tapentadol Period and Observation Period, are not comparable, due to the heterogeneity of the populations (see Section ~~18.1.3~~ for additional information~~).~~ ~~Thus, for~~ Part 2~~, various changes compared to baseline (i.e., Visit VE)~~ will be illustrated separately for the Tapentadol and Observation ~~Periods~~.	**Analysis structure** *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.* For Part 1, all presentations will be done per treatment arm, i.e., comparing the tapentadol arm to the morphine arm. *The analysis for Part 2 will take into consideration the Tapentadol Period and Observation Period of Part 2. Given that* the different periods, i.e., Tapentadol Period and Observation Period, are not comparable, due to the heterogeneity of the populations (see Section *18.1.3* for additional information*), all analyses of* Part 2 will be illustrated separately for the Tapentadol and Observation *Period as detailed below, if not specified differently*.
Section 8.1: General principles	
Additionally, the last assessment (defined in Section ~~8.2.2~~) and change from baseline to the last assessment will be summarized. ~~The data collected and derived in the trial will be~~ presented in subject data listings~~. Data listings~~ will be sorted by ~~period and arm.~~ Unscheduled measurements of laboratory parameters, vital signs and electrocardiogram will be presented in the subject data listing ~~and~~ will be considered in the derivation of the overall post-baseline value (see Section ~~18.1.12.1~~) that is used in the shift and alert	Additionally, *for Part 2,* the last assessment (defined in Section 8.2.2) and change from baseline to the last assessment will be summarized. *Data* presented in subject data listings will be sorted by *treatment if not specified differently.* Unscheduled measurements of laboratory parameters, vital signs and electrocardiogram will be presented in the subject data listing*. In general, unscheduled measurements will not be included in the analysis. However, they* will be considered in the derivation of the overall post-baseline value (see Section *18.1.12.1*) that is

Formerly read:	**Now reads:**
frequency analyses.	used in the shift and alert frequency analyses.
Section 8.1: General principles	
Summary statistics Data collected in this trial will be summarized ~~by the~~ number of ~~subjects,~~ mean, standard deviation (SD), minimum and maximum values, median and quartiles ~~for continuous~~ variables ~~and~~ absolute and relative frequencies ~~for categorical variables, as appropriate.~~ • If not defined otherwise, the percentage denominator will be the number of subjects in the analyzed population. • ~~For time~~-to-event variables~~, descriptive statistics will include the number of subjects, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Furthermore~~ Kaplan-Meier estimates ~~and graphs~~ will be provided~~. Additionally the Kaplan-Meier graph will include~~ the median time-to-event and its 95% confidence interval for all arms. Censoring mechanisms depend on the specific endpoint and will be described in the respective section.	**Summary statistics** Data collected in this trial will be summarized *according to their nature as follows:* • *Continuous variables:* number of *non-missing observations, arithmetic* mean, standard deviation (SD), minimum and maximum values, median and quartiles*. If there are less than 5 observations descriptive statistics will be presented based on the rules specified in Section 18.1.2.2.* • *Categorical* variables*:* absolute and relative frequencies*.* If not defined otherwise, the percentage denominator will be the number of subjects in the *trial at the respective time point in the* analyzed population. • *Time*-to-event variables*:* Kaplan-Meier estimates *together with the 95% confidence intervals (CI)* will be provided *with the respective number at risk and the number censored at the relevant time points. In addition,* the median time-to-event and its 95% confidence interval for all arms *will be presented. For calculating the survival estimate CI bounds, the log-log transformed estimate of CI bounds will be used.* Censoring mechanisms depend on the specific endpoint and will be described in the respective section.
Section 8.1: General principles	
Coding of eCRF-entries All Medication and additional therapies/treatments will be coded using the World Health Organization Drug Dictionary (WHO-DD) or in case of non-medicinal therapies via Medical Dictionary for Regulatory Activities ~~(MedDRA).~~ … For the final analyses, the latest version of the WHO-DD/MedDRA at the time of coding for final evaluations will be used. These might be different for Part 1 and Part 2. Coding for the DMC analyses is addressed in the DMC SAP.	**Coding of eCRF-entries** All Medication and additional therapies/treatments will be coded using the World Health Organization Drug Dictionary (WHO-DD) or in case of non-medicinal therapies via Medical Dictionary for Regulatory Activities *(MedDRA). The versions of these reference documents will be specified on the appropriate statistical outputs.* … For the final analyses, the latest version of the WHO-DD/MedDRA at the time of coding for final evaluations will be used. These might be different for *the final analyses of* Part 1 and *the final analysis of* Part 2. Coding for the DMC analyses is addressed in the DMC SAP.
Section 8.2.1: Definition of subgroup	
• Underlying pain condition – Cancer related pain. – Non-cancer related pain. • ~~Randomization strata:~~	• Underlying pain condition *(based on information from the eCRF at Visit V1)* – Cancer related pain. – Non-cancer related pain.

Formerly read:

~~The four combinations of age and underlying pain condition strata.~~

Now reads:

Section 8.2.1: Definition of subgroup, Table 4: Subgroup analyses

Formerly read:

	Age group	**Underlying pain condition**	**~~Randomization strata~~**
Subject disposition	Enrolled Set	Enrolled Set	~~Enrolled Set~~
Demographics + baseline characteristics	SAF~~/FAS~~	SAF~~/FAS~~	~~SAF/FAS~~
~~Exposure~~	~~SAF~~	~~SAF~~	-
Descriptive statistics of primary efficacy endpoint	FAS~~/PPS~~	FAS~~/PPS~~	~~FAS/PPS~~
Exploratory statistical analysis and forest plots of primary efficacy endpoint as described in Section 13.1.3	FAS	FAS	~~FAS~~
Pain assessments	FAS	FAS	-
Acceptability and palatability questionnaire	FAS	-	-
Rescue medication	FAS	~~FAS~~	~~FAS~~
~~Vital signs~~	~~SAF~~	~~SAF~~	-
~~Laboratory parameters~~	~~SAF~~	~~SAF~~	-
~~Modified constipation assessment scale~~	~~SAF~~	~~SAF~~	~~SAF~~
~~Physical examination~~	~~SAF~~	~~SAF~~	~~SAF~~
Serum concentrations of tapentadol and tapentadol-O-glucuronide	PK-Set	PK-Set	-
Incidence of TEAEs by SOC and PT	SAF	SAF	~~SAF~~

Now reads:

	Age group	**Underlying pain condition**
Subject disposition	Enrolled Set	Enrolled Set
Demographics + *other* baseline characteristics *(excluding medical history and prior and concomitant medication)*	SAF	SAF
Descriptive statistics of primary efficacy endpoint	FAS	FAS
Exploratory statistical analysis and forest plots of primary efficacy endpoint as described in Section 13.1.3	FAS	FAS
Pain assessments	FAS	FAS
Acceptability and palatability questionnaire	FAS	-
Rescue medication	FAS	-
Serum concentrations of tapentadol and tapentadol-O-glucuronide	PK-Set	PK-Set
Incidence of TEAEs by SOC and PT *(selected analyses)*	SAF	SAF

Section 8.2.2: Further definitions

Formerly read:

On-treatment-period, Part 1:

- Subjects continuing in the Tapentadol Period ~~directly~~ after the Treatment Period ~~or discontinuing the trial during Part 1~~:
  a. Start: First IMP administration (included)
  ~~b.~~ End: ~~First occurrence of one of~~ the ~~following events:~~
  i. Last administration of IMP during Part 1 + 72 hours (included,

Now reads:

On-treatment-period, Part 1:

- Subjects continuing in the Tapentadol Period after the Treatment Period:
  a. Start: First IMP administration *of Part 1* (included)
  b. End:
  iii. *If* the *last administration of IMP during Part 1 is more than 3 days before Visit VE:* Last administration of IMP during Part 1 + 72 hours (included, therapeutic

Formerly read:	**Now reads:**
therapeutic reach) ii. Visit VE (included) • Subjects continuing in the ~~Observation~~ Period ~~directly~~ after the Treatment Period: c. Start: First IMP administration (included) On-treatment-period, Part 2: Tapentadol Period only: a. Start: Visit VE (excluded) Treatment completers, Part 1: Completion of the 14-day Treatment Period means that a subject performs the End of Treatment Visit (Visit VE) in the allowed ~~-~~window of 15 ± 1 days, i.e., at or later than Day 14. Treatment completers, Part 2: Completion of the 12-month Tapentadol Period means that a subject. performs the 12-month follow-up visit (F12M) in the window of 365 ± 14 days, i.e., at or later than 351 days after Visit VE~~.~~ Trial completers, Part 1: 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~~).~~ Baseline values, Treatment Period: • For pain assessment, 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.	reach) iv. *If the last administration of IMP during Part 1 is less than 3 days before Visit VE:* Visit VE (included) • Subjects *not* continuing in the *Tapentadol* Period after the Treatment Period: c. Start: First IMP administration (included) On-treatment-period, Part 2: Tapentadol Period only: a. Start: Visit VE (excluded *in case VE is included in the on-treatment period of Part 1; included in case VE is not included in the on-treatment period of Part 1*) Treatment completers, Part 1: Completion of the 14-day Treatment Period means that a subject performs the End of Treatment Visit (Visit VE) in the allowed window of 15 ± 1 days, i.e., at or later than Day 14*, and has the last IMP intake of part 1 no earlier than Day 13 in the evening*. Treatment completers, Part 2: Completion of the 12-month Tapentadol Period means that a subject. performs the 12-month follow-up visit (F12M) in the window of 365 ± 14 days, i.e., at or later than 351 days after Visit VE*, as part of the Tapentadol Period.* Trial completers, Part 1: Subjects who fully completed the extension period*, i.e.,* either subjects completing the Tapentadol Period and the follow-up visit (*F12M and* F7D) or subjects completing the Observation Period (F12M*)* not earlier than 351 days after Visit VE. Baseline values, Treatment Period: • For pain assessment, 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. *Details on the programming aspects regarding the baseline pain intensity can be found in Section 18.1.5.3.*
Section 9: Subject populations	
	Allocated Set *Analysis of the Allocated Set will be conducted according to the allocated treatment.* **Safety Set** *The analysis on the SAF will be conducted on the actual*

<table>
<tr><th>Formerly read:</th><th>Now reads:</th></tr>
<tr><td></td><td>treatment received.
Full Analysis Set
The analysis on the FAS will be conducted according to the allocated treatment.
Per Protocol Set
The analysis on the PPS will be conducted according to the allocated treatment.</td></tr>
<tr><td colspan="2">Section 9.7: Application of analysis sets</td></tr>
<tr><td></td><td>As SAF and FAS are expected to be identical, the analysis of demographics and baseline characteristics, including medical history and prior and concomitant medication, will only be presented for the SAF. In case of differences resulting in a need for an additional presentation for the FAS, the analysis will be provided as an additional analysis.
Demographics and other baseline characteristics are planned for SAF in PK Set. In case these two analysis sets coincide, presentations will only be prepared for the SAF.</td></tr>
<tr><td colspan="2">Section 9.7: Application of analysis sets, Table 5: Use of analysis sets</td></tr>
<tr><td>
<table>
<tr><th></th><th>Enrolled Set</th><th>Allocated Set</th><th>SAF</th><th>FAS</th><th>PPS</th><th>PK Set</th></tr>
<tr><td>Subject disposition</td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subject discontinuations</td><td></td><td>~~X~~</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Protocol deviations</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Demographics</td><td></td><td></td><td>X</td><td>~~X~~</td><td>~~X~~</td><td>X</td></tr>
<tr><td>Other baseline characteristics</td><td></td><td></td><td>X</td><td>~~X~~</td><td>~~X~~</td><td>X</td></tr>
<tr><td>Subject medical history</td><td></td><td></td><td>X</td><td>~~X~~</td><td></td><td></td></tr>
<tr><td>Previous and concomitant medication</td><td></td><td></td><td>X</td><td>~~X~~</td><td></td><td>~~X~~</td></tr>
<tr><td>Exposure</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Compliance</td><td></td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>Primary endpoint</td><td></td><td></td><td></td><td>X</td><td>X</td><td></td></tr>
<tr><td>~~Exploratory~~ efficacy endpoints</td><td></td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>Secondary safety endpoints</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Other safety parameter</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
</table>
</td><td>
<table>
<tr><th></th><th>Enrolled Set</th><th>Allocated Set</th><th>SAF</th><th>FAS</th><th>PPS</th><th>PK Set</th></tr>
<tr><td>Subject disposition</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Subject discontinuations</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Protocol deviations</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Demographics</td><td>X</td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Other baseline characteristics</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Subject medical history</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Previous and concomitant medication</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Exposure</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Compliance</td><td></td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>Serum concentrations and pharmacokinetics</td><td></td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Primary endpoint</td><td></td><td></td><td></td><td>X</td><td>X</td><td></td></tr>
<tr><td>Other efficacy endpoints</td><td></td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>Secondary safety endpoints</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
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Formerly read:	**Now reads:**
	Other safety parameter X
Section 10: Disposition	
~~For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be presented overall.~~	
Section 10.1: Subject disposition	
~~The~~ following populations will be summarized~~.~~ • Subjects enrolled (only overall) • Subjects enrolled but not allocated and reason for non-allocation (only overall) • Subjects allocated • SAF • FAS • PPS • PK-Set • Trial completers • Treatment completers (for ~~Part 2: Tapentadol~~ Period ~~only~~) • Subjects allocated and discontinued the trial • Subjects allocated and discontinued IMP (~~for Part 2:~~ Tapentadol Period only) … ~~In addition~~, an overview table will be prepared presenting the number of subjects enrolled, allocated, in the SAF, ~~-~~in the FAS and the PK-Set per country.	*All presentations for subject disposition will be as described in Section 8.1. For all Periods, descriptive summaries will also be presented overall.* *For describing the subject disposition, the* following populations will be summarized *for each of the three different trial periods if applicable:* • Subjects enrolled (only overall *for Treatment Period*). • Subjects enrolled but not allocated and reason for non-allocation (only overall *for Treatment Period*). • Subjects allocated *(Treatment Period only).* • *Subjects allocated but not treated and reason for not being treated (Treatment Period only).* • SAF. • FAS. • PPS *(Treatment Period only).* • PK-Set *(Treatment Period only).* • Trial completers. • Treatment completers (*not applicable* for *Observation* Period). • Subjects allocated and discontinued the trial. • Subjects allocated and discontinued IMP (*not applicable for Observation Period).* • *Subjects switched from Tapentadol to Observation Period (*Tapentadol Period only). … *For the Tapentadol and Observation Period, the information will be presented based on the subjects in the SAF entering these periods. The percentage denominator will be the corresponding number of subjects in the SAF.* … *Furthermore*, an overview table will be prepared presenting the number of subjects enrolled, allocated, *allocated and treated,* in the SAF, in the FAS and the PK-Set per country.
Section 10.2: Subject discontinuations	
Part 1 Discontinuations from the trial and from IMP will be	**Part 1** Discontinuations from the trial and from IMP will be

Formerly read:	**Now reads:**
presented for ~~allocated subjects~~. Reasons for discontinuations from the trial and from IMP will be presented for • Subjects ~~allocated and~~ discontinued the trial • Subjects ~~allocated and~~ discontinued IMP	presented for *the SAF overall, per country and per site*. Reasons for discontinuations from the trial and from IMP will be presented for • Subjects discontinued *from* the trial • Subjects discontinued *from* IMP **Part 2** … *Presentation will be done overall, per country and per site.*
Section 10.2: Subject discontinuations	
Part 1 and Part 2 The details for "other reasons" will be presented in a listing if applicable. If more than 10% of subjects discontinue the ~~trial/IMP~~ the distribution of the time to discontinuation from ~~trial/~~IMP will be summarized using time-to-event methods. Time will be in days until discontinuation for Part 1 and in weeks until discontinuation for ~~Part 2. A~~ graphical display using Kaplan-Meier methods displaying subjects at risk per time-point will also be produced. The calculation of time to ~~trial/~~IMP discontinuation and the censoring algorithm are described in Section ~~18.1.4.1~~. If more than 10% of subjects discontinue the ~~trial/~~IMP due to lack of efficacy, time to discontinuation due to lack of efficacy will be calculated and evaluated as described above only for subjects who discontinued due to lack of efficacy. Additionally to the censoring algorithm described in Section ~~18.1.4.1~~, subjects who discontinue ~~the trial/~~IMP for reasons other than lack of efficacy will be censored at the time of discontinuation. If more than 10% of subjects discontinue ~~the trial/~~IMP due to an adverse event (AE), time to withdrawal due to AEs will be calculated and evaluated as described above only for subjects who discontinued due to AEs. Additionally to the censoring algorithm described in Section ~~18.1.4.1~~, subjects who discontinue the ~~trial/~~IMP for reasons other than AE will be censored at the time of discontinuation.	**Part 1 and Part 2** The details for "other reasons" will be presented in a listing *sorted by site and treatment* if applicable. If more than 10% of subjects *in the SAF per treatment group of Part 1* discontinue the *IMP in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period respectively,* the distribution of the time to discontinuation from IMP will be summarized using time-to-event methods. Time will be in days until discontinuation for Part 1 and in weeks until discontinuation for *the Tapentadol Period. For the Tapentadol Period, a* graphical display using Kaplan-Meier methods displaying subjects at risk per time-point will also be produced. The calculation of time to IMP discontinuation and the censoring algorithm are described in Section *18.1.4.1*. If more than 10% of subjects *in the SAF per treatment group of Part 1* discontinue the IMP *in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period* due to lack of efficacy, *the* time to discontinuation due to lack of efficacy will be calculated and evaluated as described above only for subjects who discontinued due to lack of efficacy. Additionally to the censoring algorithm described in Section *18.1.4.1*, subjects who discontinue IMP for reasons other than lack of efficacy will be censored at the time of discontinuation. If more than 10% of subjects *in the SAF per treatment group of Part 1* discontinue IMP *in the Treatment Period or if more than 10% of subjects entering the Tapentadol Period discontinue the IMP in the Tapentadol Period* due to an adverse event (AE), time to withdrawal due to AEs will be calculated and evaluated as described above only for subjects who discontinued due to AEs. Additionally to the censoring algorithm described in Section *18.1.4.1*, subjects who discontinue the IMP for reasons other than AE will be censored at the time of discontinuation.

Formerly read:	**Now reads:**
Section 11: Demographics and other baseline characteristics	
Subject demographics and baseline characteristics will be summarized descriptively as described in Section 8.1. For Part 1, in addition to the presentation by ~~treatment arm,~~ descriptive summaries will also be presented overall. Furthermore, the subgroups as given in Table 4 will be displayed ~~using the SAF and FAS~~.	Subject demographics and baseline characteristics will be summarized descriptively as described in Section 8.1. For Part 1 *and Observation Period Part 2*, in addition to the presentation by *the arms as specified in Section 8.1,* descriptive summaries will also be presented overall. *Subject demographics will also be presented for the enrolled set (Part 1); presentation will be without treatment group but only for overall.* Furthermore, the subgroups as given in Table 4 will be displayed *for subject demographics and other baseline characteristics, excluding medical history and prior and concomitant medication*.
Section 11.1: Subject demographics	
Age will be collected at visit V1, V2 and VE. • Age at Visit V2 will be used for subject demographics of both parts. Date of signing the informed consent/assent form ~~as well as age at visit V1 and VE~~ will be included in the subject data listings only.	*Age groups will be 6-<12 years and 12-<18 years.* … *For completeness, baseline values of height and weight are tabulated with subject demographics as well.* Age will be collected at visit V1, V2 and VE. • Age at Visit V2 will be used for subject demographics of both parts. Date of signing the informed consent/assent form will be included in the subject data listings only.
Section 11.2: Other baseline characteristics	
For parameters collected on more than one occasion during the trial including baseline, the assessment at Baseline Visit will be presented with assessments collected later on in the trial and not separately for baseline. These parameters are • … • Dip stick urinalysis • ~~Pain~~ • Modified constipation assessment scale (mCAS) • ~~Serum pharmacokinetics~~ • Physical examination ~~The remaining~~ baseline characteristics ~~will be summarized descriptively~~: • Pain cause (cancer-related pain, non-cancer-related pain) • Type of pain (neuropathic, nociceptive/somatic, nociceptive/visceral) • ~~Test results of urine test for drugs of abuse (Part 1 only). Results will be displayed for each substance.~~	For parameters collected on more than one occasion during the trial including baseline, the assessment at Baseline Visit will be presented with assessments collected later on *and earlier* in the trial and not separately for baseline. These parameters are • ... • Dip stick urinalysis. • Modified constipation assessment scale (mCAS). • Physical examination. *As a parameter of special interest, baseline pain will be reported together with the assessments collected later on and earlier and in addition as* baseline characteristics*.* *Further baseline characteristics to be presented are*: • Pain cause (cancer-related pain, non-cancer-related pain). • Type of pain (neuropathic, nociceptive/somatic, nociceptive/visceral *and all possible combinations*). *Baseline pain intensity, pain cause and type of pain will be summarized descriptively.*

Formerly read:	**Now reads:**
The underlying diagnosis/reason for pain which qualified the subject for inclusion will be included in the subject data listings only.	The underlying diagnosis/reason for pain which qualified the subject for inclusion*, as well as the results of urine test for drugs of abuse,* will be included in the subject data listings only.
Section 11.4: Prior and concomitant medication or therapy	
	Therapies will only be displayed in the subject data listings. *Prior and concomitant medication is collected in the eCRF as per enrollment.*
Section 11.4: Prior and concomitant medication or therapy	
In addition the number of subjects with medication ~~started after last dose of~~ IMP for the ~~different parts~~ (flag definition see Section ~~18.1.5.5~~) will be displayed. Medication or therapy ~~started after last dose of IMP~~ during the Treatment Period of Part 1 ~~will be flagged in the subject data listing of Part 1. Medication~~ or therapy ~~started after last dose of~~ IMP ~~during~~ the Tapentadol Period of Part 2 will be flagged in the subject data listing ~~of Part 2~~.	In addition the number of subjects with medication *taken during* IMP *administration* for the *Treatment and Tapentadol Period* (flag definition see Section *18.1.5.5*) will be displayed. Medication or therapy *taken* during *IMP administration for* the Treatment Period of Part 1 *as well as medication* or therapy *taken during* IMP *administration for* the Tapentadol Period of Part 2 will be flagged in the subject data listing.
Section 12.1: Exposure	
Part 1 The ~~average~~ daily doses of IMP per kg body weight will be determined for each subject and summarized descriptively for each day of the Treatment Period. ~~In addition, these summary tables will be presented for the subgroups as specified in Table 4.~~ A graphical illustration will illustrate the means and 95% confidence intervals of the ~~average~~ daily doses of IMP (Tapentadol equivalents) of each day separately for the two treatment arms. … **Part 2** … ~~In addition, these summary tables will be presented for the subgroups as specified in Table 4.~~	**Part 1** The daily doses of IMP per kg body weight will be determined for each subject and summarized descriptively for each *calendar* day of the Treatment Period. A graphical illustration will illustrate the means and 95% confidence intervals of the daily doses of IMP *per kg body weight* (Tapentadol equivalents) of each day separately for the two treatment arms. … **Part 2** … *In case of more than one modal dose value for an interval, the average of those will be considered.*
Section 13.1: Primary endpoint	
The primary efficacy endpoint is ~~the proportion of subjects classified~~ as ~~responders. Responders are subjects who meet~~ both of the following criteria: … Pain assessments during the last 3 days of the Treatment Period means the last six scheduled pain assessments before Visit VE whether these fall across 3 ~~or 4 calendar days~~.	The primary efficacy endpoint is *a binary variable "responder". A subject is defined* as *"responder" if* both of the following criteria *are met*: … Pain assessments during the last 3 days of the Treatment Period means the last six scheduled pain assessments before Visit VE whether these fall across 3 *(morning assessment 3 days before VE until evening assessment 1*

Formerly read:	**Now reads:**
Summary statistics for the primary efficacy endpoint will be provided.	*day before VE) or 4 calendar days (evening assessment 3 days before VE until morning assessment at day of VE). The information which pain assessments should be considered can be obtained from the eDiary: If the morning diary of VE is available and assigned to the Treatment Period, this pain assessment will be included; if the morning diary of VE is not assigned to the Treatment Period, the assessments of the 3 calendar days before will be used.* Summary statistics for the primary efficacy endpoint *for the FAS and PPS* will be provided.
Section 13.1.1: Main analysis	
~~95~~% -confidence interval	*80*% -confidence interval
Section 13.1.2: Sensitivity analysis	
~~4.~~ Bayesian Analysis …	4. *Different adjustment factors:* *To assess the robustness of the results with respect to different explanatory variables in the logistic regression model, the analysis of the primary endpoint will be repeated* o *Once discarding baseline pain intensity.* o *And once including the IMP dose level during the last 3 days of the Treatment Period as specified in Section 18.1.6.1.* *5.* Bayesian Analysis: … *For this sensitivity analysis, the responder status as derived based on the alternative imputation method described in sensitivity analysis 3. above will be used.* *6. Exclusion of CRPS patients:* *The main analysis of the primary endpoint will be repeated excluding subjects with CRPS as underlying diagnosis/reason for pain as provided in the eCRF.*
Section 13.1.3: Other analysis	
Furthermore, as exploratory analyses, for subgroup levels that include at least ~~15%~~ of ~~overall data~~, the differences in Maximum Likelihood-estimators between morphine and tapentadol and their confidence intervals obtained by the Farrington Manning method will be provided and illustrated together in one forest plot.	Furthermore, as exploratory analyses, for subgroup levels that include at least *5 subjects in each* of *the two treatment groups*, the differences in Maximum Likelihood-estimators between morphine and tapentadol and their *80%* confidence intervals obtained by the Farrington Manning method will be provided and illustrated together in one forest plot. *In addition, summary statistics for the primary endpoint per IMP dose level during the last 3 days of the Treatment Period will be presented.*
Section 13.3: Other endpoints	

Formerly read:	**Now reads:**
13.3 ~~Exploratory~~ endpoints	**13.3 *Other* endpoints**
Section 13.3.2: Rescue medication	
For each day of the Treatment Period (day 1 until day 16) the two endpoints • Number of daily doses • ~~Mean total~~ daily dose (mg/kg) will be summarized descriptively and compared to the mean amount of IMP (morphine equivalent) within the treatment arms of that day. The ~~mean~~ amount of IMP will be compared over time to the two endpoints with Pearson's and Spearman's correlation coefficients (see Section ~~18.1.9~~ for details). … The percentage of days with rescue medication will be summarized descriptively as a categorical variable~~.~~	For each day of the Treatment Period (day 1 until day 16) the two endpoints • Number of daily doses. • *Total* daily dose (mg/kg). will be summarized descriptively and compared to the mean amount of IMP (morphine equivalent) within the treatment arms of that day. The *individual daily* amount of IMP will be compared over time to the two endpoints with Pearson's and Spearman's correlation coefficients (see Section *18.1.9* for details). … The percentage of days with rescue medication *intake* will be summarized descriptively as a categorical variable *using the following percentage categories: 0, (0-10), [10-20), [20-30),…, [90-100), 100. The percentages will be calculated considering the day of the first IMP intake up to the day of the last IMP intake of Part 1 (both included).*
Section 14: Analysis of pharmacokinetic and pharmacodynamics parameters	
Descriptive statistics of the observed concentrations of tapentadol and tapentadol-O-glucuronide at the respective time points will be presented~~.~~ The concentrations will be descriptively summarized by • … ~~and graphically displayed for the PK Set.~~ In addition, ~~descriptive statistics~~ will be ~~presented for the~~ subgroups as specified in ~~Table 4.~~ …	Descriptive statistics of the observed concentrations of tapentadol and tapentadol-O-glucuronide at the respective time points will be presented *for all subjects and for subgroups as specified in Table 4.* The concentrations will be descriptively summarized by • … In addition, *the data* will be *graphically displayed:* • *Boxplots of plasma concentrations of tapentadol and tapentadol-O-glucuronide (on linear scale) by subgroups as specified in Table 4.* • *Mean plasma concentration and 95% confidence interval of tapentadol and tapentadol-O-glucuronide (on linear scale) by subgroups as specified in Table 4.* … *Therefore, the population pharmacokinetic/pharmacodynamic analysis is not subjects of this SAP.*
Section 15: Safety analyses	
	Unless otherwise specified, separate descriptive analyses will be performed for the different trial periods and respective treatment groups.

Formerly read:	**Now reads:**
Section 15.1.1: Constipation assessed by the modified constipation assessment scale	
~~In addition, descriptive statistics will be presented for the subgroups as specified in Table 4.~~	
Section 15.1.2: Adverse events	
Definition of treatment emergent adverse events (TEAE) • All adverse events occurring or worsening on-treatment (defined in Section 8.2.2) are defined as TEAEs … In case of partial dates or times, this assessment is done after imputation of missing date/time information~~.~~	**Definition of treatment emergent adverse events (TEAE)** • All adverse events occurring or worsening on-treatment *in one of the trial periods* (defined in Section 8.2.2) are defined as TEAEs *of this period. Due to the consideration of the therapeutic reach in the definition of the on-treatment period, a TEAE that occurred during the on-treatment period of the Treatment or Tapentadol Period will be assigned to this trial period, although it actually might have started during the Observation Period.* … In case of partial dates or times, this assessment is done after imputation of missing date/time information*; an AE will be considered treatment emergent unless the information available will clearly exclude it.*
Section 15.1.2.1: Analyses of adverse events	
1. Summary of the number and percentage of subjects with at least one • TEAE • … ~~•~~ For Part ~~2~~ in addition: TEAE of Part 1, that are ongoing during ~~Part 2~~ o ~~For Observation Period of Part 2 in addition: TEAE of~~ Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2 o ~~TEAEs during the Observation Period are AEs~~ that started during the therapeutic reach of the ~~previous treatment.~~	1. Summary of the number and percentage of subjects with at least one • TEAE • ... • For Part *1* in addition: o TEAE of Part 1, that are ongoing during *the* Tapentadol Period of Part 2 o *TEAE of Part 1*, that are ongoing during the Observation Period of Part 2 o *TEAE of Part 1,* that *actually* started during the *Observation Period of Part 2 (within the* therapeutic reach of the *last IMP intake of the Treatment Period)* • *For Tapendatol Period of Part 2 in addition:* o *TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2* o *TEAE of Tapentadol Period of Part 2, that actually started during the Observation Period of Part 2 (within the therapeutic reach of the last IMP intake of the Tapentadol Period)* o *TEAE of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2*

Formerly read:	**Now reads:**
3. Summary of the number and percentage of TEAEs for • TEAEs • … o For Part ~~2~~ in addition: TEAE~~s~~ of Part 1, that are ongoing during Part 2 o For ~~Observation~~ Period of Part 2 in addition: ~~TEAEs~~ of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2	• 3. Summary of the number and percentage of TEAEs for • TEAEs • … • For Part *1* in addition: a. TEAE of Part 1, that are ongoing during *the Tapentadol Period of* Part 2 *b. TEAE of Part 1, that are ongoing during the Observation Period of Part 2* *c. TEAE of Part 1, that actually started during the Observation Period of Part 2* • For *Tapendatol* Period of Part 2 in addition: *d. TEAE of Part 1, that are ongoing during the Tapentadol Period of Part 2* *e. TEAE of Tapentadol Period of Part 2, that actually started during the Observation Period of Part 2* f. *TEAE* of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2 *In addition, these overview tables will be presented for subgroups as specified in Table 4.*
Section 15.1.2.2: Incidence, incidence rates and numbers of events	
For Part 1 and the Tapentadol Period of Part 2, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by System Organ Class (SOC) and PT (sorted alphabetically) for each • TEAEs • serious TEAEs • related TEAEs The incidence, incidence rate, the number of events and	***Analysis by Preferred Term*** … *Percentages will be calculated related to the total number of subjects/events presented in the table, i.e., the number of subjects with TEAEs and the total number TEAEs for the respective trial Period.* ***Analysis by System Organ Class and Preferred Term*** For Part 1 and the Tapentadol Period of Part 2, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by System Organ Class (SOC) and PT (sorted alphabetically) for each • TEAEs • Serious TEAEs • *Non-serious TEAEs* • Related TEAEs … *For serious TEAEs, the incidence, incidence rate, the number of events and the percentage of events will also be presented for serious related TEAEs, serious fatal*

Formerly read:	**Now reads:**
the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each • Pre-treatment … • Post-treatment (~~Observation Period~~ of ~~Part 2 only~~) – non-TEAE o ~~non-TEAEs of Part 1, that are ongoing during Part 2~~ o ~~non-TEAEs of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2~~ – serious non-TEAE o ~~serious non-TEAEs of Part 1, that are ongoing during Part 2~~ o ~~serious non-TEAEs of Tapentadol Period of Part 2, that are ongoing during the Observation Period of Part 2~~ ~~For Part 1, post-treatment non-TEAEs will only include AEs that occur after 72 hours after last IMP but before Visit VE. These non-TEAEs will only be listed. All other post-treatment non-TEAEs will only be included in Part 2.~~ ~~For the Tapentadol Period of Part 2, post-treatment non-TEAEs will only include AEs that either occur after the therapeutic reach after last IMP regarding Visit F12M or that occur after 72 hours after last IMP but before Visit ET for subjects who switch to Observation Period. These non-TEAEs will only be listed. All other post-treatment non-TEAEs will be included in the Observation Period of Part 2.~~ For Part 1 and the Tapentadol Period of Part 2, the number and percentage of events will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors. Presentations will be for TEAEs only. • Intensity: mild, moderate, severe • … • Action taken with IMP: dose increased, dose reduced, drug interrupted, drug withdrawn, dose not changed, not applicable, unknown • Duration of TEAEs: Duration will be analyzed in days with measures of dispersion and variation. • Time to onset of TEAE will be analyzed in days with measures of dispersion and variation. Denominator for percentage calculation will be the number of all TEAEs~~/post-treatment non-TEAE~~ for presentation over all SOCs, and the number of	*TEAEs and serious fatal related TEAEs.* *Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of SOC and PT for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.* *For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.* The incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each • Pre-treatment … • Post-treatment (*all trial Periods together, SAF, presenting the arms* of *the Observation Period*) – Non-TEAE – Serious non-TEAE *Percentages will be calculated related to the total number of subjects/events presented in the respective table as outlined above for the TEAE tables by SOC and PT.* ***Analysis by System Organ Class, Preferred Term and descriptors*** For Part 1 and the Tapentadol Period of Part 2, the number and percentage of events will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors. Presentations will be for TEAEs only. • Intensity: mild, moderate, severe

Formerly read:	**Now reads:**
TEAEs~~/post-treatment non-TEAE~~ per SOC or PT for the presentation per SOC and PT, respectively. ~~For the Observation Period of Part 2, the~~ number and percentage of post-treatment non-TEAEs will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors: The following listings will be produced for all enrolled subjects: • …	• … • Action taken with IMP: dose increased, dose reduced, drug interrupted, drug withdrawn, dose not changed, not applicable, unknown • *Measures of location and variation will be calculated for:* • Duration of TEAEs: Duration will be analyzed in days with measures of dispersion and variation. • Time to onset of TEAE will be analyzed in days with measures of dispersion and variation. Denominator for percentage calculation will be the number of all TEAEs for presentation over all SOCs, and the number of TEAEs per SOC or PT *respectively* for the presentation per SOC and PT, respectively. *The* number and percentage of *all* post-treatment non-TEAEs *(all Periods together)* will be summarized by SOC and PT (sorted alphabetically) for the following AE descriptors: ***Listings*** The following listings will be produced for all enrolled subjects: • … • *AEs leading to IMP dose decrease or interruption of IMP.* • *AEs starting on the day of Visit VE (including the last IMP intake of Part 1 and first IMP intake of Part 2 [eDiary and dispense information])*
Section 15.1.2.3: Exposure adjusted incidence rate	
To overcome the difficulties of interpreting the incidence rate in the presence of subjects who prematurely discontinue in ~~a~~ trial, the exposure-adjusted incidence rate (EAIR) will be used (Siddiqui 2009) in addition to the CIR. ~~(1-α) confidence intervals for differences of incidence rates are defined in Section 20.1.11.9 and are regarded as exploratory analyses.~~ ~~**Part 1**~~ For TEAEs ~~with a CIR of at least 5% in~~ the ~~either arm, the point estimates and confidence intervals of the EAIR and CIR for each treatment arm will be presented side by side with the difference in EAIR and CIR between treatments (tapentadol minus morphine) and the respective 95% confidence intervals for the difference. Sorting will be by PT.~~ **Tapentadol Period ~~of Part 2~~**	To overcome the difficulties of interpreting the incidence rate in the presence of subjects who prematurely discontinue in *the Tapentadol Period of the* trial, the exposure-adjusted incidence rate (EAIR) will be used (Siddiqui 2009) in addition to the CIR. For TEAEs *of* the Tapentadol Period with a CIR of at least 5% in either arm defined in Section 8.1, the point estimates of the EAIR and CIR will be presented for each arm. Sorting will be by PT.

Formerly read:	**Now reads:**
~~For TEAEs~~ with a CIR of at least 5% in either arm defined in Section 8.1, the point estimates ~~and confidence intervals~~ of the EAIR and CIR will be presented for each arm. Sorting will be by PT. ~~**Observation Period of Part 2**~~ ~~For post-treatment non-TEAEs with a CIR of at least 5% in either arm of subjects continuing in the Observation Period directly after Part 1, the point estimates and confidence intervals of the EAIR and CIR will be presented for each arm. Sorting will be by PT.~~	
Section15.2: Other endpoints	
15.2 ~~Exploratory and o~~ther endpoints	**15.2 *O*ther endpoints**
Section 15.2.1: Laboratory parameters	
Hematology panel: Hemoglobin, Hematocrit, Mean cell volume (MCV), Red blood cell (RBC) count, White blood cell (WBC) count ~~(if WBC abnormal, also differential count)~~, Platelet count	**Hematology panel:** Hemoglobin, Hematocrit, Mean cell volume (MCV), Red blood cell (RBC) count, *Red blood cell morphology,* White blood cell (WBC) count, *White blood cell differential count,* Platelet count, *White blood cell morphology*
Section 15.2.1: Laboratory parameters	
For summary statistics, only values obtained from the central laboratory will be used. The creatinine clearance (CL_{CR}) will be calculated using a central laboratory standard age appropriate formula and will also be analyzed. … Shift tables from baseline for the different visits and overall ~~(worst value on treatment,~~ see Section ~~18.1.12.1 for definition of worst)~~ will be generated for each laboratory parameter for categories low, normal and high, based on the reference ranges of the central laboratory. … ~~In addition, the above descriptive statistics and graphs will be presented for the subgroups as specified in Table 4.~~ A listing of subjects with PCI values will be provided. … All laboratory values will be presented in the subject data listing of the respective part. Values out of reference ranges will be flagged as H (above the reference range) or L (below the reference range) in the listing.	For summary statistics *and for the classification of values based on the reference and alert ranges*, only values obtained from the central laboratory will be used. The creatinine clearance (CL_{CR}) will be calculated *in the eCRF* using a central laboratory standard age appropriate formula and will also be analyzed. … Shift tables from baseline for the different visits and overall *post-baseline (*see Section *18.1.12.1)* will be generated for each laboratory parameter for categories low, normal and high, based on the reference ranges of the central laboratory. … A listing of subjects with PCI values will be provided. *A listing of subjects with any laboratory results outside the reference ranges will be provided.* … All laboratory values will be presented in the subject data listing of the respective part. Values out of reference ranges will be flagged as H (above the reference range) or L (below the reference range) in the listing. *If a value classified as high or low is in addition also out of alert ranges, it will be flagged as H* or L* in the listing.*
Section 15.2.2: Electrocardiogram	
	A subject data listing of all abnormal, clinically relevant findings as documented by the investigator in the eCRF will be created.

Formerly read:	**Now reads:**
Section 15.2.3: Vital signs	
~~In addition, descriptive summaries and graphs will be presented for the subgroups as specified in Table 4.~~ ~~For each part separately, a~~ listing of subjects with vital sign results outside the sponsor defined alert ranges will be provided (Table 10). All vital signs values will be presented in the subject data listing of the respective part. Values out of normal ranges (Table 9) will be flagged as H (above the normal range) or L (below the normal range) in the listing. Table 9: Normal ranges of vital signs ~~and oxygen saturation~~ Table 10: Potentially clinically important values for vital signs ~~and oxygen saturation~~	*A* listing of subjects with vital sign results outside the sponsor defined alert ranges will be provided (Table 10). All vital signs values will be presented in the subject data listing of the respective part. Values out of normal ranges (Table 9) will be flagged as H (above the normal range) or L (below the normal range) in the listing. *If a value classified as high or low is in addition also out of alert ranges, it will be flagged as H* or L* in the listing.* Table 9: Normal ranges of vital signs Table 10: Potentially clinically important values for vital signs
Section 15.2.4: Urine pregnancy test	
Results of ~~the~~ pregnancy test will be ~~summarized descriptively for each visit. For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be~~ presented ~~overall.~~ ~~A~~ listing ~~of subjects with positive pregnancy test will be provided~~ including all information collected on the respective eCRF-page.	Results of *all urine* pregnancy test*s* will be presented *in a subject data* listing*,* including all information collected on the respective eCRF-page.
Section 15.2.5: Physical examination	
~~For each visit, answers on the questions are summarized descriptively. For Part 1, in addition to the presentation by treatment arm, descriptive summaries will also be presented overall.~~ ~~In addition, descriptive statistics will be presented for the subgroups as specified in Table 4.~~	*Results of all physical examinations will be presented in a subject data listing, including the descriptions of abnormalities.*
Section 15.2.6: Constipation assessed by the modified constipation assessment scale	
~~Details on the programming aspects regarding the mCAS can be found in Section 20.1.13.~~	
Section 15.2.7: Height	
Part 1 Assessments will be summarized descriptively for each visit. **Part 2** Assessments and changes from baseline will be summarized descriptively.	**Part 1** Assessments *of height and changes from baseline* will be summarized descriptively *by age subgroups* for each visit. **Part 2** Assessments *of height* and changes from baseline will be summarized descriptively *by age subgroups*. *The patient's height will be transformed into an age and sex*

Formerly read:	**Now reads:**
	adjusted Z-score. The Z-score and change from baseline in Z-score will be summarized by visit, by treatment arm and overall. *Details on the programming aspects regarding the height Z-Score can be found in Section 18.1.5.2.*
Section 15.2.9: Subjective opiate withdrawal scale (SOWS)	
The SOWS questionnaire will be completed once daily starting from • Part 1: ~~(including)~~ Visit VE (baseline) until ~~Visit F7D (included)~~ • Part 2: ~~(including)~~ Visit ET/F12M of the Tapentadol Period (baseline) until ~~Visit F7D (included)~~ The total score of the SOWS questionnaire and the change from baseline will be descriptively analyzed per day after last IMP intake~~, up to day 7 after last IMP intake.~~ For subjects stopping IMP intake prior to Visit VE/ET/F12M, the information of the last IMP intake (End of Trial page of eCRF) will be used to determine the day after last IMP intake. ~~SOWS scores after 7 days after last IMP will only be included in the subject data listing.~~	The SOWS questionnaire will be completed once daily starting from • Part 1: *the day after* Visit VE (baseline) until *the seventh day after the last intake of IMP for subjects not entering the Tapentadol Period.* • Part 2: *the day after* Visit ET/F12M of the Tapentadol Period (baseline) until *the seventh day after the last intake of IMP for subjects entering the Tapentadol Period* The total score of the SOWS questionnaire and the change from baseline will be descriptively analyzed per day after last IMP intake. For subjects stopping IMP intake prior to Visit VE/ET/F12M, the information of the last IMP intake (End of Trial page of eCRF) will be used to determine the day after last IMP intake.
Original Section 16: Other data	
	Section 16 deleted as 16.1 Acceptability and palatability shifted to Section 13 (13.4).
Original Section 17: Interim analysis	
	Complete Section 17 deleted, as due to the sample size reduction, the interim analysis was discarded.
Section 16: References (original Section 18)	
~~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.~~	*Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen, W. Analysis of clinical trials using SAS®: a practical guide, Cary, NC: SAS Institute Inc.; 2005.p 308 ff.* *WHO Multicentre Growth Reference Study Group (2006). WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization; pp 312 (web site: http://www.who.int/childgrowth/publications/en/)*
Section 18.1.2.2: Presentation of descriptive statistics (original Section 20.1.2.2), Table 11	
	Footnotes added: *n = number of values, sd = standard deviation, min = minimum, Q1 = first quartile, Q3 = third quartile, max=maximum*
Section 18.1.2: General specifications (original Section 20.1.2)	
	The following sections were added. Please see sections for further details.

Formerly read:	**Now reads:**
	18.1.2.3 Presentation of differences and changes *18.1.2.4 Trial day count* *18.1.2.5 Conversion of time intervals* *18.1.2.6 Presentation of units* *18.1.2.7 Presentation of dates* *18.1.2.8 Handling of missing values* *18.1.2.11 First and last IMP intake*
Section 18.1.2.10: Trial phases and period (original Section 20.1.2.4)	
Tapentadol Period • The Tapentadol Period end date is the date ~~of Visit F12M. If Visit F12M is not performed, the date~~ assessed on the End of Period page of the eCRF at the end of the Tapentadol Period ~~is used~~.	Tapentadol Period • The Tapentadol Period end date is the date assessed on the End of Period page of the eCRF at the end of the Tapentadol Period.
Section 18.1.4.1 Subjects discontinuation (original Section 20.1.4.1)	
Completion status Treatment completer: • Part 1: ~~If (End of Treatment Visit date − Randomization date) ≥ 13~~ • Part 2, Tapentadol Period only: If (F12M date − End of Treatment Visit date) ≥ 351	**Completion status** Treatment completer: • Part 1: – *If* $(End\ of\ Treatment\ Visit\ date - Randomi$ 13 *and either* $(Last\ IMP\ intake\ of\ the\ Treatment\ Perio$ $Randomization\ date) \geq 13$ *or* $(Last\ IMP\ intake\ of\ the\ Treatment\ Perio$ $Randomization\ date) = 12$ *with last IMP intake of the Treatment Period in the evening* • Part 2, Tapentadol Period only: – If $(F12M\ date -$ $End\ of\ Treatment\ Visit\ date) \geq 351$
Time to discontinuation Time to treatment discontinuation will be calculated in days for Part 1 as: $~~End~~\ of\ Treatment\ ~~Visit\ date~~ - ~~Randomization\ date\ + 1~~$ ~~Time to trial discontinuation will be calculated in days for Part 1 as:~~ $~~date\ of\ End\ of\ Trial\ page\ in\ eCRF~~ - Randomization\ date + 1$ Time to treatment discontinuation will be calculated in weeks for Part 2 as: $(date\ of\ ~~Visit\ ET - date\ of\ Visit\ VE + 1)/7~~$ ~~Time to trial discontinuation will be calculated in weeks~~	**Time to discontinuation** Time to treatment discontinuation will be calculated in days for Part 1 as: $date\ of\ Last\ IMP\ intake\ of\ the\ Treatment\ Period - Randomization\ date + 1$ Time to treatment discontinuation will be calculated in weeks for Part 2 as: $(date\ of\ Last\ IMP\ intake\ of\ the\ Tapentadol\ Period - date\ of\ Visit\ VE + 1)/7$

Formerly read:	**Now reads:**
~~for Part 2 as:~~ ~~$(date\ on\ End\ of\ Trial\ page\ in\ eCRF - date\ of\ Visit\ VE + 1)/7$~~ Censoring algorithm ~~• Time to trial discontinuation:~~ ~~– Part 1: time will be censored at~~ ~~o the final post treatment visit F7D for subjects entering the Observation Period, i.e., with "… will proceed in the Observation Period" is ticked on the subject eligibility page in the eCRF.~~ ~~o date of Visit VE for subjects entering the Tapentadol Period, i.e., with "… will proceed in the Tapentadol Period" is ticked on the subject eligibility page in the eCRF~~ ~~– Part 2: time will be censored at~~ ~~o Date of final post treatment visit (F7D) for subjects completing the Tapentadol Period and the follow-up visit~~ ~~Date of visit 12 month after Visit VE for subjects completing the Observation Period.~~	Censoring algorithm
Section 18.1.5.2: Other baseline characteristics (see Section 20.1.5.2)	
~~Not applicable.~~	***Derivation of height Z-Scores*** *The height Z-Scores will be calculated using the WHO Child Growth Standards. The Z-scores can be calculated using the algorithm as implemented in the SAS igrowup package (www.who.int/childgrowth/software/en/) and the required reference files for subjects from 6-<18 years old provided by the WHO (http://www.who.int/growthref/who2007_height_for_age/en/) .*
Section 18.1.5.3 Baseline pain intensity of the Treatment Period (new Section)	
	According to the protocol, the first dose of IMP should be taken during Visit V2, within 24 hours after randomization. Therefore, the actual day of first IMP intake is not necessarily the same as the day of randomization, but might be the day after the randomization. Based on this, from a programming perspective baseline pain will be derived as follows: • *The pain assessment in the eDiary on the day and at the day time (morning/evening) of the first IMP intake of the Treatment Period will be used as baseline pain.* • *In case this eDiary entry is missing, the last*

<table>
<tr><th>Formerly read:</th><th>Now reads:</th></tr>
<tr><td></td><td>available pain assessment before this time point will be used.
• In case this eDiary entry is missing and there is no earlier pain assessment available, baseline pain will be set to missing.</td></tr>
<tr><td colspan="2">Section 18.1.5.5: Prior and concomitant medication or therapy (original Section 20.1.5.4)</td></tr>
<tr><td>
Assignment of categories “prior” and “concomitant”

Part 1:
Prerequisite is a complete date of first dose of IMP ~~(first IMP entry in eDiary)~~.

Part 2:
~~Prerequisite is a complete date of first dose of IMP (first IMP entry in eDiary).~~
<table>
<tr><th>Date of medication</th><th>Condition</th><th>Category</th></tr>
<tr><td>Complete stop date is available</td><td>Stop date is earlier than or equal to date of Visit VE</td><td>prior</td></tr>
<tr><td>Stop date with missing month</td><td>Year of stop date is earlier than year of Visit VE</td><td>prior</td></tr>
<tr><td>Stop date with missing day</td><td>Month/year of stop date are earlier than month/year of Visit VE</td><td>prior</td></tr>
<tr><td>Tapentadol Period: Complete start date is available</td><td>Start date is later than Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td>Tapentadol Period: Start date with missing month</td><td>Year of start date is later than year of Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td>Tapentadol Period: Start date with missing day</td><td>month/year of start date is later than month/year of Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td colspan="2">otherwise</td><td>concomitant</td></tr>
</table>
~~Prerequisite is a complete date of first dose of IMP (first~~
</td><td>
Assignment of categories “prior” and “concomitant”

Part 1:
Prerequisite is a complete date of first dose of IMP.

Part 2:
<table>
<tr><th>Date of medication</th><th>Condition</th><th>Category</th></tr>
<tr><td>Complete stop date is available</td><td>Stop date is earlier than or equal to date of Visit VE</td><td>prior</td></tr>
<tr><td>Stop date with missing month</td><td>Year of stop date is earlier than year of Visit VE</td><td>prior</td></tr>
<tr><td>Stop date with missing day</td><td>Month/year of stop date are earlier than month/year of Visit VE</td><td>prior</td></tr>
<tr><td>Tapentadol Period: Complete start date is available</td><td>Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period:
Start date is later than Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td>Tapentadol Period: Start date with missing month</td><td>Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period:
Year of start date is later than year of Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td>Tapentadol Period: Start date with missing day</td><td>Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period:
month/year of start date is later than month/year of Visit ET</td><td>Not considered for Tapentadol period</td></tr>
<tr><td colspan="2">otherwise</td><td>concomitant</td></tr>
</table>
</td></tr>
</table>

Formerly read:

~~IMP entry in eDiary).~~

Assignment of ~~post-IMP flag~~

Part 1:

The following rules are used to identify medications or therapies which ~~started after last dose of IMP~~ during the Treatment Period of Part 1.

Prerequisite is a complete date of last dose of IMP ~~(first IMP entry in eDiary)~~.

Start of medication or therapy date	**Condition**	**~~Start after last dose of IMP~~**
complete date is available	start date is later than date of last dose of IMP, but before Visit VE	~~yes~~
Otherwise (due to short Treatment Period)		~~no~~

Part 2:

The following rules are used to identify medications or therapies which ~~started after last dose of IMP during~~ the Tapentadol Period of Part 2.

Prerequisite is a complete date of last dose of IMP ~~(first IMP entry in eDiary)~~.

Start of medication or therapy date	**Condition**	**~~Start after last dose of IMP~~**
complete date is available	start date is later than date of last dose of IMP	~~yes~~
missing month	year of start date is later than year of last dose of IMP	~~yes~~
missing day	month/year of start date are later than month/year of last dose of IMP	~~yes~~
Otherwise		~~no~~

Now reads:

Assignment of *flag for medication/therapy taken during IMP administration*

Part 1:

The following rules are used to identify medications or therapies which *were taken* during *IMP administration of* the Treatment Period of Part 1.

Prerequisite is a complete date of last dose of IMP *for the Treatment Period*.

Start of medication or therapy date	**Condition**	***Flag for medication during IMP administration***
Medication/therapy is not a concomitant medication of Part 1		*no*
complete date is available	start date is later than date of last dose of IMP, but before Visit VE	*no*
Otherwise (due to short Treatment Period)		*yes*

Part 2:

The following rules are used to identify medications or therapies which *were taken during IMP administration of* the Tapentadol Period of Part 2.

Prerequisite is a complete date of last dose of IMP *for the Tapentadol Period.*

Start of medication or therapy date	**Condition**	***Flag for medication during IMP administration***

<table>
<tr><th>Formerly read:</th><th>Now reads:</th></tr>
<tr><td></td><td>
<table>
<tr><td>Medication/therapy is not a concomitant medication of the Tapentadol Period of Part 2</td><td></td><td>no</td></tr>
<tr><td>complete date is available</td><td>start date is later than date of last dose of IMP</td><td>no</td></tr>
<tr><td>missing month</td><td>year of start date is later than year of last dose of IMP</td><td>no</td></tr>
<tr><td>missing day</td><td>month/year of start date are later than month/year of last dose of IMP</td><td>no</td></tr>
<tr><td colspan="2">Otherwise</td><td>yes</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Section 18.1.6: Exposure (original Section 20.1.6)</td></tr>
<tr><td></td><td><u>Original text denoted as Section 18.1.6.2: Average daily doses during the Tapentadol Period and additional Section 18.1.6.1: Dose level for the sensitivity analysis of the primary endpoint added. Please see sections for further details.</u></td></tr>
<tr><td colspan="2">Section 18.1.8: Primary endpoint (original section 20.1.7)</td></tr>
<tr><td>Calculating the confidence interval and p-value based on the Farrington-Manning test
…
• N_2: sample size of morphine arm in Part ~~2~~
• …
• $b = -[1 + r + \hat{p}_T + r * \hat{p}_C ~~+~~ \delta * (r + 2)]$
• $c = \delta^2 ~~+~~ \delta(2 * \hat{p}_T + r + 1) + \hat{p}_T + r * \hat{p}_C$
• $d = ~~-~~\hat{p}_T * \delta * (1 ~~+~~ \delta)$
…
~~95~~% -confidence interval
$\alpha = 0.~~025~~$.
Handling missing data
In this case Multiple Imputation will be used to impute</td><td><u>New Section 18.1.8 Primary endpoint introduced, with original Section 20.1.8 Primary analysis as subsection 18.1.8.2. New subsection 18.1.8.1 Missing baseline pain intensity for the Treatment Period added. Please see section for further details.</u>
Calculating the confidence interval and p-value based on the Farrington-Manning test
…
• N_2: sample size of morphine arm in Part 1
• …
• $b = -[1 + r + \hat{p}_T + r * \hat{p}_C - \delta * (r + 2)]$
• $c = \delta^2 - \delta(2 * \hat{p}_T + r + 1) + \hat{p}_T + r * \hat{p}_C$
• $d = \hat{p}_T * \delta * (1 - \delta)$
…
80% -confidence interval
$\alpha = 0.1$.
Handling missing data
In this case Multiple Imputation will be used to impute missing values:</td></tr>
</table>

Formerly read:	**Now reads:**
missing values: ~~1. Let~~ the vector of the last 6 scheduled pain measurements ~~be~~ denoted by $(Y_1, \dots, Y_6)$ ~~with~~ $(Y_1, \dots, Y_6) \sim MVN(\mu, \Sigma)$. ~~For each of the eight combinations of~~ ~~g. Treatment (tapentadol/morphine)~~ ~~h. Age group ([6y,12y), [12y,18y))~~ ~~i. Underlying pain condition (cancer/non-cancer)~~ ~~PROC MI is used~~ to ~~impute~~ the missing pain assessments~~.~~... ~~In case of difficulties to establish a specific covariance matrix Σ for all eight combinations of treatment, age group and underlying pain condition due to low sample sizes, one common covariance matrix will be determined using the overall population (FAS). This covariance matrix will then be used for each of the eight combinations.~~ *3.* With $(\hat{\theta}_1, \hat{v}_{0,1}), \dots, (\hat{\theta}_{200}, \hat{v}_{0,200})$ as input, PROC MIANALYZE will be applied to obtain the test statistic T_{MI} and confidence interval CI_{MI} as follows: … with $t_{\vartheta,1-\alpha}$ being the $(1-\alpha)$-quantile of the *t*-distribution with $\alpha = 0.$~~025~~ and ϑ degrees of freedom.	1. For each treatment group, a multivariate normal distribution for the vector of the last 6 scheduled pain measurements during the Treatment Period, denoted by $(Y_1, \dots, Y_6)$, is assumed $(Y_1, \dots, Y_6) \sim MVN(\mu, \Sigma)$. Missing observations are assumed to depend on the observed values of the subjects in the same treatment group. Therefore, in both treatment arms, missing pain assessments will be imputed using information from an imputation model that is only based on the subjects in the respective arm, with baseline pain intensity, age group and underlying pain condition as explanatory variables. *The multiple imputations will be done via SAS PROC MI. The imputation model will be based on the default Markov chain Monte Carlo (MCMC) method for general patterns of missingness (Dmitrienko et al. 2005).* *For the sake of reproducibility of the results, the seed for pseudo-random number generation will be set to 550366 for each of both treatment arms.* *3.* With $(\hat{\theta}_1, \sqrt{\hat{v}_{0,1}}), \dots, (\hat{\theta}_{200}, \sqrt{\hat{v}_{0,200}})$ as input, PROC MIANALYZE will be applied to obtain the test statistic T_{MI} and confidence interval CI_{MI} as follows: … with $t_{\vartheta,1-\alpha}$ being the $(1-\alpha)$-quantile of the *t*-distribution with $\alpha = 0.1$ and ϑ degrees of freedom.
Section 18.1.8.3: Bayesian analysis – Details (original Section 20.1.9)	
~~95~~% credibility interval	*80*% credibility interval
Section 18.1.9: Pain assessed using a VAS and FPS-R scale (new Section)	
	Section was added. Please see sections for further details.
Section 18.1.10: Rescue medication (original Section 20.1.10)	
The summary table for the number of daily doses and ~~mean~~ total daily dose include the mean amount of IMP (morphine equivalents). … **Time to first rescue medication intake** The information of date/time of first rescue medication intake ~~and first IMP intake~~ will be taken from the eDiary.	The summary table for the number of daily doses and total daily dose *per day of the Treatment Period* include the mean amount of IMP (morphine equivalents). … *The correlation coefficients will be calculated using PROC CORR.* **Time to first rescue medication intake** The information of date/time of first rescue medication intake will be taken from the eDiary.

Formerly read:	**Now reads:**
Section 18.1.11.3: Assessment of TEAEs (original Section 20.1.9.3)	
The assessment whether an AE is a TEAE, a pre-treatment or a post-treatment non-TEAE of the different trial periods will be done after replacement of missing date~~/time~~ information.	The assessment whether an AE is a TEAE, a pre-treatment or a post-treatment non-TEAE of the different trial periods will be done after replacement of missing date information.
Section 18.1.11.4: Handling different episodes of the same adverse event	
In the following causal relationship is ordered in descending order starting with the worst expression: 1) certain, 2) conditional/unclassified, ~~3~~) unassessable/unclassifiable, ~~4) possible, 5) probable/likely,~~ 6) unlikely, 7) not related	In the following causal relationship is ordered in descending order starting with the worst expression: 1) certain, 2) *probable/likely, 3) possible, 4)* conditional /unclassified, *5*) unassessable/unclassifiable, 6) unlikely, 7) not related
Section18.1.11.7: Time to onset of AE	
	In case the time of first administration of IMP is missing, time equal "00:00" will be used for calculation.
Section 18.1.12: Laboratory, vital signs and ECG parameters (original Section 20.1.10)	
~~**20.1.12.1 Frequency table of potentially clinically important values**~~ ~~Percentages for the PCI tables will be calculated as:~~ ~~2. Summary by visit for all subjects:~~ ~~% subjects with PCI values at visit x (total) =~~ ~~# subjects with a post − baseline PCI value at visit x / # subjects with a post − baseline assessment at visit x * 100~~ ~~4. Summary overall post-baseline for all subjects:~~ ~~% subjects with PCI values (total) =~~ ~~# subjects with at least 1 post − baseline PCI value / # subjects with at least 1 post − baseline assessment * 100~~	***Ordering of parameters*** *Laboratory parameters, vital signs and ECG parameters will be ordered alphabetically within their parameter group (e.g., hematology, clinical chemistry, and urinalysis). Visits will be sorted chronologically. If changes from BL are displayed by visit all visits will be displayed first followed by all the changes from baseline.* ***Not exact values*** *Not exact laboratory values such as < x, > x will not be included in the analysis of continuous parameters. The frequency of occurrence of not exact values will be displayed in the respective table where applicable.* ***Categorical parameters*** *For categorical parameters, 2 types of tables are created:* *1. Frequency tables display the pre-defined categories by visit and overall post-baseline.* *2. Shift tables display the shift from baseline at each visit and overall.* *Both types of tables show the number of subjects still in the trial (n) at the visit and the number of missing values (nMiss) at the visit. For the overall presentation, all post-baseline values on treatment are taken into account and nMiss is the number of subjects without any on-treatment post-baseline values.* *In tables where parameters are classified as abnormal low, normal, abnormal high based on reference ranges, and alert low, normal, alert high based on sponsor-defined alert ranges the available pre-defined categories must be displayed in tables even if there are categories to which no subjects belong. Categories that are not*

Formerly read:	**Now reads:**
	applicable must be omitted.
Original Section 20.1.11.9: Confidence intervals for difference in incidence rates	
	Section with programming specifications for the confidence intervals for difference in incidence rates deleted, as no confidence intervals for incidence rates will not be presented.
Section 18.1.12.1: Overall post-baseline value (original Section 20.1.10.2)	
Therefore, all post-baseline assessments, including unscheduled assessments, are taken into account ~~and the "worst" of those will be considered~~. ~~"Worst" for the different parameters is defined as follows:~~ ~~PCI xxx > PCI yyy: PCI xxx is worse than PCI yyy, and in case both PCI xxx and PCI yyy for the corresponding parameter is observed post-baseline during the respective period of interest (treatment period, Tapentadol Period, Observation Period), PCI xxx will be counted for this parameter.~~	Therefore, all post-baseline assessments, including unscheduled assessments, are taken into account. *For the overall post-baseline summary subjects might have both low and high values. These subjects will be categorized in a new category "high and low" and excluded from the categories "high" and "low". The inclusion of this category in the frequency and shift tables is only required if there are any subjects falling into this category.*
Original Section 20.1.11: Modified constipation assessment scale	
~~The answer to each item will be entered in the eCRF. The eCRF will calculate the total score as sum of the individual answers. Thus the total score will be available in the SDTM data set.~~ ~~If at least one answer is missing or at least one answer is "Unable to Assess", the eCRF will assign the total score to "Unable to Assess".~~	Section deleted.
Original Section 20.1.13: Interim analysis – Algorithm to determine actual CP_{min}	
	Section deleted.
Section 18.2: Sponsor defined alert ranges for laboratory parameters (original Section 20.2)	
~~Table 12: Potentially clinically important values for laboratory parameters~~	*Potentially clinically important values for laboratory parameters are assessed based on the sponsor defined alert ranges, and can be both, either alert high or alert low values. The sponsor defined alert ranges were defined in the laboratory statement of work and are implemented in the SDTM data. Therefore, they are not repeated here.*

18 APPENDIX

18.1 Programming specifications

18.1.1 Introduction

The purpose of this section is to give technical details for SAP text implemented as Statistical Analysis System (SAS) code.

18.1.2 General specifications

18.1.2.1 Percentages and decimal places

If not otherwise specified, the following rules are applied:

- Study Data Tabulation Model (SDTM) or Analysis Data Model ADaM data sets will contain unrounded values.
- For presentations, the following rounding rules apply:
  - Percentages are presented to 1 decimal point.
  - Percentages equal to 0 or 100 are presented as such without a decimal point.
  - For descriptive summary statistics, the same number of decimal places as in the raw data are presented when reporting minimum and maximum values, 1 more decimal place when reporting mean, median, quartiles and confidence interval (CI) and standard deviation (SD).
  - P-values are presented to 4 decimal points.
  - Ratios are presented to 3 decimal points.

The above described displaying rules must not be changed (e.g., rounding) for the ICTR text and are used 1:1 in the body report as well.

18.1.2.2 Presentation of descriptive statistics

Calculation of mean: if not otherwise specified (e.g., for pharmacokinetic data), the arithmetic mean is used.

Table 11: Presentation of descriptive statistics in clinical trials

Number of non-missing values	n	missing n	mean	SD	min	Q1	median	Q3	max
0	+	+	-	-	-	-	-	-	-
1.2.3.4	+	+	+	-	+	-	+	-	+
≥5	+	+	+	+	+	+	+	+	+

+ summary statistic will be presented; - summary statistic will not be presented.

n = number of values, SD = standard deviation, min = minimum, Q1 = first quartile, Q3 = third quartile, max=maximum

18.1.2.3 Presentation of differences and changes

For differences between active and active comparator, active will constitute the minuend and comparator the subtrahend.

For changes from baseline, the baseline value will constitute the subtrahend and the later value the minuend.

18.1.2.4 Trial day count

The day of first IMP intake is defined as trial Day 1.

Calculate the trial day according to the following rules:

- If date < trial Day 1 then trial day = Date – trial Day 1.
- If date ≥ trial Day 1 then trial day = Date – trial Day 1 +1.

18.1.2.5 Conversion of time intervals

If a time interval was calculated in minutes, hours or days and needs to be converted into months or years, the following conversion factors will be used:

- 1 month = 30 days
- 1 year = 365.25 days

18.1.2.6 Presentation of units

If applicable, parameters will be displayed together with the used unit of measurement. The unit of measurement is enclosed in square brackets ([ ]).

18.1.2.7 Presentation of dates

Where applicable (e.g., in listings), dates will be displayed in ISO8601 format (example: 2014-09-29T12:16, see CDISC 2013). In case of incomplete dates, both the original value and the imputed value (if available) is displayed.

18.1.2.8 Handling of missing values

At each time point/visit, all subjects still in the trial are reported. Missing values will be taken into account as missing in the analysis. The number of observed values and the number of missing values must sum up to the number of subjects in the trial at the respective time point/visit.

If missing values are imputed, the result of all imputation strategies and newly derived information must be stored in the ADaM data set. The shifts required for the shift tables should already be included in the ADaM data set.

Imputed values will be listed in the subject data listing and be marked as imputed.

18.1.2.9 Visit time windows

See Section 5.1.

18.1.2.10 Trial phases and periods

Treatment Period

- The Treatment Period start date is the allocation date as documented on the *Allocation to Treatment page* in the eCRF.

- The Treatment Period end date is the date of the End of Treatment Visit as documented in the eCRF.

Tapentadol Period

- The Tapentadol Period start date is the date of the End of Treatment Visit as documented in the eCRF.
- The Tapentadol Period end date is the date assessed on the *End of Period* page of the eCRF at the end of the Tapentadol Period.

Observation Period

- For subjects entering the Observation Period after Part 1, the Observation Period start date is the date of the End of Treatment Visit as documented in the eCRF.
- For subjects who discontinue the Tapentadol Period and enter the Observation Period during Part 2, the Observation Period start date is the date assessed on the *End of Period* page in the eCRF at the end of the Tapentadol Period.
- The Observation Period end date is the date of Visit F12M. If Visit F12M is not performed, the date assessed on the End of Trial page of the eCRF will be used.

18.1.2.11 First and last IMP intake

The first and last IMP intake of the Treatment Period and of the Tapentadol Period will be specified based on the start and end dates provided on the IMP dispense form of the eCRF, supported by the eDiary data.

First IMP intake of the Treatment Period

The first IMP intake of the Treatment Period will be the date and time of the day (morning/evening) of the earliest start entry in the eCRF for the Treatment Period.

The time will be set to the time of the corresponding eDiary entry at that date and time of the day if available; else the time will be missing.

First IMP intake of the Tapentadol Period

The first IMP intake of the Tapentadol Period will be the date and time of the day of the earliest start entry in the eCRF for the Tapentadol Period.

The time will be set to the time of the corresponding eDiary entry at that date and time of the day if available; else the time will be missing.

Last IMP intake of the Treatment Period

The last IMP intake of the Treatment Period will be the date and time of the day of the latest end entry in the eCRF for the Treatment Period.

The time will be set to the time of the corresponding eDiary entry at that date and time of the day if available; else the time will be missing.

Last IMP intake of the Tapentadol Period

The last IMP intake of the Tapentadol Period will be the date and time of the day of the latest end entry in the eCRF for the Tapentadol Period.

The time will be set to the time of the corresponding eDiary entry at that date and time of the day if available; else the time will be missing.

In case the required information from the IMP Dispense form of the eCRF is not available, the first and last IMP intake assigned to the Treatment and Tapentadol Period in the eDiary will be used. In case the switch of the eDiary from the Treatment Period to the Tapentadol Period was missed, the date of Visit VE will be used for the last IMP intake of the Treatment Period and the first IMP intake of the Tapentadol Period, with time of the day and time missing.

18.1.3 Population heterogeneity during Part 2

For Part 2, the different periods, i.e., Tapentadol Period and Observation Period, are not comparable. Subjects in the Tapentadol Period continue to receive tapentadol throughout this period, while patients in the Observational Period do not receive any further IMP. One part of subjects are expected to enter the Observational Period because they are no longer in need of treatment with tapentadol because of an improvement of the underlying pain condition. Other subjects may enter the Observation Period due to worsening of the underlying disease. Subjects may therefore not be sufficiently treated in the Tapentadol Period as they may require higher doses or a different route of administration. Due to the heterogeneity of the subject populations during Part 2 of the trial, no comparisons between the Tapentadol Period and Observation Period will be performed.

18.1.4 Disposition

18.1.4.1 Subject discontinuation

Reasons for subject discontinuation as specified in the End of Trial page or End of Period page of the eCRF.

Completion status

Treatment completer:

- Part 1:
  - If $(End\ of\ Treatment\ Visit\ date -$ First IMP intake of the Treatment Period $date) \geq 13$ and either $(Last\ IMP\ intake\ of\ the\ Treatment\ Period\ date -$ First IMP intake of the Treatment Period$) \geq 13$ or $(Last\ IMP\ intake\ of\ the\ Treatment\ Period\ date -$ First IMP intake of the Treatment Period$) = 12$ with last IMP intake of the Treatment Period in the evening.
- Part 2, Tapentadol Period only:
  - If $(F12M\ date - End\ of\ Treatment\ Visit\ date) \geq 351$ with F12M completed as part of Tapentadol Period.

Trial completer:

- Part 1: Treatment completer Part 1 with either
  - Visit F7D performed, if subject entered Observation Period or
  - Subject entered Tapentadol Period
- Part 2: Either

- Treatment completer Part 2 with Visit F7D performed or
- Subjects with F12M of the Observation Period performed with $(F12M\ date - End\ of\ Treatment\ Visit\ date) \geq 351$

Time to discontinuation

Time to treatment discontinuation will be calculated in days for Part 1 as:

$$date\ of\ Last\ IMP\ intake\ of\ the\ Treatment\ Period - date\ of\ First\ IMP\ intake\ of\ the\ Treatment\ Period + 1$$

Time to treatment discontinuation will be calculated in weeks for Part 2 as:

$$(date\ of\ Last\ IMP\ intake\ of\ the\ Tapentadol\ Period - date\ of\ First\ IMP\ intake\ of\ the\ Tapentadol\ Period + 1)/7$$

Censoring algorithm

Censoring algorithm is defined as follows:

- Time to IMP discontinuation:
  - Part 1: time will be censored at the date of last IMP intake of the Treatment Period for treatment completers Part 1.
  - Part 2, Tapentadol Period: time will be censored at the date of last IMP intake of the Tapentadol Period for treatment completers Part 2.

18.1.4.2 Protocol deviations

Protocol deviations are based on the analysis data set ADDV. Major protocol deviations are retrieved from the respective SDTM data set (DV.DVCAT). No further protocol deviations are programmed in the analysis data sets for ADDV.

18.1.5 Demographics and other baseline characteristics

18.1.5.1 Subject demographics

Derivation of age

Age as entered directly in the eCRF and available in DM.AGE.

Derivation of BMI:

The BMI is not in the SDTM data set and will be derived from WEIGHT [KG] and HEIGHT[M] of the DM data set. BMI is calculated and rounded to 1 decimal place using the following formula:

BMI [KG/M²] = WEIGHT [KG] / HEIGHT²[M]

18.1.5.2 Other baseline characteristics

Derivation of height Z-Scores

The height Z-Scores will be calculated using the WHO Child Growth Standards. The Z-scores can be calculated using the algorithm as implemented in the SAS igrowup package (www.who.int/childgrowth/software/en/) and the required reference files for subjects from 6-<18 years old provided by the WHO (http://www.who.int/growthref/who2007_height_for_age/en/).

As age in months is required for this calculation, it will be derived by multiplying the recorded age in years by 12 and adding 6 months.

18.1.5.3 Baseline pain intensity of the Treatment Period

According to the protocol, the first dose of IMP should be taken during Visit V2, within 24 hours after randomization. Therefore, the actual day of first IMP intake is not necessarily the same as the day of randomization, but might be the day after the randomization. Based on this, from a programming perspective baseline pain will be derived as follows:

- The pain assessment in the eDiary on the day and at the day time (morning/evening) of the first IMP intake of the Treatment Period will be used as baseline pain.
- In case this eDiary entry is missing, the last available pain assessment before this time point will be used.
- In case this eDiary entry is missing and there is no earlier pain assessment available, baseline pain will be set to missing.

18.1.5.4 Medical history

Not applicable.

18.1.5.5 Prior and concomitant medication or therapy

Assignment of categories "prior" and "concomitant"

Part 1:

The following rules are used to define the categories "prior" and "concomitant" medication.

Prerequisite is a complete date of first dose of IMP.

Date of medication	Condition	Category
Complete stop date is available	stop date is earlier than date of first dose of IMP	prior
Stop date with missing month	year of stop date is earlier than year of first dose of IMP	prior
Stop date with missing day	month/year of stop date are earlier than month/year of first dose of IMP	prior
Complete start date is available	Start date is later than Visit VE	Not considered for Part 1
start date with missing month	Year of start date is later than year of Visit VE	Not considered for Part 1
start date with missing day	month/year of start date is later than month/year of Visit VE	Not considered for Part 1
Otherwise		concomitant

Part 2:

For all presentations except displaying subjects in the Observation Period that have switched from the Tapentadol Period to the Observation Period, the following rules apply to define the categories "prior" and "concomitant" medication.

Medication ticked as "continued" will be classified as concomitant for the Observation Period and also for the Tapentadol Period if considered (see below).

Date of medication	Condition	Category
Complete stop date is available	Stop date is earlier than or equal to date of Visit VE	prior
Stop date with missing month	Year of stop date is earlier than year of Visit VE	prior
Stop date with missing day	Month/year of stop date are earlier than month/year of Visit VE	prior
Tapentadol Period: Complete start date is available	Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period: Start date is later than Visit ET	Not considered for Tapentadol period
Tapentadol Period: Start date with missing month	Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period: Year of start date is later than year of Visit ET	Not considered for Tapentadol period
Tapentadol Period: Start date with missing day	Only applicable for subjects that discontinue from the Tapentadol Period and switch to the Observation Period: month/year of start date is later than month/year of Visit ET	Not considered for Tapentadol period
otherwise		concomitant

For presenting subjects of the Observation Period that have switched from the Tapentadol Period to the Observation Period, the following rules apply to define the categories “prior” and “concomitant” medication.

Medication ticked as “continued” will be classified as concomitant.

Date of medication	Condition	Category
Complete stop date is available	Stop date is earlier than date of Visit ET	prior
Stop date with missing month	Year of stop date is earlier than year of Visit ET	prior
Stop date with missing day	Month/year of stop date are earlier than month/year of Visit ET	prior
otherwise		concomitant

Assignment of flag for medication/therapy taken during IMP administration

Part 1:

The following rules are used to identify medications or therapies which were taken during IMP administration of the Treatment Period of Part 1.

Prerequisite is a complete date of last dose of IMP for the Treatment Period.

Start of medication or therapy date	Condition	Flag for medication during IMP administration
Medication/therapy is not a concomitant medication of Part 1		no
complete date is available	start date is later than date of last dose of IMP, but before Visit VE	no
Otherwise (due to short Treatment Period)		yes

Part 2:

The following rules are used to identify medications or therapies which were taken during IMP administration of the Tapentadol Period of Part 2.

Prerequisite is a complete date of last dose of IMP for the Tapentadol Period.

Start of medication or therapy date	Condition	Flag for medication during IMP administration
Medication/therapy is not a concomitant medication of the Tapentadol Period of Part 2		no
complete date is available	start date is later than date of last dose of IMP	no
missing month	year of start date is later than year of last dose of IMP	no
missing day	month/year of start date are later than month/year of last dose of IMP	no
Otherwise		yes

18.1.6 Exposure

18.1.6.1 Dose level for the sensitivity analysis of the primary endpoint

The IMP dose level during the last 3 days of treatment in the Treatment Period will be specified based on the information from the *Initial Dose/Dose Adjustment*-page of the eCRF.

Therefore, the last six scheduled IMP intakes of the Treatment Period, i.e., the last IMP of Part 1 and the 5 predecessing intakes, will be considered, analogous to the pain intensity assessments considered for the primary endpoint assessment.

For each of the six considered IMP intakes, the dose level (1 to 5) of the dose as given in the eCRF will be determined based on the tapentadol PR and morphine PR dosing tables provided in the trial protocol. The most frequent dose level will then be used as IMP dose level during the last 3 days of treatment in the Treatment Period. In case several different dose levels occur equally often among these 6 time points, the highest dose level of these will be used.

18.1.6.2 Average daily doses during the Tapentadol Period

For the Tapentadol Period, the average daily doses of IMP per kg body weight will be determined for each four-week interval and summarized descriptively per interval. The timeframe of the *i*-th interval of subject *j* is defined as

$$(Date\ of\ TP_{i-1,j}\ , Date\ of\ TP_{i,j}]$$

where $TP_{i,j}\ , i = 1, \ldots, 13$, is the *i*-th visit of subject *j* during the Tapentadol Period (excluding visits M1 and M2 for subjects who were allocated to morphine in the Treatment period). $TP_{0,j}$ is equal to Visit VE of subject *j*. $TP_{13,j}$ is equal to Visit F12M of subject *j*.

For subjects terminating the Tapentadol Period between two scheduled visits, i.e.,

$$Date\ of\ TP_{i-1,j}\ <\ Date\ of\ Visit\ ET_j$$

the average daily doses of IMP per kg body weight in the time interval

$$(Date\ of\ TP_{i,-1j}\ , Date\ of\ Visit\ ET_j]$$

will be determined and included in the descriptive summary of the time interval

$$(TP_{i-1}\ , TP_i]$$

In case of a missing intermediate visit, it will be artificially introduced for this analysis by dividing the available surrounding visit interval to two equally sized subintervals. Hence, if the i-th visit for a subject j is missing ($Date\ of\ TP_{i,j}$), this visit will be estimated as the midpoint of the surrounding visit interval $(Date\ of\ TP_{i-1,j}\ , Date\ of\ TP_{i+1,j}]$ and the two newly introduced timeframes $\left(Date\ of\ TP_{i-1,j}\ , Date\ of\ TP_{i,j}\right]$ and $(Date\ of\ TP_{i,j}\ , Date\ of\ TP_{i+1,j}]$ will be used for further calculations. In case the length of the available visit interval is not a multiple of 2, it will be splitted such that the first time interval is 1 day longer than the second one.

18.1.7 Compliance

Compliance to the IMP dose regimen (%) is defined as the amount of IMP actually taken by a subject divided by the expected IMP amount the subject should have taken in the respective period and multiplied by 100.

Expected IMP amount:

For each subject the *Initial Dose/Dose Adjustment*-page of the eCRF collects for every entry/dose adjustment *i*

- The dose level in mg, denoted by d_i
- The start date (DD MMM YYYY) of dose level d_i, denoted by $t_i^{(S)}$
- The information whether dose level d_i starts with the morning- or evening-dose of the start date. This will be denotes by $S_i^{(S)}$ and coded $S_i^{(S)} = 1$ for "evening", $S_i^{(S)} = 2$ for "morning".
- The end date (DD MMM YYYY) of dose level d_i, denoted by $t_i^{(E)}$
- The information whether dose level d_i ended with the morning- or evening-dose of the start date. This will be denotes by $S_i^{(E)}$ and coded $S_i^{(E)} = 1$ for "morning", $S_i^{(E)} = 2$ for "evening".

- The period the above information belongs to, either being Treatment Period or Tapentadol Period. This implies that at the End of Treatment Visit VE, the investigator has to fill out the *Initial Dose/Dose Adjustment*-page of the eCRF, entering end date and information on $S_i^{(E)}$ even if the subjects continues on tapentadol with the same dose.

Let p_l be the index of the maximum start/end date where period equals treatment $(l = 1)$ or tapentadol $(l = 2)$ and $p_0 := 0$.

The expected amount of IMP is calculated for each subject by:

$$\sum_{i=p_{l-1}+1}^{p_l} \left[d_i * \left(2 * \left(t_i^{(E)} - t_i^{(S)} - 1 \right) + S_i^{(S)} + S_i^{(E)} \right) \right] \ , \ l = 1,2$$

Actual IMP amount:

IMP kits will be dispensed at every visit, but only to cover treatment until the next visit.

The drug-accountability page of the eCRF assessed for every kit *j*

- Date of dispense $t_j^{(D)}$
- IMP dose of kit *j* per tablet, denoted by d_j
- Number of tablets dispensed with kit j, denoted by $m_j^{(D)}$
- Date return $t_j^{(R)}$
- Number of tablets returned regarding kit j, denoted by $m_j^{(R)}$

First, for every kit *j*, the IMP amount in mg at dispense of kit j, denoted by $y_j^{(D)}$ and the remaining IMP amount in mg at return of kit j, denoted by $y_j^{(R)}$, will be calculated:

$$y_j^{(D)} = d_j * m_j^{(D)}$$

$$y_j^{(R)} = d_j * m_j^{(R)}$$

Kits that are returned before or at Visit VE, i.e., $t_j^{(R)}$ is lower or equal to the date of Visit VE, the difference $y_j^{(D)} - y_j^{(R)}$ is fully and uniquely assigned to Part 1.

Kits that are dispense after or at Visit VE, i.e., $t_j^{(D)}$ is greater or equal to the date of Visit VE, the difference $y_j^{(D)} - y_j^{(R)}$ is fully and uniquely assigned to Part 2.

Kits that are dispensed before Visit VE, i.e., $t_j^{(D)}$ is lower than the date of Visit VE, but returned after Visit VE due to any reason, i.e., $t_j^{(R)}$ is greater than the date of Visit VE, the difference $y_j^{(D)} - y_j^{(R)}$ cannot uniquely be assigned to either part. In this case, at Visit VE the investigator should remind the subject not to continue IMP intake from that kit, but the ones dispense at Visit VE as compliant with the protocol. As the IMP of that particular kit should have been taken during Part 1, this kit will also be assigned to Part 1 for statistical analysis.

Let $\tilde{t}$ be the date of Visit VE.

Part 1

The actual amount of IMP will be calculated as:

$$\sum_{\{j:\, t_j^{(D)} < \tilde{t}\}} \left(y_j^{(D)} - y_j^{(R)} \right)$$

Part 2

The actual amount of IMP will be calculated as:

$$\sum_{\{j:\, t_j^{(D)} \geq \tilde{t}\}} \left(y_j^{(D)} - y_j^{(R)} \right)$$

18.1.8 Primary endpoint

18.1.8.1 Missing baseline pain intensity for the Treatment Period

For descriptive statistics of the baseline pain intensity for the Treatment Period, missing baseline pain values will be considered as such.

For the derivation of the primary endpoint, the "responder" status of a subject, a missing baseline pain intensity value will be considered as missing, so that the responder criterion based on the baseline pain intensity cannot be assessed and therefore cannot lead to a "responder" status.

For the primary endpoint analysis (main analysis and sensitivity analyses if applicable), including baseline pain intensity as an explanatory variable in the analysis model, missing values will be imputed by the values resulting from the multiple imputation for the missing pain values during the 3 last days of treatment in the Treatment Period as explained in the "Handling missing data" paragraph of the following section. For those analyses based on primary endpoint data from multiple imputation, the corresponding imputed baseline values of the respective dataset will be used. For those analyses of the primary endpoint based on observed data, the average of the baseline values for the 200 multiple imputation datasets for a subject will be used for imputation of this missing baseline value.

18.1.8.2 Primary analysis

Calculating the confidence interval and p-value based on the Farrington-Manning test

Maximum-Likelihood estimates $\hat{p}_T$, $\hat{p}_C$ for p_T, p_C will be obtained fitting a logistic regression model to the response using baseline pain intensity, age group, treatment and underlying pain condition as explanatory variables.

Baseline pain intensity is measured on different scales (FPS-R, VAS) depending on the age group of the subject. To synchronize the scales, for the logistic regression the FPS-R baseline pain intensity, within a range of [0,10], will be multiplied by 10. This transformation allows for a common range of baseline pain intensities of [0,100].

The method introduced by Farrington and Manning (1990) will be used to determine the variance estimator

$$\hat{v}_0 = \frac{\tilde{p}_T(1-\tilde{p}_T)}{N_1} + \frac{\tilde{p}_C(1-\tilde{p}_C)}{N_2}$$

with

- N_1: sample size of tapentadol arm in Part 1
- N_2: sample size of morphine arm in Part 1
- $\tilde{p}_C = \tilde{p}_T + \delta$
- $\tilde{p}_T = 2 * \mathrm{u} * \cos(\mathrm{w}) - \mathrm{b}/(3\mathrm{a})$
  - $r = N_2/N_1$
  - $a = 1 + r$
  - $b = -[1 + r + \hat{p}_T + r * \hat{p}_C - \delta * (r + 2)]$
  - $c = \delta^2 - \delta(2 * \hat{p}_T + r + 1) + \hat{p}_T + r * \hat{p}_C$
  - $d = \hat{p}_T * \delta * (1 - \delta)$
  - $w = (\pi + \cos^{-1}(v/(u^3)))/3$
  - $v = b^3/(3a)^3 - (b * c)/(6a^2) + d/(2a)$
  - $u = sign(v)[b^2/(3a)^2 - c/(3a)]^{1/2}$

Based on $\hat{p}_T, \hat{p}_C$ and the Farrington-Manning variance estimate $\hat{v}_0$, the realization T_0 of the test-statistic

$$T = \frac{\hat{p}_T - \hat{p}_C + \delta}{\sqrt{\hat{v}_0}}$$

will be obtained. The p-value of the Farrington-Manning test regarding non-inferiority will be determined by calculating the probability

$$p = P(X > T_0)$$

where X is a standard normally distributed random variable.

Furthermore the 80% -confidence interval of the difference in responder rates

$$CI = \left[\hat{p}_T - \hat{p}_C - z_{1-\alpha} * \sqrt{\hat{v}_0}\,, \hat{p}_T - \hat{p}_C + z_{1-\alpha} * \sqrt{\hat{v}_0}\right]$$

will be determined, where $z_{1-\alpha}$ is the $(1-\alpha)$-quantile of the standard normal distribution with $\alpha = 0.1$.

Handling missing data

The above elaboration describes the analysis procedure in the event of no missing data. For the proposed imputation method missing at random (MAR) will be assumed.

Information on the pain assessments during the last 3 days of treatment in the Treatment Period might only be partially available. In this case *Multiple Imputation* will be used to impute missing values:

1. For each treatment group, a multivariate normal distribution for the vector of the age group (AGE), underlying pain condition (PAIN) and baseline pain intensity (BASE), as well as the last 6 scheduled pain measurements during treatment of the Treatment Period, denoted by $(Y_1, \ldots, Y_6)$, is assumed $(AGE, PAIN, BASE, Y_1, \ldots, Y_6) \sim MVN(\mu, \Sigma)$. Missing observations are assumed to depend on the observed values of the subjects in the same treatment group. Therefore, in both treatment arms, missing pain assessments will be imputed using information from an imputation model that is only based on the subjects in the respective arm..

   The multiple imputation will be performed once for all subjects using VAS, and once for all subjects using FPS-R. To ensure that the imputed values are within the range of the respective pain scale (0-10 for FPS-R and 0-100 for VAS), minimum and maximum values for the variable to be imputed should be specified.

   The multiple imputations will be done via SAS PROC MI. The imputation model will be based on the default Markov chain Monte Carlo (MCMC) method for general patterns of missingness (Dmitrienko et al. 2005). A BY statement will be used to implement the imputation by treatment group. The variables will be given the following order: age group, pain condition, baseline pain, last 6 scheduled pain assessments starting with the earliest one.

   For the sake of reproducibility of the results, the seed for pseudo-random number generation will be set to 550366.

   The number *K* of imputed data sets will be set to 200, resulting in 200 complete data sets:

   - Number of imputed data sets: $K = 200$

   Imputed values for missing baseline pain intensities, to be used as explanatory variable in the logistic regression model, will also be obtained from the multiple imputation.

2. Each complete data set $k = 1, \ldots, K$ will be analyzed as described above in case of no missing data up to the step where $\hat{p}_{T,k}$, $\hat{p}_{C,k}$ and the Farrington-Manning variance estimate $\widehat{v}_{0,k}$ are obtained. Let $\hat{\theta}_k = \hat{p}_{T,k} - \hat{p}_{C,k}$.

3. With $(\hat{\theta}_1, \sqrt{\widehat{v}_{0,1}}), \ldots, (\hat{\theta}_{200}, \sqrt{\widehat{v}_{0,200}})$ as input, PROC MIANALYZE will be applied to obtain the test statistic T_{MI} and confidence interval CI_{MI} as follows:

   - Multiple imputation estimate: $\hat{\theta}_{MI} = \frac{1}{K}\sum_{k=1}^{K} \hat{\theta}_k$
   - Within-imputation component of variance: $\hat{\sigma}_w^2 = \frac{1}{K}\sum_{k=1}^{K} \hat{\sigma}_k^2$
   - Between-imputation component of variance: $\hat{\sigma}_b^2 = \frac{1}{K-1}\sum_{k=1}^{K}\left(\hat{\theta}_k - \hat{\theta}_{MI}\right)^2$
   - Multiple imputation variance estimate: $\hat{\sigma}_{MI}^2 = \left(1 + \frac{1}{K}\right)\hat{\sigma}_b^2 + \hat{\sigma}_w^2$
   - Test statistic: $T_{MI} = \frac{\hat{\theta}_{MI} + \delta}{\hat{\sigma}_{MI}}$
   - Degrees of freedom: $\vartheta = (K-1)\left[1 + \frac{\hat{\sigma}_w^2}{\left(1+\frac{1}{K}\right)\hat{\sigma}_b^2}\right]^2$
   - Confidence interval:

$$CI_{MI} = \left[\hat{\theta}_{MI} - \hat{\sigma}_{MI}^2\, t_{\vartheta,1-\alpha}, \hat{\theta}_{MI} + \hat{\sigma}_{MI}^2\, t_{\vartheta,1-\alpha}\right]$$

with $t_{\vartheta,1-\alpha}$ being the $(1-\alpha)$-quantile of the *t*-distribution with $\alpha = 0.1$ and ϑ degrees of freedom.

Non-inferiority of tapentadol versus morphine will be assigned if the lower bound of CI_{MI} exceeds the negative non-inferiority margin $-\delta = -0.2$. Additionally, the realization $T_{MI,0}$ of the test statistics T_{MI} will be used to compute the one-sided p-value

$$p = P(X > T_{MI,0})$$

where X is a t-distributed random variable with ϑ degrees of freedom.

18.1.8.3 Bayesian analysis – Details

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 arm, 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). The treatment variable should be introduced in the model as an indicator variable with value 0 for subjects in Tapentadol and value 1 for subjects in Morphine.

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

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

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

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 KF5503-15 trial (in subjects with moderate to severe chronic malignant tumor-related pain) using a conditional power prior approach (see e.g., Neelon and O'Malley, 2010) with a down-weighting factor a = 0.4 (see below for details on the prior elicitation for the treatment effect). The prior for the subject-specific random effects ε_i, will be normal $(0, \sigma^2)$. A half-t distribution (delta=0, var=10, df=3) will be used as prior for the precision of the random effects σ. The half-t distribution is defined as the absolute value of a Student-t distribution centered at zero and is recommended as a prior distribution for the hierarchical standard deviation when the number of groups is small (see Gelman 2016 and Chen et al. 2016).

The posterior distribution for the regression coefficients will not have an analytically closed form. Therefore, Markov chain Monte-Carlo (MCMC) 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. One MCMC chain of length 1,100,000 will be run, discarding the first 100,000 and keeping every 50th. The resulting thinned sample of size 20,000 will be summarized for each model parameter by means of the posterior mean, median, standard deviation and 80% credibility interval. The difference p_T-p_C, where p_T and p_C are the response rates in the Tapentadol

and Morphine arms, respectively, will also be computed at each MCMC iteration to obtain a sample from its posterior distribution. To this end, at each MCMC iteration, a value for both response rates (on the log-odds scale) will be calculated as follows:

1. Compute:

   $\eta_T = \beta_0 + \beta_1 \overline{\text{ageg}} + \beta_2 \overline{\text{cancer}} + \beta_3 \ (\overline{\text{ageg}}*\overline{\text{baseline VAS}}) + \beta_4 \ (1- \overline{\text{ageg}})*\overline{\text{baseline FPS-R}}$

   $\eta_C = \beta_0 + \beta_1 \overline{\text{ageg}} + \beta_2 \overline{\text{cancer}} + \beta_3 \ (\overline{\text{ageg}}*\overline{\text{baseline VAS}}) + \beta_4 \ (1- \overline{\text{ageg}})*\overline{\text{baseline FPS-R}} + \beta_5$

   where $\overline{\text{ageg}}$ is the proportion of subjects aged 12 years to less than 18 years, $\overline{\text{cancer}}$ is the proportion of subjects with cancer pain, $\overline{\text{baseline VAS}}$ is the average baseline VAS pain for subjects aged 12 years to less than 18 years, and $\overline{\text{baseline FPS-R}}$ is the average baseline FPS-R pain (for subjects aged 6 years to less than 12 years).

2. Compute $p_T = \exp(\eta_T)/(1 + \exp(\eta_T))$ and $p_C = \exp(\eta_C)/(1 + \exp(\eta_C))$.
   Then compute the difference p_T-p_C. At the end of the MCMC run, the posterior sample of size 20,000 for p_T-p_C will be also summarized together with the model parameters. If the lower limit of the 80% credibility interval for the difference of the 2 response rates p_T-p_C is >-0.2, then this would support non-inferiority by this sensitivity analysis.

Elicitation of the prior distribution for the treatment effect

The KF5503-15 trial carried out in adult population included a secondary endpoint to compare the proportion of responders in the Tapentadol and Morphine treatment arms after the 2-week titration period. The response definition in that trial was comparable to the response definition considered in the present trial. It included criteria on trial completion and pain reduction. It also included a condition on the maximum limit for the rescue medication intake, which is not the case in the present study. When recalculating the response rates in the PPS of the KF5503-15 trial without the condition limiting the amount of rescue medication intake, we obtained that 83% of the 100 subjects in the Morphine arm and 81% of the 229 subjects in the Tapentadol arm responded to treatment.

As before, let p_T and p_C be the response rates in the Tapentadol and Morphine arms, respectively. Assuming for both a non-informative prior Beta(0.5, 0.5) and based on the above results of KF5503-15, the posterior distribution obtained using the conditional power approach for a certain down-weighting factor a are:

$$p_T \sim \text{Beta}(a * 100 * 0.83 + 1, a * 100 * (1 - 0.83) + 1)$$

$$p_C \sim \text{Beta}(a * 229 * 0.81 + 1, a * 229 * (1 - 0.81) + 1)$$

Considerations on similarities and differences in the design characteristics of the KF5503-15 trial and the present study led to assume a value for the down-weighting factor of a=0.4, which in a way can be interpreted as borrowing 40% of the information from the adults trial to set the prior distribution for the treatment effect in the pediatric population.

The log-odds ratio $b = \log\left(\frac{p_C}{1-p_C}\right) - \log\left(\frac{p_T}{1-p_T}\right)$, should be informative of the treatment effect β_5, because it can be seen as an unadjusted log-odds ratio. Therefore, to obtain the prior for β_5, we generated 10,000 values from the posterior distributions of p_C and p_T and used them to obtain a sample form the posterior distribution of the quantity b above. The resulting mean of 0.10 and standard deviation of 0.48 were used to set the prior for β_5.

18.1.9 Pain assessed using a VAS and FPS-R scale

For the calculation of daily average pain values of the Treatment Period per subjects, the following rules will be used:

- If the first IMP of the Treatment Period is administered in the morning, the daily average of "day 1" consists of the pain assessment in the evening of the same day and the morning pain assessment of the following day. All following daily averages will consist of an evening value and subsequent morning value.
- If the first IMP of the Treatment Period is administered in the evening, the daily average of "day 1" consists of the pain assessments in the morning and the evening of the following day. All following daily averages will consist of an morning and evening value on the same day.

18.1.10 Rescue medication

Correlation coefficients

The summary table for the number of daily doses and total daily dose per day of the Treatment Period include the mean amount of IMP (morphine equivalents; 1 mg morphine PR is equivalent to 2.5 mg tapentadol PR).

Additionally this table will provide for each day *j*, for each of the two endpoints *k* and each treatment arm *l,* Pearson's and Spearman's correlation coefficients of the tuples $(d_{i,j,l}, r_{i,j,k,l})$, where $d_{i,j,l}$ is the morphine equivalent amount of IMP of subject *i* on day *j* in treatment arm *l*, and $r_{i,j,k,l}$ is the number of daily doses (*k=1*) or mean total daily dose (*k=2*) of subject *i* on day *j* in treatment arm *l*. The correlation coefficients will be calculated using PROC CORR.

Time to first rescue medication intake

Time to first rescue medication intake will be calculated in hours as:

$$date/time\ of\ first\ rescue\ medication\ intake\ -\ date/time\ of\ first\ IMP\ intake$$

The information of date/time of first rescue medication intake will be taken from the eDiary. If the time of the first IMP intake is missing, 0:00 will be used if the first IMP intake was in the morning and 12:00 will be used if the first IMP was taken in the evening.

Censoring algorithm is defined as follows:

- Time to first rescue medication intake will be censored at the End-of-Treatment Visit (VE) regardless of whether subjects complete part 1 or perform Visit VE prior to day 14. The time to be considered for the censoring will be set to 23:59, or the time of first IMP intake of the Tapentadol Period if available.

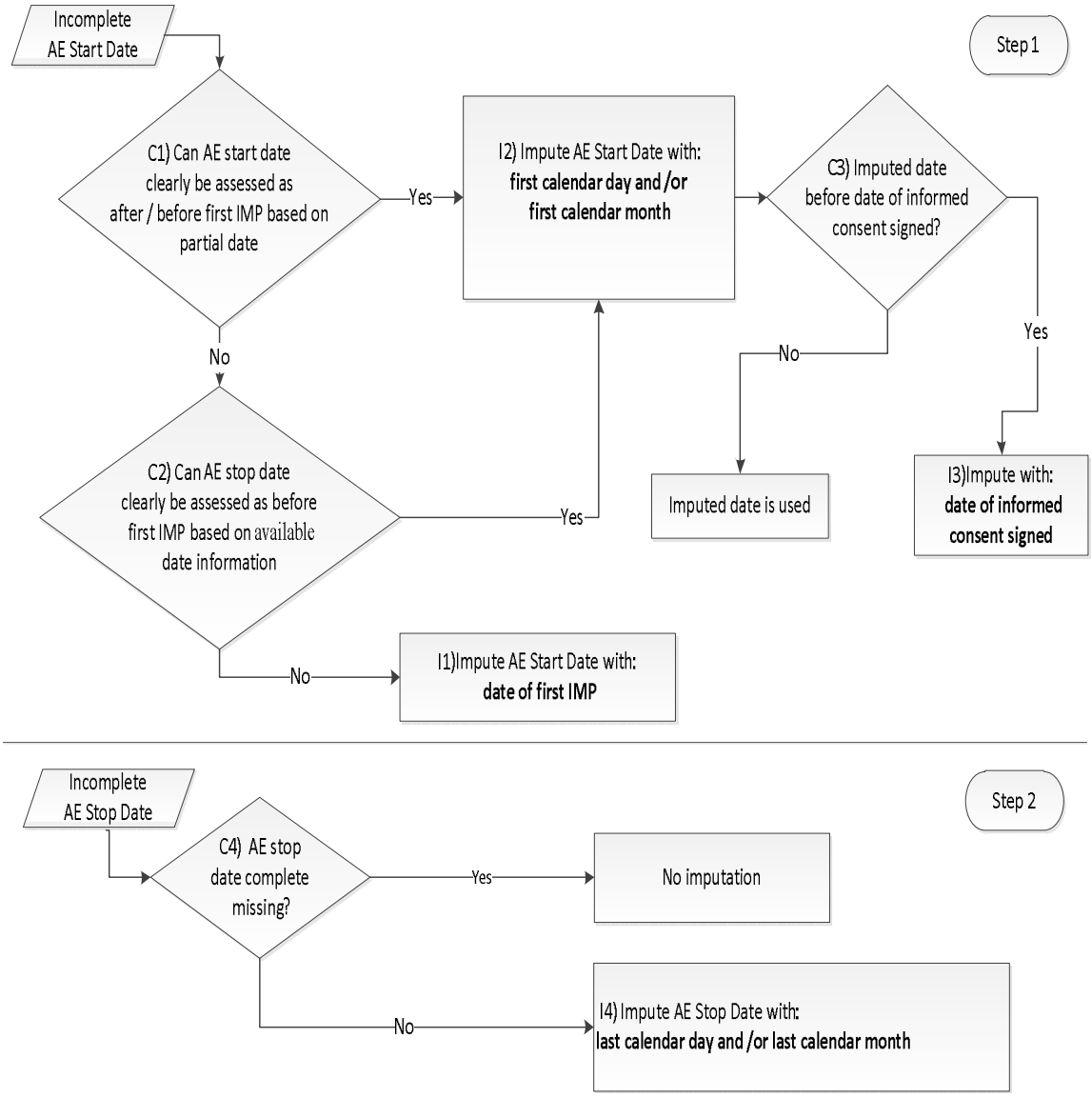
18.1.11 Adverse events

The result of all imputation strategies (e.g., incomplete start dates of AE), combination of observations (combination of consecutive AEs) and new derived information (e.g., definition of concomitant medication categories) must be stored in the analysis data set ADAE.

18.1.11.1 Handling of missing date information

The term missing date refers to a completely missing date, or to an incomplete date where parts are not available.

Missing start and end date will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration and such that, whenever the AE may potentially start after first IMP administration, the AE will be handled as a TEAE.



I1-I4: imputation steps,
C1-C4: checkpoints

Figure 2: Graphical overview about the imputation strategy

Further explanations on the flow chart: The different steps of the displayed imputation strategy must be completed from the first to the last step. All procedures in each step must be completed in the order given.

- Imputation:

- I1: impute with date of first IMP.
- I2:
  Impute with first calendar day and/or first calendar month.
  Imputation will be done based on the available partial information starting with month and then day. The respective first month and day will be chosen for imputation:

Missing date	**Imputed date**
2014-Mar	2014-Mar-*01*
2014	2014-*Jan-01*

- I3: Impute with date of informed consent signed
- I4:
  Impute with last calendar day and /or calendar last month
  Imputation will be done based on the available partial information starting with month and then day. The respective last month and day will be chosen for imputation:

Missing date	**Imputed data**
2014-Mar	2014-Mar-*31*
2014	2014-*Dec-31*

For February leap years must to be taken into account when calculating the last day in February.

- Checkpoints
  - C1: The decision must to be taken based on the available information (date) before imputation.
  - C2: AE stop date before first IMP
    1) The decision must to be taken based on the available information (date) before imputation.
    2) If the end date is completely missing (with or without the information that the AE was ongoing) this will be considered as after first IMP.
    3) If no IMP was given this will be treated as AE stop date before first IMP.
  - C3: The decision must to be taken based on the available information (date) before imputation.
  - C4: The decision must to be taken based on the available information (date) before imputation.

A replacement of missing year for AE start information is not foreseen. If needed this will be considered on a case-by-case decision which must be documented together with the documentation of ADaM data sets.

18.1.11.2 Assessments of pre-/on-/post-treatment-period

The calculation of the pre-/on-/post-treatment- period will be based on the date information given for IMP administration and for Visit VE (see Section 8.2.2).

18.1.11.3 Assessment of TEAEs

The assessment whether an AE is a TEAE, a pre-treatment or a post-treatment non-TEAE of the different trial periods will be done after replacement of missing date information.

18.1.11.4 Handling different episodes of the same adverse event

Changes in any of the attributes of an ongoing adverse event will be documented by recording a separate episode of the same adverse event. A new episode demands a new entry of start date seriousness, intensity, action taken with IMP and causal relationship to IMP, while AE number, AE term, outcome, countermeasures and end date (or continuing) will be assessed only once for the same AE.

If there are multiple consecutive episodes of one AE starting in the same subject during the same period, these episodes will be analyzed as one (combined) AE with the highest intensity, the worst causal relationship, the worst seriousness, and all actions taken with IMP. Onset of this combined event is the onset of the first event.

In the following causal relationship is ordered in descending order starting with the worst expression:

Expression
1) certain, 2) probable/likely, 3) possible, 4) conditional /unclassified, 5) unassessable/unclassifiable, 6) unlikely, 7) not related

If a non-TEAE worsens after IMP intake, it has to be reported as non-TEAE until worsening and as TEAE afterwards.

If an AE worsens in any attribute in a different trial period, it will be analyzed with the previous attribute as continuing AE for the previous period and the new attribute in the consecutive period.

If an AE improves in any attribute in a different trial period, the above methods for different episodes of the same AE in the same period apply and the AE will be reported as “ongoing” from the previous period as described in Section 15.1.2.1.

18.1.11.5 Causal relationship of TEAEs to IMP

The causal relationship of TEAEs to IMP is categorized as follows:

Category	Assessment by investigator:
related	certain probable / likely possible
not related	unlikely not related
unknown	unassessable/ unclassifiable conditional /unclassified causal relationship is missing

18.1.11.6 List of deaths

Death can be identified by outcome of AE equal “fatal”.

18.1.11.7 Time to onset of AE

Time to onset will be calculated based on first administration of IMP. Time to onset of AE will be calculated based on the imputed value for AE start date. In case the time of first administration of IMP is missing, time equal “00:00” will be used for calculation.

18.1.11.8 Duration of AE

Duration of AE will be calculated based on the imputed values for AE start date and stop date.

If duration of AE could not be calculated due to unknown date information the following assessment to categories will be used:

- If the AE is marked as “ongoing” the duration will be categorized as “ongoing”
- Otherwise the duration category will be set to “missing”.

18.1.12 Laboratory, vital signs and ECG parameters

Age determined at Visit V2/VE for Part 1/Part 2, respectively will be used for all reference ranges throughout the trial.

Ordering of parameters

Laboratory parameters, vital signs and ECG parameters will be ordered alphabetically within their parameter group (e.g., hematology, clinical chemistry, and urinalysis). Visits will be sorted chronologically. If changes from BL are displayed by visit all visits will be displayed first followed by all the changes from baseline.

Not exact values

Not exact laboratory values such as < x, > x will not be included in the analysis of continuous parameters. The frequency of occurrence of not exact values will be displayed in the respective table where applicable.

Categorical parameters

For categorical parameters, 2 types of tables are created:

1. Frequency tables display the pre-defined categories by visit and overall post-baseline.
2. Shift tables display the shift from baseline at each visit and overall.

Both types of tables show the number of subjects still in the trial (n) at the visit and the number of missing values (nMiss) at the visit. For the overall presentation, all post-baseline values on treatment are taken into account and nMiss is the number of subjects without any on-treatment post-baseline values.

In tables where parameters are classified as abnormal low, normal, abnormal high based on reference ranges, and alert low, normal, alert high based on sponsor-defined alert ranges the available pre-defined categories must be displayed in tables even if there are categories to which no subjects belong. Categories that are not applicable must be omitted.

18.1.12.1 Overall post-baseline value

For the shift table and PCI frequency table of laboratory, vital signs and ECG parameters, an overall post-baseline value will be derived. Therefore, all post-baseline assessments, including unscheduled assessments, are taken into account.

For the overall post-baseline summary subjects might have both low and high values. These subjects will be categorized in a new category “high and low” and excluded from the categories “high” and “low”. The inclusion of this category in the frequency and shift tables is only required if there are any subjects falling into this category.

18.1.13 Subjective opiate withdrawal scale

The answer to each item will be available from the eCRF and thus available in SDTM. The total score will be calculated as sum of the individual answers and available in the ADaM data set. If at least one answer is missing, the total score will be set to missing.

18.2 Sponsor defined alert ranges for laboratory parameters

Potentially clinically important values for laboratory parameters are assessed based on the sponsor defined alert ranges, and can be both, either alert high or alert low values. The sponsor defined alert ranges were defined in the laboratory statement of work and are implemented in the SDTM data. Therefore, they are not repeated here.

18.3 List of statistical output documentation

The statistical output documentation that will be included in the ICTR Section 16.1.9 will contain the original SAS-output for the analysis of the primary endpoint, including sensitivity analyses. Further details will be specified in the Tables Figures and Listings -shell specification document.