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GRÜNENTHAL
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SDR-SAP-TRIAL-02

STATISTICAL ANALYSIS PLAN

Trial number:	KF5503/65 (Grünenthal) R331333PAI3037 (Janssen)
Title of trial:	An evaluation of the efficacy and safety of tapentadol oral solution in the treatment of post-operative acute pain requiring opioid treatment in pediatric subjects aged from birth to less than 18 years old.
EudraCT number:	2012-004359-35
Development phase:	Phase III
Investigational medicinal products (IMPs):	Tapentadol oral solution. Placebo.

Version	Date	DMS version number
Original	10 Dec 2014	1.0
Amendment 01	09 Sep 2016	2.0
Amendment 02	06 Jul 2018	3.0

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUPC	Area under the pain curve
BMI	Body mass index
BUN	Blood urea nitrogen
CGIC	Clinical Global Impression of Change
CI	Confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
EU PDCO	Pediatric Committee (of the European Medicines Agency)
FAS	Full Analysis Set
FLACC	Face, Legs, Activity, Cry, Consolability (scale)
FPS-R	Faces Pain Scale–Revised
HR	Heart rate
IMP	Investigational medicinal product(s)
IV	Intravenous
IVRS/IWRS	Interactive voice/web response system
LDH	Lactic acid dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov chain Monte Carlo
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Nurse controlled analgesia
PCA	Patient controlled analgesia
PGIC	Patient Global (overall) Impression of Change
PPS	Per Protocol Set
Q1	First quartile
Q3	Third quartile

QTcF	Corrected QT interval using the Fridericia correction (ECG)
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOAM	Supplemental opioid analgesic medication
SOP	Standard operating procedure(s)
TEAE	Treatment emergent adverse event
US	United States
US FDA	Food and Drug Administration of the United States of America
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

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

DEFINITIONS OF TERMS

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

1 INTRODUCTION

This statistical analysis plan (SAP) includes all definitions and details for the analysis of the trial KF5503/65 – R331333PAI3037. The analysis will be performed in the Department of Biostatistics at [redacted] in accordance with this SAP.

The original SAP corresponds to the trial protocol of KF5503/65 – R331333PAI3037 including protocol amendment 02 dated 14 Oct 2014.

The SAP amendment 01 corresponds to the Trial Protocol of KF5503/65 – R331333PAI3037 including protocol amendment 06 dated 19 Aug 2016.

This SAP amendment 02 aligned the SAP to the Trial Protocol of KF5503/65 – R331333PAI3037 including protocol amendment 07 dated 24 Mar 2017.

2 TRIAL OBJECTIVES

Trial KF5503/65 – R331333PAI3037 is part of a pediatric development program that fulfills differing requirements of the EU PDCO and the US FDA. For the EU PDCO, to assess the efficacy and safety of tapentadol in the treatment of acute pain, subjects between 2 years and less than 18 years old will be evaluated. For the US FDA, subjects between birth and less than 17 years old will be evaluated.

The clinical hypothesis of this trial is that tapentadol oral solution reduces the total amount of supplemental opioid analgesic medication used over 12 hours (primary objective for US FDA) or 24 hours (primary objective for EU PDCO) following initiation of IMP, compared to placebo, in children and adolescents who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

The primary efficacy objective (either 12 hours or 24 hours) for 1 region is considered as the secondary efficacy objective in the other, for the different age range, as described below.

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

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

Primary objectives:

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

For US FDA: To evaluate the efficacy of tapentadol oral solution, based on the total amount of supplemental opioid analgesic medication used over 12 hours following initiation of IMP, in children and adolescents aged from birth to less than 17 years who have undergone surgery that, in

the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

For both EU PDCO and US FDA: To evaluate the safety of tapentadol oral solution in children and adolescents aged 2 years to less than 18 years (EU PDCO) and children and adolescents aged from birth to less than 17 years (US FDA) who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment.

Secondary objectives:

To assess the efficacy of tapentadol oral solution using multiple subjective and objective measures of the subject's response to treatment (see Section 11.2).

3 TRIAL DESIGN

3.1 Overall trial design and plan

This is a Phase III, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol in male and female subjects aged from birth to less than 18 years old who have undergone surgery that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment via either NCA or PCA.

A target number of 159 randomized subjects will be treated with IMP in the EU PDCO age range (2 years to less than 18 years of age) and in the US FDA age range (birth to less than 17 years of age). Due to the overlapping age groups as per regulatory requirements, it is expected that approximately 168 subjects will be treated with IMP in this trial.

Subjects will be randomly assigned to 1 of the 2 treatment arms in a 2:1 tapentadol oral solution to placebo ratio. Permuted block randomization will be stratified by predefined age groups and supplemental opioid used.

For each subject, the trial will include the following periods:

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

The duration of this period will be as per standard of care for the concerned surgery, but the start of enrollment is not to exceed 28 days before allocation/randomization to IMP, which constitutes the end of the enrollment period. Subjects may start enrollment before or after surgery. The inclusion/exclusion criteria will be assessed after surgery in order to confirm the eligibility of the subject for randomization. To qualify for randomization, after the surgery the subject must have been started on NCA/PCA with morphine or hydromorphone, with or without a background infusion. This includes subjects receiving morphine or hydromorphone via background infusion who did not actively utilize NCA/PCA. The background infusion (if any) must be with a low dose infusion of the same opioid as that used for the NCA/PCA.

Treatment and Evaluation Period (Visit 2 and Visit 3)

Visit 2 starts once the subject has been allocated to IMP. At the time of first IMP administration, the background opioid infusion (if any) will be discontinued. The IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). If the subject is sleeping at the time of the scheduled dose, they must be woken to take the IMP within a maximum of 6 hours after the previous dose. This dose must be taken as soon as possible after the subject is awake. Within the

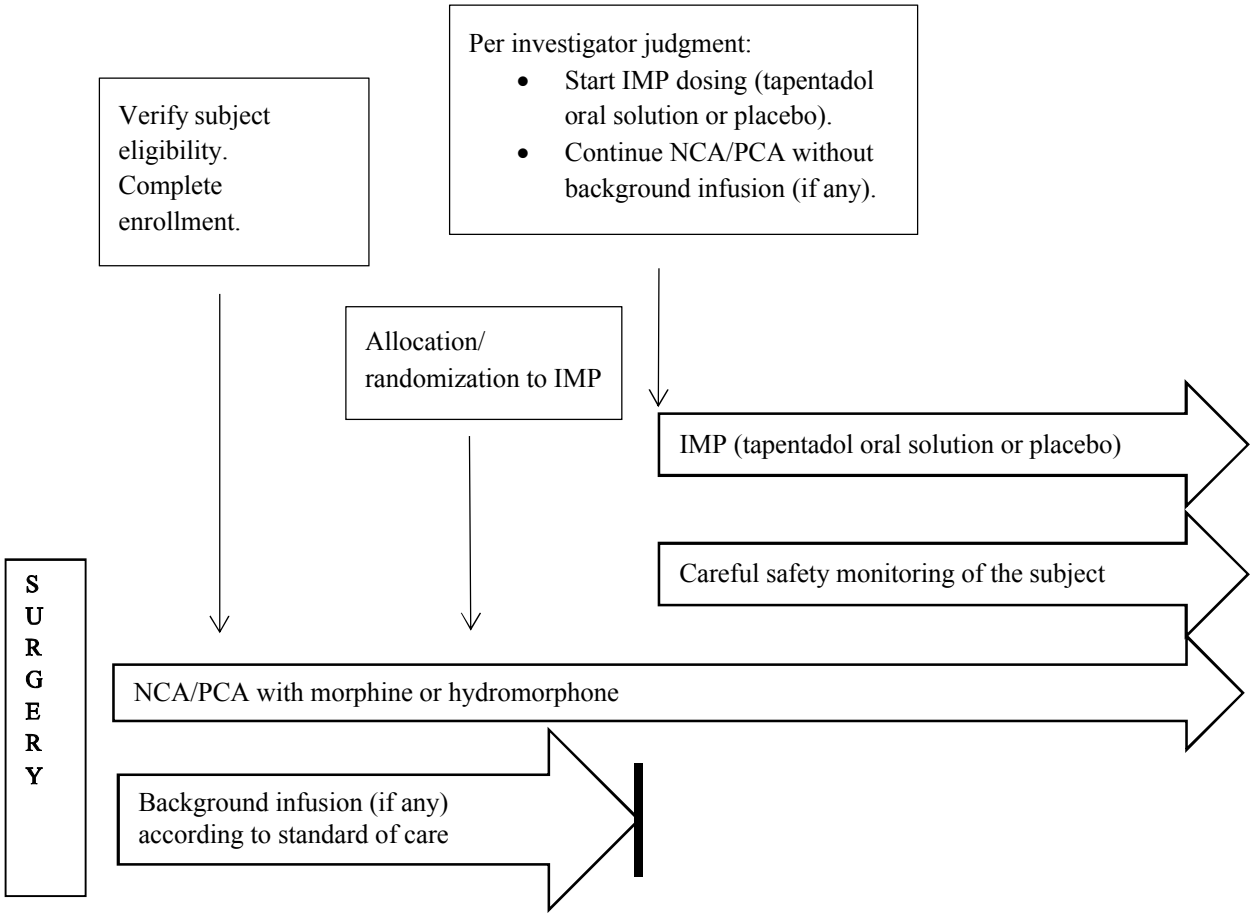
first 24 hours the dose will be 1.25 mg/kg (6 months to <18 years; the dose is still to be determined for subjects aged from birth to <6 months old). After 24 hours, the investigator may decrease the dose of IMP to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia. Dosing with IMP will be stopped when opioid analgesic medication is no longer needed, a switch to exclusively oral opioid analgesic medication takes place, or 72 hours after first IMP administration.

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

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

Only adverse events (AEs) and intake of concomitant medication and therapies will be assessed at this visit, which may be performed by telephone.

For a summary of the trial as a flow diagram, see Figure 1; for the schedule of events see Table 1.



NCA = nurse controlled analgesia; PCA = patient controlled analgesia; IMP = investigational medicinal product.

Figure 1: Immediate post-operative timeline

Table 1: Schedule of events

Period:	**Enrollment**		**Treatment and evaluation**					**Follow -up**
Visit:	**1**		**2**				**3**	**4**
Time:	**≤28 days before allocation/ randomization**		**First dose Day 1**		**Subsequent doses**		**End of Treat-ment**	**Day 10 to Day 14**
			Before	**After**	**Before**	**After**		
	Any time	After surgery						
Obtain informed consent/assent	X							
Record date of signing the informed consent/assent form, sex, race/ethnicity, and height.	X							
Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight)		X						
Record age at time of allocation/randomization		X						
Record clinically relevant medical/surgical history	X							
Record details about the surgery		X						
Perform a physical examination	X						X	
Record intake of prior/concomitant medication and therapies, as appropriate	X		X	<----------	----------	---------->		X
Detailed recording of analgesics		X		X	X		X	
Record C-SSRS		X					X	
Continuous heart- and respiratory-rate recording for 24 hours after first IMP			<----------	----------	---------->			
Record vital signs		X	X		X		X	
Record sedation score			X		X			
Continuous oxygen saturation measurement until 4 hours after the last administration of IMP			<----------	----------	----------	---------->		
Record oxygen saturation		X	X		X		X	
Record 12-lead electrocardiogram		X					X	
Take blood for safety laboratory (clinical chemistry and hematology)		X					X	
Perform a pregnancy test	X							
Check inclusion/exclusion criteria		X						
Allocate subject to IMP		X						
Stop background infusion (if any) of opioids at time of first IMP dose			X					
Detailed recording of NCA/PCA and background infusion (if any)		X		<----------	----------	----------	---------->	
				no background infusion				
Administer IMP (record time and dose)			X		X			
Record pain intensity			X	X	X		X	
Record pain intensity before each NCA/PCA activation				<----------	----------	----------	---------->	
Record palatability and acceptability				X			X	
Global impression of change							X	
Perform and document drug accountability							X	
Assess and record adverse events	<----------	----------	----------	----------	----------	----------	---------->	
Assess discontinuation criteria			X		X		X	

Period:	Enrollment	Treatment and evaluation					Follow -up
Visit:	1	2				3	4
Time:	≤28 days before allocation/ randomization	First dose Day 1		Subsequent doses		End of Treat-ment	Day 10 to Day 14
		Before	After	Before	After		
Dispense subject trial card	X						

C-SSRS = Columbia-Suicide Severity Rating Scale; IMP = investigational medicinal product; NCA = nurse controlled analgesia; PCA = patient controlled analgesia.

3.2 Sample size

The sample size determination was based on the primary efficacy endpoint variable for the respective Full Analysis Sets (FASs). A linear relationship is assumed between the 12 hour and 24 hour supplemental opioid analgesic use for the purposes of the sample size calculation and the final analyses.

The sample size calculation was based on results, summarized in Table 2, from previously conducted trials in post-surgical pediatric subjects where supplemental opioid use was measured.

Table 2: Differences in amount of supplemental opioid use in previously conducted trials in post-surgical pediatric subjects

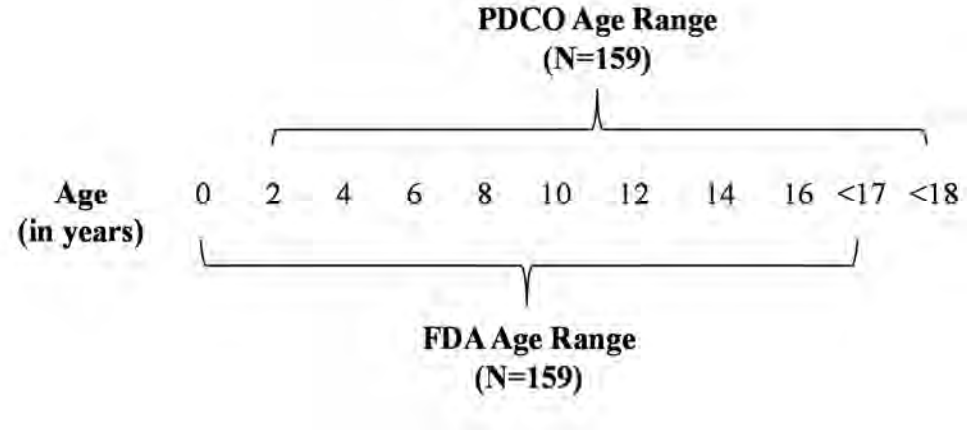
Reference	Supplemental opioid use (morphine or morphine-equivalent) in original units	Converted to cumulative use over 24 hours (mg/kg)	Treatment group difference based on cumulative use over 24/12 hours (mg/kg)
Rusy et al. 2010	Placebo: 0.055 ± 0.017 mg/kg per h	Placebo: 1.32 ± 0.408	
	Gabapentin: 0.046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

For the current trial, a value of 0.20 mg/kg in 24 hours (0.10 mg/kg in 12 hours) for the between-treatment group difference and a more conservative value of 0.42 mg/kg in 24 hours (0.21 mg/kg in 12 hours) for the standard deviation (SD) were considered adequate assumptions. The standardized effect size based on these values (0.20/0.42 = 0.48) is more conservative than the standardized effect sizes observed in Rusy et al. 2010 (approximately 0.55) or Rugyte and Kokki 2007 (approximately 0.80). A smaller effect size was chosen to account for additional variability in the trial due to local standards of care.

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

Since there is only 1 primary endpoint for each regulatory authority (EU PDCO/US FDA), no multiplicity adjustment will be performed.

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



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

Figure 2: Depictions of regulatory-required age ranges

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

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

The trial enrollment for the EU PDCO set (see Section 6 for the definition of the analysis populations) will complete when the following criterion is met:

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

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

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

An additional objective of the trial is to meet a US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age who have been exposed to tapentadol for at least 48 hours. As medically appropriate, every effort will be made to enroll subjects in this trial to meet this objective. A combination of blinded and unblinded monitoring will ensure the 3 above criteria as well as a minimum target of randomized subjects within all cohorts are met. The respective processes are described in a separate document.

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

3.3 Randomization

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

Randomization will be outsourced to a Central Randomization Center ([redacted]) which will develop an IVRS/IWRS. The IVRS/IWRS will be used to assign a subject number at the Enrollment Visit (Visit 1) as well as a randomization number and medication kit number at randomization. The IVRS/IWRS will also be used to support the drug supply chain management processes of distribution and return. Subjects who comply with all inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to 1 of the 2 treatment arms in a 2:1 tapentadol oral solution to placebo ratio.

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

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

Once the EU PDCO set has completed recruitment and data for these subjects is locked, unblinding will be performed for those subjects aged 2 years and older. The additional age groups under 2 years old will be unblinded at the end of the trial.

4 OVERVIEW OF PLANNED ANALYSES

4.1 Final analyses

The EU final analysis will be performed after all subjects in the EU PDCO set have completed the trial, the data for the EU PDCO set was locked and subjects aged over 2 years were unblinded. The second final analysis will be performed after all subjects (EU PDCO set and US FDA set) have completed the trial, the database was locked, and subjects aged under 2 years were unblinded (the EU PDCO set being already locked and unblinded).

For information on the final reporting for EU PDCO and US FDA see Section 16.6 of the protocol amendment 06.

The final reporting for US FDA will be based on the EU PDCO reporting and extended by a descriptive analysis of all subjects less than 2 years old. Further details are provided in Section 5.2.2.

4.2 Interim analyses

No formal interim analysis of efficacy is planned in the trial.

An independent data monitoring committee (DMC) will be established to perform, on a regular basis, an independent and objective review of the safety data, and to provide recommendations about continuing or terminating the trial or about any other modification to the trial protocol or trial conduct as described in the DMC charter.

All analyses performed for the DMC will be described in a separate document. Results of the analyses performed for the DMC will not be included in the final study reports.

5 DOCUMENT AND CHANGE HISTORY

5.1 Changes in analysis compared to the trial protocol

Not applicable.

5.2 SAP amendment rationale

5.2.1 Amendment 01

The amendment 01 to the final SAP was prepared to include changes of protocol amendment 04, 23rd June 2015 to protocol amendment 06, 19th Aug 2016. Hence it is mainly supposed to reflect the analysis of the EU PDCO data set for regulatory requirements prior to completion of the US FDA data set. Furthermore, the following additional changes have been embedded.

- Reflect adaptations to populations as per protocol amendments and introduction of "Allocated Set" to cope for subjects that have been allocated but were not treated.
- Prior and concomitant medication section was adapted for consistency to standard wording.
- Removal of the analysis of non-opioid analgesic medication as a secondary endpoint for logistical reasons.
- Compliance calculation algorithm was adapted and updated.
- Embed analysis of clinician bolus or intravenous bolus of morphine or hydromorphone if the subject had unbearable pain in exceptional cases.
- Removal of analysis reducing primary endpoint analysis to subjects who received at least 2 doses of IMP.
- For global impression of change questionnaires Cochran-Mantel-Haenszel testing was removed.
- For subjects younger than 2 years only local laboratory analyses are performed, and therefore for these age groups laboratory values will not be part of summary statistics.
- Physical examination derived 2 times during trial will only be presented in subject data listing.
- Treatment period start date/time was changed to data/time of first IMP intake instead of allocation date/time.

- Adaptations and additions were made to the derivation of the amount of morphine or hydromorphone from different electronic case report form (eCRF) pages and how to handle missing information.

Some adaptations adding clarifications to individual analyses or done for sake of consistency are not specified here.

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

5.2.2 Amendment 02

This amendment has been enacted after the database for the EU analysis (all subjects 2 years to less than 18 years old) has been fully locked and the EU analysis has been performed, in order to further describe how the original US objective of analyzing subjects aged between birth and less than 17 years will now be implemented.

- US primary endpoint analysis: The primary and sensitivity analyses for the primary endpoint (ANOVA) will now be performed on the *FAS-EU* data set. For subjects less than 2 years old the primary endpoint will be analyzed descriptively (*FAS-US <2*). For details please refer to Section 11.1.
- Secondary efficacy endpoints: Subjects aged 2 years and above (*FAS-EU*) have already been covered in the analysis performed for EU reporting. This analysis will be complemented with a descriptive analysis of subjects less than 2 years old (*FAS-US <2*) in order to achieve complete reporting for the age range required by US FDA. For details please refer to Section 11.2.
- Safety analysis: Subjects aged 2 years and above (*SAF-EU*) have already been covered in the analysis performed for EU reporting. The main safety analyses will be complemented with a descriptive analysis of subjects less than 2 years old (*SAF-US <2*) in order to achieve complete reporting for the age range required by US FDA. For details please refer to Section 13.

By this approach the analysis for the US endpoints includes subjects aged 17 years old. These subjects were originally not required to be analyzed and reported for the US endpoints based on a Written Request for tapentadol agreed with the FDA. However, there is strong evidence that adolescents aged 17 years old and younger adolescents show a comparable physiological response to exposure with tapentadol (with regards to efficacy, safety and tolerability). These subjects will add further value and reliability to the analysis, and is not expected to, based upon currently available scientific information, bias the study outcomes. It therefore was decided to include these subjects in the evaluation of US endpoints as well.

On the other hand subjects less than 2 years old are analyzed separately. This does not effect secondary endpoint and safety analysis as the relevant data complement the already reported data. Also for the primary endpoint, the analysis will unlikely be impacted considerably given the limited number of 15 subjects planned in this age range.

Furthermore, the imputation strategy for the sensitivity analyses for the US FDA primary endpoint is adapted within this amendment based on a request by the FDA (see Section 11.1.2).

Except for disposition displays no combined display of subjects below and above 2 years will be done.

6 SUBJECT POPULATIONS

Most analyses planned on the US or overall population for the final report will be limited to subjects less than 2 years old. Those will be denoted with the extention *<2,* e.g., analyses on subjects less than 2 years old and on the *FAS-US* will be denoted by *FAS-US <2* and on the *SAF-US* will be denoted by *SAF-US <2*.

6.1 Enrolled Set

The Enrolled Set will include all enrolled subjects (as defined in the protocol) of the trial. In the following sections, this set will be denoted by *Enroll-All*.

For the EU PDCO, the Enrolled Set will include all enrolled subjects (as defined in the protocol) from 2 years to less than 18 years of age and be denoted by *Enroll-EU*; for the US FDA, the Enrolled Set (*Enroll-US*) will include all enrolled subjects (as defined in the protocol) from birth to less than 17 years of age. The latter will be reported by presentation of the *Enrolled-EU* complemented by the *Enrolled-US <2*, which denotes those subjects less than 2 years old and is identical to the *Enrolled-All <2*.

6.2 Allocated Set

The overall Allocated Set will include all enrolled subjects that are allocated (randomized) to IMP. This set will be denoted by *Allocated-All*.

For the EU PDCO, the Allocated Set will include allocated subjects 2 years to less than 18 years of age and will be denoted by *Allocated-EU*; for the US FDA, the Allocated Set (*Allocated-US*) will include allocated subjects from birth to less than 17 years of age. The latter will be reported by presentation of the *Allocated-EU* complemented by the *Allocated-US <2*, which denotes those subjects less than 2 years old and is identical to the *Allocated-All <2*.

6.3 Safety Set

The Safety Set (SAF) comprises all treated subjects in the required age ranges for the EU PDCO and US FDA. The overall Safety Set will include all treated subjects of the trial. This set will be denoted by *SAF-All*. The EU PDCO Safety Set will include subjects 2 years to less than 18 years of age and will be denoted by *SAF-EU*; the US FDA Safety Set (*SAF-US*) will include subjects from birth to less than 17 years of age. The latter will be reported by presentation of the *SAF-EU* complemented by the *SAF-US <2*, which denotes those subjects less than 2 years old and is identical to the *SAF-All <2*. A subject will be considered as treated if administered any amount of IMP.

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

6.4 Full Analysis Set

The overall FAS includes all subjects that are allocated and treated. This set will be denoted by *FAS-All*. The EU PDCO FAS will include allocated and treated subjects aged 2 years to less than 18 years old and will be denoted by *FAS-EU*; the US FDA FAS (*FAS-US*) will include allocated and treated subjects from birth to less than 17 years of age. The latter will be reported by presentation of the *FAS-EU* complemented by the *FAS-US <2*, which denotes those subjects less than 2 years old and is identical to the *FAS-All <2*.

If by error a subject does not receive the medication to which she/he was allocated, the subject will be evaluated as allocated within the FAS following the intention-to-treat principle.

6.5 Per Protocol Set

The EU PDCO or US FDA Per Protocol Sets (PPSs) define subsets of the subjects in the FASs without any major protocol deviations affecting the primary efficacy endpoint. The major protocol deviations which will lead to the exclusion of a subject from the PPS(s) will be decided during blinded data review meetings which will be held before locking and unblinding the data for the EU PDCO set and before database lock and unblinding for subjects aged less than 2 years. Corresponding to the *FAS-EU* and *FAS-US*, the PPSs will be denoted by *PPS-EU* and *PPS-US,* with *PPS-EU* excluding those subjects from the *FAS-EU* with major protocol deviations for the EU primary endpoint (24 hours) and *PPS-US* excluding those subjects from the *FAS-US* with major protocol deviations affecting the US primary endpoint (12 hours). Furthermore, *PPS-EU-12h* will denote the analysis set covering the EU PDCO age range (2 years to less than 18 years old) without any major protocol deviations affecting the US primary efficacy endpoint (12-hour time frame).

7 ANALYSIS CONVENTIONS

7.1 General principles

If an analysis defined in the SAP is specified to be conducted in 2 (or more) analysis sets and the analysis sets represent the same group of subjects, presentations will only be prepared once.

Programming specifications for this SAP are described in Section 16.1, giving more information about technical details of SAP text.

Unless stated otherwise, all data collected in this trial will at least be summarized by descriptive methods (see Section 16.1.1 and Section 16.1.2), based on the nature of the variable:

- For continuous variables, descriptive statistics will include the number of observations, number of missing observations, arithmetic mean, SD, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. If there are fewer than 5 non-missing values, only a subset of these statistics, depending on the number of non-missing observations, will be displayed.
- For categorical variables, frequency counts and percentages will be used to summarize the results. The number of non-missing values will be used as denominator in percentage calculations.

- For time-to-event variables, descriptive statistics will include the number of observations, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Furthermore, Kaplan-Meier estimates and graphs will be provided. The Kaplan-Meier graph will additionally provide the respective number at risk and the Kaplan-Meier estimates at 6 hours, 12 hours, 18 hours, 24 hours, 48 hours and 72 hours. Additionally, the Kaplan-Meier graph will include the median time-to-event and its 95% confidence interval (CI) for both treatment groups. Censoring mechanisms depend on the specific endpoint and will be described in the respective section.

For statistical analyses, pain intensity scores assessed by all 3 age-dependent measurements will be regarded as a continuous variable. Other ordinal variables will be analyzed as categorical variables.

The main analysis will focus on the treatment, thus all summaries and graphical presentations will be displayed by assigned treatment group.

Unless specified otherwise, statistical tests and CIs are 2-sided and use a significance level of $\alpha = 0.05$.

Subject data will be presented in subject data listings.

Unscheduled measurements will generally be presented only in the subject data listing and will not be included in summary statistics. However, there are 3 exceptions to this rule:

1. In case of unscheduled baseline measurements (see Section 9.2) between the last scheduled measurement before first administration of IMP and administration of first IMP, the latest of these unscheduled measurements replaces the scheduled baseline measurement.
2. Values outside of sponsor defined alert ranges (potentially clinically important values) for vital signs, oxygen saturation, and laboratory parameters resulting from unscheduled assessments will be included with scheduled measurements in the respective analyses. Furthermore, abnormal electrocardiogram (ECG) values based on measurement from the ECG central reader and clinically relevant abnormal values assessed by the investigator resulting from unscheduled assessments will be included in the respective analyses.
3. For unscheduled and thus multiple assessments of vital signs, oxygen saturation, and pain intensity (excluding pain intensities measured related to NCA/PCA) between 2 doses of IMP, the latest occurring assessment before the subsequent dose will be used for statistical analyses. The remaining records, unless they yield values outside the sponsor defined alert ranges (potentially clinically important values, see above), will only be included in the subject data listing.

All medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD).

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

For the final analysis, the latest version of the WHO-DD/MedDRA at the time of coding for final evaluation will be used. Coding for the DMC analyses is addressed separately in the SAP for the DMC. For the EU final analysis (first database lock) the latest version at that time point will be used. Recoding will be performed for the final analysis if applicable and changes to EU analysis might be possible.

Two reports will be prepared for the trial. Further details on the reports are given in Section 16.6 of the protocol.

If not otherwise specified analysis of subjects less than 2 years old will be descriptive and presented separately. Most analyses planned on the *FAS-US* or *FAS-All* will be conducted for the *FAS-US <2* population only and most analyses planned on the *SAF-US* or *SAF-All* will be conducted for the *SAF-US <2*. Further details are provided in the respective sections.

7.2 Definitions

For all differences between tapentadol and placebo, tapentadol will constitute the minuend and placebo the subtrahend of the difference.

In this trial, *baseline* is defined as the last non-missing assessment before first IMP intake. Depending on the parameter, this is either the assessment at the Enrollment Visit (before or after surgery), the assessment done at Visit 2 before first administration of IMP, or an unscheduled measurement between the last scheduled measurement before first administration of IMP and administration of first IMP.

7.3 Definition of subgroups

Subgroup analyses, e.g., according to age categories or supplemental opioid used, may also be explored as appropriate.

If stated in this SAP that a summary will be displayed *for relevant age groups*, it means the following:

- For the EU PDCO (analysis sets ending in -*EU*):
  - 2 years to less than 6 years
  - 6 years to less than 12 years
  - 12 years to less than 18 years
- For the US FDA (analysis sets ending in -*US*):
  - Birth to less than 30 days
  - 30 days to less than 6 months
  - 6 months to less than 2 years
  - 2 years to less than 6 years
  - 6 years to less than 12 years
  - 12 years to less than 17 years
- For the overall trial population (analysis sets ending in -*All*):
  - Birth to less than 30 days
  - 30 days to less than 6 months
  - 6 months to less than 2 years
  - 2 years to less than 6 years
  - 6 years to less than 12 years
  - 12 years to less than 17 years

- 17 years to less than 18 years

For inferential analyses which include age group as a factor, age groups might be pooled if there are insufficient numbers of subjects, i.e. less than 6 subjects, in any of the age groups. If for an analysis it is stated in this SAP that age groups will be pooled, the following pooling algorithm applies separately to the 3 age groups of subjects less than 2 years old and the remaining 3 age groups of subjects older than or equal to 2 years:

1. The age subgroup with fewest subjects is pooled with the adjacent age group with the smaller number of subjects.
    a. If the threshold of 6 subjects is not reached, the pooled subgroup is pooled with the remaining age group and the algorithm terminates.
    b. If the threshold of 6 subjects is reached, the algorithm proceeds with step 2.
2. Check if the remaining subgroup consists of fewer than 6 subjects.
    c. If the remaining subgroup consists of fewer than 6 subjects, it will be pooled with the pooled age group of step 1 and the algorithm terminates.
    d. If the remaining subgroup consists of at least 6 subjects, the algorithm terminates.

In case of discrepancies between the IVRS/IWRS recording and the eCRF for age group and/or supplemental analgesia used for NCA/PCA (morphine/hydromorphone), the entry in the eCRF will be used for all analyses unless explicitly stated otherwise.

Geographical regions are the following:

- Europe
- USA

Type of administration of supplemental opioid analgesia:

- PCA
- NCA

Supplemental opioid analgesia used:

- Hydromorphone
- Morphine

Race:

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Other

Sex:

- Female
- Male

For analysis of subjects less than 2 years old, no subgroup analysis will be performed apart from age group analyses due to the low number of subjects.

7.4 Further definitions

Supplemental opioid analgesic medication is defined as morphine or hydromorphone that is administered via intravenous NCA/PCA or intravenous bolus in case of NCA/PCA pump failure or clinician bolus or any other intravenious administered opioid after first administration of IMP up to the End of Treatment Visit and will be evaluated as morphine IV equivalents. Details regarding the relationship to the eCRF can be found in Section 16.1.6.

8 DISPOSITION

Unless stated otherwise subject disposition will be displayed for the following analysis sets:

- Enroll-All
- Enroll-EU
- Enroll-US <2

Time to discontinuation and protocol deviations will be displayed for the following analysis sets:

- FAS-EU
- FAS-US <2 (only protocol deviations)

8.1 Subject disposition

Subject disposition will be descriptively summarized (per treatment group and overall) in terms of the number (N) and percentage (%) for the following populations:

- Subjects enrolled (only N, only overall)
- Subjects enrolled but not allocated and reason for non-allocation (only overall)
- Subjects allocated
- SAF
- FAS
- PPS
- Treatment period completers and treatment period discontinuations at 12 hours and 24 hours after first IMP intake. For the derivation of treatment period completion status at both time points, see Section 16.1.7.
- Trial completers and trial discontinuations at 12 hours and 24 hours after first IMP intake. For the derivation of trial completion status at both time points, see Section 16.1.7.

For subjects enrolled but not allocated and for the reasons for not being allocated, the percentage denominator will be the number of enrolled subjects. For the SAF, FAS, and the PPS the percentage denominator will be the number of allocated subjects.

For the summaries of treatment period and trial completion/discontinuation, 2 analyses will be performed. For the first analysis, the percentage denominator will be the number of subjects in the FAS and if a subject discontinues treatment, the subject will be considered a discontinuation for all

subsequent time points as well. As an additional analysis, the percentage denominator will be the number of subjects in the FAS who are "at risk" for discontinuation at the given time point: For the 12-hour time point, this will be the number of subjects in the FAS. For the 24-hour time point, this will be the number of subjects in the FAS who completed the 12-hour time point.

For the Enroll-All set (and Enroll-EU for EU PDCO), the above information will also be displayed per each relevant age group (1 table), per each type of supplemental opioid analgesic medication used (1 table), and per each country (1 table).

The reasons for treatment and trial discontinuations will be summarized for all allocated subjects, overall and separately for allocated subjects discontinuing

- Before first IMP (trial discontinuations only)
- After first IMP but before or at 12 hours after first IMP
- After 12 hours but before or at 24 hours after first IMP
- After 24 hours after first IMP

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

The details for "other reasons" will be presented in a listing, if applicable.

8.2 Time to discontinuation

The distribution of the time from first IMP intake to discontinuation from treatment (see Section 16.1.8 for details) before 72 hours after first IMP will be summarized using time-to-event methods. For subjects who reach the maximum duration of treatment (72 hours, see Section 16.1.4), the time to discontinuation will be censored at 72 hours after first IMP intake.

Time to discontinuation due to lack of efficacy will be evaluated as described in Section 11.2.8.

Time to discontinuation due to an AE will be evaluated as described in Section 13.1.

8.3 Protocol deviations

Major protocol deviations will be summarized by FAS-EU and FAS-US <2 and grouped into different categories such as

- Violation of inclusion/ exclusion criteria
- Time schedule deviations
- Non-compliance regarding intake of IMP/supplemental analgesia
- Missing essential data
- Subject not discontinued as per protocol of trial
- Other non-compliance

Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

Subject listings of major protocol deviations will be sorted by country and site.

9 DEMOGRAPHICS AND OTHER SUBJECT CHARACTERISTICS

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

Unless stated otherwise demographic and baseline data will be displayed for the following analysis sets:

- FAS-All
- FAS-EU
- FAS-US <2

Medical history and previous and concomitant medication will be displayed for the following analysis sets:

- SAF-EU
- SAF-US <2

Pain intensity related to NCA/PCA will be displayed for the following analysis sets:

- FAS-EU
- FAS-US

9.1 Subject demographics

Subjects demographics are age [years], weight [kg], height [cm], body mass index (BMI) [kg/m^2], sex, race, ethnicity, and trial-relevant age group. Further additional age groups will also be considered: birth to <28 days, 28 days to <2 years, 2 years to <12 years, 12 years to <16 years and 12 years to <18 years .

All data as recorded in the eCRF are used for the analyses of subject demographics.

- Regarding age, the age at the time of allocation is recorded in the eCRF.
  - For age recorded in months for subjects aged 60 days to less than 2 years, the following conversion rule is used:

$$\frac{Age\ [months]}{12\ \frac{months}{year}} = Age\ [years]$$

  - For age recorded in days for subjects aged less than 60 days, the following conversion rule is used:

$$\frac{Age\ [days]}{365.25\ \frac{days}{year}} = Age\ [years]$$

  - For age converted from days/months to years, the resulting value is rounded to 3 decimal places.

Subject demographics will be summarized with descriptive statistics for each treatment group and overall. For the FAS-All and FAS-EU, subject demographics will be summarized with descriptive statistics for each trial-relevant age group (no display of age group) and for FAS-EU also by type of supplemental opioid analgesic medication used.

Age groups as recorded in the IVRS/IWRS will be summarized with descriptive statistics.

Both values, age (eCRF) and age (IVRS/IWRS), will be displayed in the subject data listing. The listings will also include the ages of eCRF and IVRS/IWRS converted into years.

9.2 Baseline characteristics

Baseline characteristics will be descriptively summarized for each treatment group and overall. For the FAS-All and FAS-EU, baseline characteristics will be summarized with descriptive statistics for each trial-relevant age group.

Continuous baseline characteristics are:

- Amount of (post-operative) morphine or hydromorphone taken within 24 hours prior to first IMP administration (mg/kg of morphine equivalent). See Section 16.1.6 for details.
- Amount of (post-operative) non-opioid analgesic medication taken within 24 hours prior to first IMP administration, grouped by WHO-DD coding and route of administration. See Section 11.2.6 for a description of how standardized dose amounts are calculated. See Section 16.1.6 and Section 16.1.7 for further details.
- Duration of surgery (in minutes).
- Time between end of surgery and administration of first IMP.

Categorical baseline characteristics are:

- Type of surgery.
- Type of opioid analgesia used (hydromorphone/morphine).
- Type of administration (NCA/PCA) and additionally
  - Opioid analgesia used (hydromorphone/morphine) for NCA. The percentage denominator will be the total number of subjects on NCA in the respective treatment groups.
  - Opioid analgesia used (hydromorphone/morphine) for PCA. The percentage denominator will be the total number of subjects on PCA in the respective treatment groups.
- Application of background infusion (yes/no) and additionally
  - Opioid analgesia used (hydromorphone/morphine) for background infusion. The percentage denominator will be the total number of subjects with background infusion in the respective treatment groups.
- Results of pregnancy test.

Furthermore, type of opioid analgesia used (hydromorphone/morphine) as recorded per IVRS/IWRS will be summarized with descriptive statistics. Both information (type of opioid analgesia used based on IVRS/IWRS and based on eCRF) will be displayed in the subject data listing.

For the following parameters, collected on more than 1 occasion during the trial including baseline, assessment at baseline will be presented with assessments later on in the trial and not separately for baseline:

- Pain intensity

  - Face, Legs, Activity, Cry, Consolability scale (FLACC) for children who are less than 6 years or in older children who are not able to report their pain using the other scales
  - Faces Pain Scale-Revised (FPS-R) for children between 6 years and less than 12 years
  - Visual analog scale (VAS) for children between 12 years and less than 18 years.
- Physical examination
- Vital signs
- Oxygen saturation before first IMP intake
- Safety laboratory parameters
- 12-lead ECG
- Sedation score

Further subject characteristic data collected according to the protocol, i.e. date of signing the informed consent/assent form, date, start and completion time of surgery, the indication, and further information collected on opioid analgesic medication given before first dose of IMP (as per protocol) will be included in the subject data listing only.

9.3 Subject medical history

The assessment of a disease being previous or concomitant is entered directly in the eCRF by the investigator and will be evaluated as documented on the relevant medical history page of the eCRF.

- Previous diseases:
  - A table will summarize the number of subjects with (at least 1) previous disease(s) and the number of subjects per each previous disease, sorted alphabetically by primary System Organ Class and Preferred Term.
- Concomitant diseases:
  - A table will summarize the number of subjects with (at least 1) concomitant disease(s) and the number of subjects per each concomitant disease, sorted alphabetically by primary System Organ Class and Preferred Term.

9.4 Prior and concomitant medication

This section covers all prior and concomitant medication as per Section 16.1.6 received and additional therapies and treatments performed within 28 days prior to randomization to IMP up to the end of the trial (excluding anesthetics and medication used during the surgery).

The terms *prior* and *concomitant* are defined as follows:

- 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, regardless of its start date

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical (ATC) 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 started after last dose of IMP will be displayed.

Medication or therapy started after last dose of IMP will be flagged in the subject data listing.

- Details of the WHO-DD Preferred Name and the reason for use will also be given in the listings together with the MedDRA coding of the indication, the regimen, route, start, and stop date and time. The listings will differentiate between prior and concomitant medications.

9.5 Pain intensity related to NCA/PCA

Pain intensity scores related to NCA/PCA (including IV administration in case of NCA/PCA failure or clinician bolus) will be assessed, when possible, prior to each administration of supplemental opioid analgesia by NCA/PCA. These pain intensities are recorded on the pain intensity page of the eCRF with “Time-point” equal “before NCA/PCA”.

For each subject, all non-missing pain intensity scores obtained prior to NCA/PCA will be grouped in 5 time intervals: [0 h, 12 h], (12 h, 24 h], (24 h, 48 h], (48 h, 72 h] and (72 h, 96 h] after first IMP intake. The date/time of the pain assessment, as per eCRF, will determine the corresponding time interval, not the date/time of the subsequent NCA/PCA administration. For each subject and each of the 5 time intervals, all non-missing pain intensity scores will be averaged. For each time interval, these averages will be summarized descriptively.

10 EXPOSURE AND COMPLIANCE

Exposure data will be displayed for the following analysis sets:

- SAF-US <2
- SAF-EU

Compliance data will be displayed for the following analysis sets:

- FAS-EU
- FAS-US <2

10.1 Exposure

Extent of exposure will be summarized with descriptive statistics

For the Treatment Period, the amount of IMP (in mg/kg) and the number of IMP intakes will be summarized descriptively, separately for the intervals:

- [0 h, 12 h]
- (12 h, 24 h]
- (24 h, 48 h)
- [48 h, 72 h]

and over the entire 24-, 48-, and 72-hours periods ([0 h, 24 h], [0 h, 48 h] , [0 h, 72 h]).

The calculation of amount of IMP (in mg/kg) per administration will be calculated based on the following formula using the values provided in the eCRF “Administration of IMP” page:

$$amount\ of\ IMP\ \left[\frac{mg}{kg}\right] = \frac{approximate\ volume\ administered\ [mL] * dose\ strength\ [\frac{mg}{mL}]}{body\ weight\ [kg]}$$

The duration of exposure will also be summarized using descriptive statistics. Furthermore, the number of subjects with at least 12 hours and at least 24 hours duration of exposure will be summarized. The duration of exposure is defined as the time between the first IMP intake and the last intake of IMP.

In addition, the number of subjects with the last intake of IMP at least 44 hours after the first IMP intake will be presented to address the US FDA request to evaluate at least 25 subjects in the age range birth to less than 17 years of age exposed to tapentadol for at least 48 hours.

Subject listings of exposure will be presented for all treated subjects.

10.2 Compliance

Dosing compliance for a subject will be calculated based on the specifications in Section 16.1.12. Compliance will be summarized as 12-h and 24-h compliance by age group and treatment using descriptive statistics on the FAS-EU and the FAS-All.

Subject listings of complicance will be presented for all treated subjects.

11 EFFICACY ANALYSES

Unless stated otherwise, all efficacy analyses with the exception of *Palatability and Acceptability* and the results of the Bayesian analysis will be displayed for the following analysis sets:

- FAS-EU
- FAS-US <2

The Palatability and Acceptability questionnaire as well as results of the Bayesian analysis will be displayed only for the following analysis set:

- FAS-EU

Summary statistics for all efficacy endpoints will be provided. Furthermore, for the primary efficacy endpoint, summary statistics will additionally be displayed for each of the conducted sensitivity analyses.

11.1 Primary endpoint

The primary efficacy endpoints for the US FDA and EU PDCO are the amount of supplemental opioid analgesic medication used within the first 12 hours and 24 hours after first IMP intake, respectively. Supplemental opioid analgesia will be expressed in mg/kg of morphine IV equivalents. The primary efficacy endpoints will be analyzed as described in the following section on all subjects aged 2 years to <18 years (FAS-EU) for both US FDA and EU PDCO. The primary efficacy endpoint for US FDA for subjects less than 2 years old will be descriptively summarized using summary statistics for continuous variables as outlined in Section 7.1.

Hydromorphone doses will be multiplied by 5 to obtain the morphine equivalent.

11.1.1 Primary analyses

Let $\mu_{Tap,T}$, $\mu_{Pbo,T}$ be defined as

$\mu_{Tap,T}$: Expected value of supplemental opioid analgesic medication (SOAM) used in the tapentadol group

within the first *T* hours after first IMP intake

$\mu_{Pbo,T}$: Expected value of SOAM used in the placebo group

within the first *T* hours after first IMP intake

The primary null hypothesis to be tested for the EU PDCO is that $\mu_{Tap,24}$ is equal to $\mu_{Pbo,24}$. The alternative hypothesis is that $\mu_{Tap,24}$ is different from $\mu_{Pbo,24}$. I.e:

$$H_0: \mu_{Tap,24} - \mu_{Pbo,24} = 0 \quad \text{vs} \quad H_1: \mu_{Tap,24} - \mu_{Pbo,24} \neq 0.$$

The primary null hypothesis to be tested for the US FDA is that $\mu_{Tap,12}$ is equal to $\mu_{Pbo,12}$. The alternative hypothesis is that $\mu_{Tap,12}$ is different from $\mu_{Pbo,12}$. I.e:

$$H_0: \mu_{Tap,12} - \mu_{Pbo,12} = 0 \quad \text{vs} \quad H_1: \mu_{Tap,12} - \mu_{Pbo,12} \neq 0.$$

The primary null hypotheses for each region will be tested using an analysis of variance (ANOVA) which includes treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors.

In case of fewer than 6 subjects in an age group, age groups will be pooled according to the rules described in Section 7.3. If fewer than 6 subjects received hydromorphone or if fewer than 6 subjects received morphine, the factor supplemental opioid analgesia used will not be included in the ANOVA model.

Treatment effects will be estimated based on least squares means of the difference. The 95% CI and p-value will be presented for the difference in least squares means. Additionally descriptive 95% CIs will be presented for the individual least squares means of both treatments.

Two scatter plots, 1 for T=12 and 1 for T=24 will be provided, illustrating the pairs (w_i, y_i^T), where w_i denotes the weight of subject *i* and y_i^T the total amount of supplemental opioid analgesia (morphine equivalents in mg/kg body weight) used within the first T=12 or T=24 hours after first IMP intake.

For subjects who discontinue from the treatment prior to 24 hours after first IMP intake, the following imputation rule will be used for the primary endpoint:

- Let t be the time difference between first IMP intake and time of discontinuation, as per eCRF.
- Let X be the cumulative sum of the amounts of supplemental opioid analgesia (mg/kg) of all NCA/PCA usages before discontinuation.
- Discontinuation due to any other reason than “opioid analgesic medication is no longer needed” or “switch to exclusively oral opioid analgesic medication”:
  - Time of discontinuation prior to 12 hours after first IMP intake (t<12 h):

  - 12 h endpoint: Cumulative use over 12 hours will be estimated as (X/t)*12 mg/kg
  - 24 h endpoint: Cumulative use over 24 hours will be estimated as (X/t)*24 mg/kg
- Time of discontinuation between 12 hours and 24 hours after first IMP intake (12 h≤t<24 h):
  - 12 h endpoint: For cumulative use over 12 hours the exact value is used.
  - 24 h endpoint: Cumulative use over 24 hours will be estimated as (X/t)*24 mg/kg

This extrapolation assumes a uniform use (in mg/kg per hour) of supplemental opioid over 24 hours.

- Discontinuation due to reason "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication":
  - Time of discontinuation prior to 12 hours after first IMP intake (t<12 h):
    - 12 h endpoint: Cumulative use over 12 hours will be estimated as X mg/kg
    - 24 h endpoint: Cumulative use over 24 hours will be estimated as X mg/kg
  - Time of discontinuation between 12 hours and 24 hours after first IMP intake (12 h≤t<24 h):
    - 12 h endpoint: For cumulative use over 12 hours the exact value is used.
    - 24 h endpoint: Cumulative use over 24 hours will be estimated as X mg/kg

Further detail on respective eCRF pages used for the calculation of amount of supplemental opioid analgesic medication per subject is given in Section 16.1.6. Also, further information on calculation of amounts of supplemental opioid analgesia (mg/kg) for subjects with missing NCA/PCA information is given.

11.1.2 Sensitivity analyses

The following sensitivity analyses will be performed for the primary endpoint of both regions.

The analyses of the primary endpoints will be repeated for the PPS. This means that the analyses of the primary endpoints will be repeated for the following analysis sets:

- PPS-EU for the EU primary endpoint (24 hours)
- PPS-EU-12h for the US primary endpoint (12 hours).

Furthermore, 2 different imputation rules, not relying on a uniform use of supplemental opioid over 24 hours (EU PDCO primary endpoint) / 12 hours (US FDA primary endpoint), will be used for subjects discontinuing treatment due to any other reason than "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication". For subjects discontinuing treatment due to the reason "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication" the same imputation method as for the primary analysis will be used for these sensitivity analyses.

1.) Placebo mean imputation rule:

The placebo mean imputation rule will use only information of subjects receiving placebo to impute the unknown amount of supplemental opioid analgesia between the time of discontinuation and 12/24 hours after first IMP intake for subjects in both treatment arms. Assuming that placebo subjects will require more supplemental opioid analgesia, this approach is conservative, but reflects the increased need of supplemental opioid analgesia after terminating treatment with tapentadol.

Let X be the set of all amounts of supplemental opioid analgesia (morphine equivalents, mg/kg) used by all placebo subjects after first IMP intake.

Each $x_i \epsilon X$ corresponds to a time of NCA/PCA-activation (hours after first IMP intake), denoted by $t_i$and a number n_i of placebo subjects still on treatment at time t_i, constituting a triple (t_i, x_i, n_i).

Without loss of generality, these triples will be sorted by time t_i, i.e. for (t_i, x_i, n_i), $(t_j, x_j, n_j), i < j$, it holds $t_i \leq t_j$. For $t \in [0,24]$, let m denote the integer for which $t_m \leq t < t_{m+1}$.

The average cumulative use of supplemental analgesia in the placebo group up to time t will be calculated by

$$F(t) = \sum_{i=1}^{m} \frac{x_i}{n_i}$$

For subjects terminating treatment prematurely after t_0 < T, $T \epsilon \{12, 24\}$, hours after first IMP intake with an amount of x_0 mg/kg of supplemental opioid analgesia (morphine equivalents) used up to t_0, amount of supplemental opioid analgesia up to T hours will be imputed by

$$x_0 + \mathrm{F(T)} - \mathrm{F}(t_0)$$

For an illustration of this procedure, see Figure 3.

2.) Treatment mean imputation rule:

The treatment mean imputation rule will use information of the subject's treatment group to impute the unknown amount of supplemental opioid analgesia between the time of discontinuation and 12/24 hours after first IMP intake for subjects in both treatment arms. This approach more closely reflects the actual expected amount of supplemental opioid analgesia needed by the subject, if the subject did not prematurely terminate the particular treatment.

Let X_{Pbo} be the set of all amounts of supplemental opioid analgesia (morphine equivalents, mg/kg) used by all placebo subjects after first IMP intake.

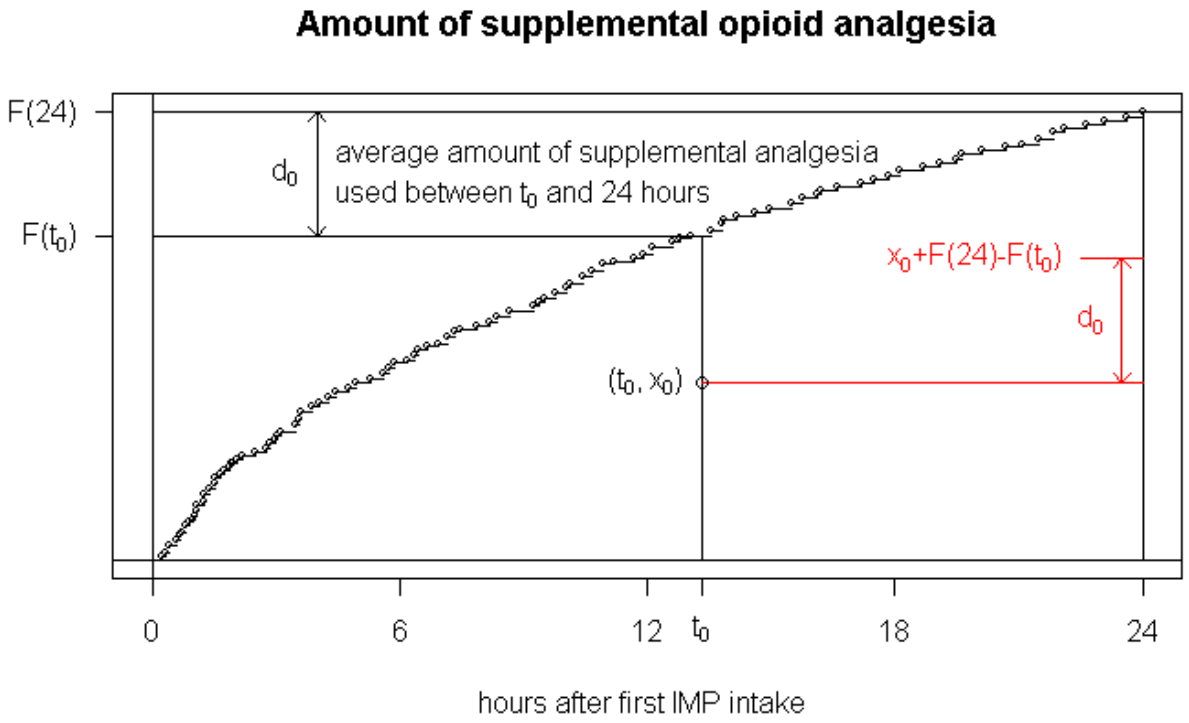
Let X_{Tap} be the set of all amounts of supplemental opioid analgesia (morphine equivalents, mg/kg) used by all tapentadol subjects after first IMP intake.

The above procedure for *1.) Placebo mean imputation rule* will be applied to both sets X_{Pbo} and X_{Tap}, yielding the average cumulative use of supplemental analgesia functions F_{Pbo} and F_{Tap}, respectively.

For subjects terminating treatment prematurely after $t_0 < T$, $T \in \{12, 24\}$, hours after first IMP intake with an amount of x_0 mg/kg of supplemental opioid analgesia (morphine equivalents) used up to t_0, amount of supplemental opioid analgesia up to T hours will be imputed according to the function of the corresponding treatment group, i.e.

$x_0 + F_{Pbo}(T) - F_{Pbo}(t_0)$, for subjects on placebo

$x_0 + F_{Tap}(T) - F_{Tap}(t_0)$, for subjects on tapentadol



IMP = investigational medicinal product.

Figure 3: Average amount of supplemental opioid analgesia used after first IMP intake

For the US FDA primary endpoint, the following sensitivity analyses will be performed in addition as requested by the FDA.

The primary analysis of the primary endpoint and the respective PPS analysis will be repeated with subjects who "switch to exclusively oral opioid analgesic medication" not handled in the same way as subjects who discontinue due to reason "opioid analgesic medication is no longer needed" but as all others, i.e. assuming a uniform use of supplemental opioid over 12 hours.

The analyses of the US FDA primary endpoint using the placebo mean imputation rule and the treatment mean imputation rule will be repeated, applying those 2 imputation rules also for subjects discontinuing treatment due to "switch to exclusively oral opioid analgesic medication".

11.1.3 Other analysis

There will be no multiplicity adjustments for any of these analyses, thus all of them will be conducted at a significance level of $\alpha = 0.05$ and regarded as exploratory.

11.1.3.1 ANCOVA including pain intensity at baseline (based on each age-defined pain scale) as a covariate

The following analysis will be done for the 24-hour endpoint in subjects 2 years and above (FAS-EU) only.

An analysis of covariance (ANCOVA) including treatment and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors and age at baseline and pain intensity at baseline as covariates will be conducted. Since different pain scales were used for different age groups, the analysis will be performed on the following 3 subgroups:

1. Children less than 6 years and older children who were not able to report their pain using the other scales and used the FLACC, including the FLACC score at baseline as covariate
2. Children between 6 years and less than 12 years old, including the FPS-R score at baseline as covariate
3. Children between 12 years and less than 18 years old, including the VAS score at baseline as covariate

Estimation of least squares means, determination of the p-value and CIs, and application of the missing data imputation method will be done as described in Section 11.1.1 for the primary analysis.

11.1.3.2 ANCOVA including amount of opioid analgesia (morphine or hydromorphone) used prior to IMP as a covariate

The following analysis will be done for the 24-hour endpoint in subjects 2 years and above (FAS-EU) only.

An ANCOVA including treatment, baseline age group (pooled, if applicable), and the opioid analgesic medication used (morphine versus hydromorphone) as factors and the amount (mg/kg of morphine equivalents) of morphine/hydromorphone used 24 hours prior to IMP intake as a covariate will be conducted. Estimation of least squares means and CIs and application of the missing data imputation method will be done as described in Section 11.1.1 for the primary analysis.

11.1.3.3 Subgroup analyses

The following analysis will be done for subjects 2 years and above (FAS-EU) only.

Summary statistics for the primary endpoint will be provided for each level of the following factors:

- Relevant age groups (12-hour and 24-hour endpoint)
- Sex (only 24-hour endpoint)
- Race (only 24-hour endpoint)
- Geographical region (only 24-hour endpoint)
- Type of administration of supplemental opioid analgesia: NCA/PCA (12-hour and 24-hour endpoint)

- Supplemental opioid analgesia used: Hydromorphone/morphine (only 24-hour endpoint)

Furthermore, for factor levels that include at least 15% of overall data, the difference in least squares means between tapentadol and placebo and their CI will be provided and illustrated in forest plots for the 24-hour endpoint. Basis for the least squares means will be an ANOVA including treatment, baseline age group and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors (pooled if applicable). For the subgroup investigations of relevant age groups and supplemental opioid analgesia used, the respective factor will be excluded from the model.

11.1.3.4 Bayesian analysis for the EU PDCO population only

For the EU PDCO, for the primary endpoint, a Bayesian ANOVA that includes treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors will be conducted. The Bayesian framework allows the incorporation of 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 down-weighting of the prior information in the final analysis. A detailed description of this analysis can be found in Section 16.1.5.

11.2 Secondary endpoints

All non-descriptive analyses of secondary endpoints will be conducted at a significance level of $\alpha = 0.05$ and regarded as exploratory. No adjustment for multiplicity for any of the analyses of the secondary endpoints will be made. If not stated differently subjects less than 2 years old will be separately analyzed using the FAS-US <2.

11.2.1 Supplemental opioid analgesic medication

The primary endpoint for the US FDA evaluated on the FAS-EU will be used as a secondary endpoint for the EU PDCO. The same ANOVA model as defined above for the primary efficacy endpoints will be used to assess treatment differences. Summary statistics will also be provided for each relevant age group. The primary analysis on the FAS-EU for the primary efficacy endpoint for the EU PDCO, the amount of supplemental opioid analgesic medication used within the first 24 hours after first IMP intake, will be considered as a secondary endpoint for the US FDA. Furthermore, the primary efficacy endpoint for the EU PDCO will be descriptively summarized for the FAS-US<2 and the respective age groups.

In addition, the total amount of supplemental opioid analgesic medication received, assessed in 12-hour intervals from 24 hours to 96 hours (see Section 16.1.6 for details), will be summarized descriptively for the FAS-EU and FAS-US <2.

The intervals will be:

- (24 hours, 36 hours]
- (36 hours, 48 hours]
- (48 hours, 60 hours]
- (60 hours, 72 hours]
- (72 hours, 84 hours]
- (84 hours, 96 hours]

For each interval, only subjects who have their End of Treatment Visit after the start of the interval will be included.

If a subject has their End of Treatment Visit at time t_0 during a given interval $(t_i, t_{i+1}]$, the subject will not be included in subsequent intervals and the missing data for the remainder of the given interval will be imputed:

- Let t:= $t_0 - t_i$ be the time difference between the lower bound of the given interval and the time of the End of Treatment Visit, as per eCRF.
- Let X be the cumulative sum of the amounts of supplemental opioid analgesia (mg/kg) of all NCA/PCA usages within the given interval $(t_i, t_{i+1}]$, i.e. between t_i and t_0.
- Discontinuation due to any other reason than "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication":

  Cumulative use within the given interval $(t_i, t_{i+1}]$ will be estimated as (X/t)*12 mg/kg.
- Discontinuation due to reason "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication":

  Cumulative use within the given interval $(t_i, t_{i+1}]$ will be estimated as X mg/kg.

11.2.2 Clinical Global Impression of Change (CGIC)

At the End of Treatment Visit, the response of the CGIC questionnaire is measured on an ordinal, 7-category scale. Results will be summarized descriptively.

Furthermore, the categories "very much improved" and "much improved", as well as the remaining 5 categories will be pooled and the resulting binary variable will be summarized descriptively. Descriptive results of the 7-categorical and the binary variable will be displayed in a single table.

11.2.3 Patient Global Impression of Change (PGIC)

At the End of Treatment Visit, the PGIC questionnaire will be completed by the subject, parent, or legal guardian. The response of the PGIC is measured on an ordinal, 7-category scale. Results will be summarized descriptively.

Furthermore, the categories "very much improved" and "much improved", as well as the remaining 5 categories will be pooled and the resulting binary variable will be summarized descriptively. Descriptive results of the 7-categorical and the binary variable will be displayed in a single table.

11.2.4 Palatability and Acceptability

The palatability and acceptability questionnaire consists of 2 dimensions (taste/swallowing). The response to each dimension is measured on an ordinal, 5-category scale. Assessments are performed after first dose of IMP and at the End of Treatment Visit in subjects aged 2 years to less than 18 years old. Missing values will not be imputed.

For each of the 2 time points and each of the 2 dimensions, responses will be summarized with descriptive statistics. The change between the 2 visits will be displayed for each dimension in a shift table. The summary statistics will be repeated for each age subgroup in the EU PDCO population.

11.2.5 Pain intensity related to administration of IMP and End of Treatment Visit

Pain assessments related to administration of IMP and the End of Treatment Visit will occur at the following times during the course of the Treatment Period:

- Before first dose of IMP (baseline)
- Between 30 minutes and 60 minutes after first dose of IMP
- Before each succeeding dose of IMP
- End of Treatment Visit

Pain intensity scores and change from baseline values will be summarized descriptively for each time point by age-defined pain scale (i.e. FLACC/FPS-R/VAS). The summary will also contain the CIs of each treatment group. For the FAS-US <2 only the FLACC summary will be used.

A figure illustrating the means ± CI for both treatments at each assessment prior dosing will be provided for each age-defined pain scale.

Furthermore the area under the pain curve (AUPC) up to 12 hours and 24 hours will be calculated:

For each pain assessment *i*, each subject *j* yields a tuple $(t_{i,j}, p_{i,j})$, where $t_{i,j}$ is the time (hours after first IMP intake) of the pain assessment *i* of subject *j* and $p_{i,j}$ is the pain intensity difference between baseline and assessment *i* of subject *j*. Baseline assessments will be denoted by *i=0*. According to the study design, subjects will have a different number of pain assessments (denoted by m_j). According to the different age groups $p_{i,j}$ will be assessed by 1 of the 3 different pain intensity instruments:

- $p_{i,j}$ = $FLACC_{0,j} - FLACC_{i,j}$ or
- $p_{i,j}$ = $FPS\text{-}R_{0,j} - FPS\text{-}R_{i,j}$ or
- $p_{i,j}$ = $VAS_{0,j} - VAS_{i,j}$

For each *j*, tupels $(t_{i,j}, p_{i,j}), i = 1, \dots, m_j$ will be linearly interpolated (see Figure 4) and the area under the curve will be determined summing the resulting trapezoids ($A_{i,j}$, i=1,…m_j) up to 12 hours ($AUPC_{12}$) and 24 hours ($AUPC_{24}$). For an illustration, see Figure 4.

<u>$AUPC_T$:</u>

1. For all i ∈ $\{1, \dots, m_j\}$ with $t_{i,j} \leq T$:

$$A_{i,j} = \frac{(p_{i,j} + p_{i-1,j}) * (t_{ij} - t_{i-1,j})}{2}$$

2. If applicable, for i ∈ $\{1, \dots, m_j\}$ with $t_{i-1,j} < T < t_{i,j}$:

$$A_{i,j} = \frac{(p_{i-1,j} + (T - t_{i-1,j}) * (p_{i,j} - p_{i-1,j})/(t_{i,j} - t_{i-1,j}) + p_{i-1,j}) * (T - t_{i-1,j})}{2}$$

3. For each subject *j* completing treatment for *T* hours, let i_T be the index *i* with $t_{i-1,j} < T \leq t_{i,j}$:

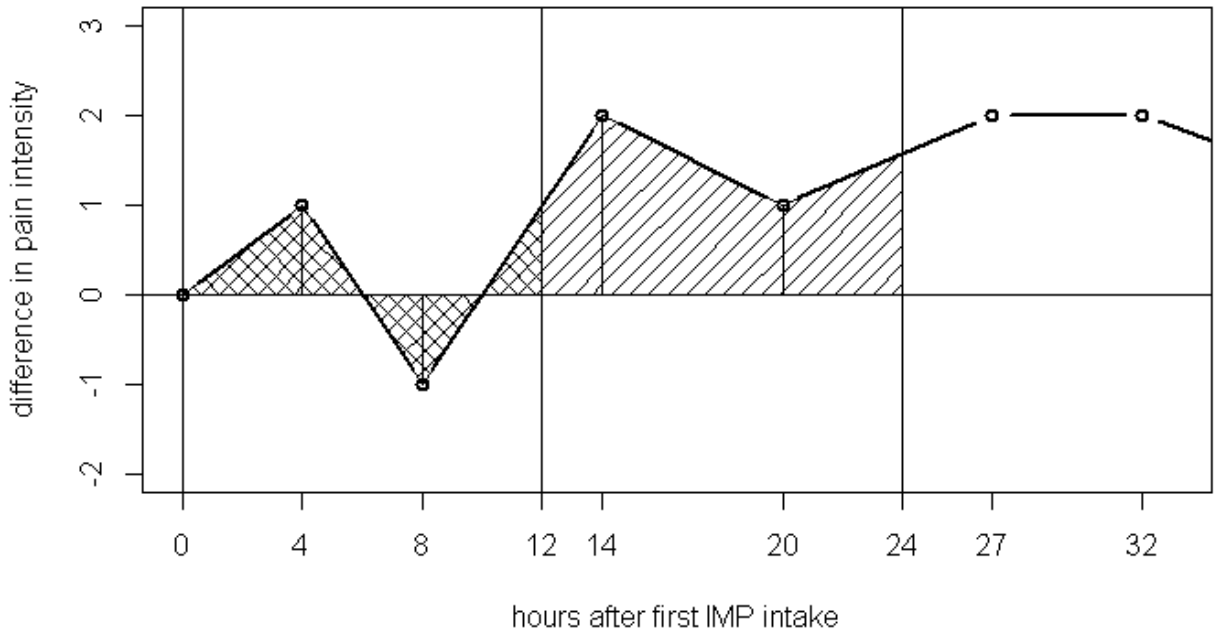
$$AUPC_{Tj} = \sum_{i=1}^{i_T} A_{i,j}$$

For subjects j who prematurely discontinue the treatment at time $\tilde{t} < T$, the following formula will be applied:

$$AUPC_{Tj} = \frac{T}{\tilde{t}} \sum_{i=1}^{m_j} A_{i,j}$$

Intermediate missing pain values will not be imputed. Missing pain values at the End of Treatment Visit will be imputed by the mean of non-missing pain scores assessed by the age-defined pain scale in the respective treatment group at the End of Treatment Visits.

The larger the $AUPC_T$, the higher the pain improvement of the particular treatment group. Note that areas below the x-axis, caused by pain values larger than baseline pain, will proportionally decrease the value of the particular $A_j s$ and thus the value of $AUPC_T$.



IMP = investigational medicinal product.

Figure 4: Area under the pain curve

The $AUPC_T$ for 12 hours ($AUPC_{12}$) and 24 hours ($AUPC_{24}$) will be descriptively summarized for each treatment group and age-defined pain scale.

11.2.6 Supplemental non-opioid analgesic medication

The number and proportion of subjects taking non-opioid analgesic medications (irrespective of the indication) within the first 12 hours and 24 hours after first IMP intake (see Section 16.1.6 and Section 16.1.7 for details) will be grouped according to WHO-DD coding and will be summarized descriptively by treatment group.

11.2.7 Time to first and time to second NCA/PCA after first IMP

The time to first and time to second NCA/PCA (including IV administration in case of NCA/PCA failure or clinician bolus) after the first dose of IMP will be summarized descriptively using time-to-event methods and displayed overall. Additionally treatment groups will be compared using the log-rank test for the overall population. The hazard ratio of the 2 treatment groups will be provided. Subjects who complete the End of Treatment Visit (Visit 3) before their first/second use of NCA/PCA or subjects who terminate treatment before their first/second use of NCA/PCA will be censored at the End of Treatment Visit. Kaplan-Meier graphs will be provided.

11.2.8 Time to treatment discontinuation due to lack of efficacy

In case of more than a total of 9 treatment discontinuations due to lack of efficacy, for the FAS-All the distributions of the time from the first dose of IMP to treatment discontinuation (see Section 16.1.8 for details) due to lack of efficacy will be summarized descriptively using time-to-event methods and compared between the treatment groups using the log-rank test. The hazard ratio of the 2 treatment groups will be provided. Subjects who reach the maximum duration of treatment (72 hours, see Section 16.1.4) will be censored at 72 hours after first IMP intake. Subjects who discontinue during the Treatment Period for reasons other than lack of efficacy will be censored at the time of the decision to discontinue treatment.

This analysis will not be done for the FAS-US <2 due to the small number of subjects.

12 ANALYSIS OF PHARMACOKINETIC AND PHARMACODYNAMICS PARAMETERS

Not applicable.

13 SAFETY ANALYSES

The analysis of safety data will be performed for the EU PDCO Safety Set for the EU PDCO report and for the EU PDCO Safety Set and US FDA Safety Set for subjects less than 2 years for the final report.

All data regarding adverse events, laboratory parameters, vital signs, oxygen saturation, ECG, physical examination, Columbia-Suicide Severity Rating Scale (C-SSRS), and the sedation score will be displayed on the EU PDCO Safety Set (*SAF-EU*) for the EU PDCO report. For the final report the EU PDCO report will be amended with data of subjects less than 2 years old using the *SAF-US <2* if not indicated differently.

13.1 Adverse events

Any AE that occurs at or after first administration of IMP and up to the end of the therapeutic reach of last administration of IMP is considered as treatment emergent AE (TEAE). The therapeutic reach is the time after IMP intake that a subject is still considered to be potentially affected by a study drug. For tapentadol oral solution, the therapeutic reach is defined as 48 hours after (last) IMP intake. An AE starting before the first dose of IMP and worsened in intensity between the first administration of IMP and the end of the therapeutic reach of last administration of IMP will also qualify as a TEAE. Handling rules for (partially) missing dates and times of AEs are described in Section 16.1.11.

Pre-existing diseases or conditions occurring before enrollment are considered to be medical history and should be recorded as AEs only if they worsen (untoward change in intensity, frequency, or quality) after enrollment.

For AEs where the intensity changes over time, the maximum intensity observed during the whole duration of the AE will be documented and captured in the database. If the AE stopped and reoccurred with a different or the same intensity, it will be entered as new AE in the eCRF.

All AEs with start date/time after enrollment but before first administration of IMP and that do not worsen after IMP intake, and all AEs with start date/time after the therapeutic reach of last IMP will be regarded as non-TEAE.

Related TEAEs are TEAEs that are at least possibly related to the IMP as documented in the eCRF (possible, probable/likely, certain).

The following 3 overview tables will be generated by treatment group and overall for the SAF-EU. The first and the second table will also be summarized for the SAF-EU for each relevant age group. Information of the first table for the SAF-EU will also be provided for each geographical region, sex, race and ethnicity.

1. Summary of the number of subjects with
   - At least 1 TEAE
   - At least 1 non-serious TEAE
   - At least 1 serious TEAE
   - At least 1 related serious TEAE
   - At least 1 related TEAE
   - At least 1 TEAE leading to discontinuation from the treatment (i.e. TEAE with “Action taken with IMP”: “drug withdrawn”)
   - At least 1 TEAE leading to discontinuation from the trial (i.e. TEAE with “Countermeasures”: “trial discontinuation”)
   - A TEAE with a fatal outcome
2. Summary of the number of subjects
   - Categorized by number of TEAEs per subject (0, 1, 2, 3, 4, 5, and >5)
3. Summary of the number of subjects with
   - At least 1 non-TEAE
   - At least 1 serious non-TEAE

For subjects less than 2 years old the first overview table as outlined above will be provided for the *SAF-US <2*.

Unless stated otherwise, the following TEAE summaries will be presented by treatment group as well as for relevant age groups:

By Preferred Term (sorted by decreasing incidence in the tapentadol group), the number of subjects will be summarized per each TEAE occurring in at least 5% of subjects in at least 1 treatment arm (only SAF-EU).

By System Organ Class and Preferred Term (sorted alphabetically), the number of subjects will be summarized per each

- TEAE
- Serious TEAE (only overall, not for relevant age groups)
- TEAE leading to discontinuation from the treatment (for *SAF-US <2* only for relevant age groups)

The following TEAE summaries will be presented by treatment group only:

Number of subjects by System Organ Class and Preferred Term and 1 of the following TEAE descriptors:

- Intensity (mild, moderate, severe)

  For multiple occurrences of a TEAE in a subject the worst intensity, i.e. the most to the right in parentheses above, is used for the summary table.
- Relationship to the IMP (not related, not assessable/unclassifiable, conditional/unclassified, unlikely, possible, probable/likely, certain)

  For multiple occurrences of a TEAE in a subject the most related, i.e. the most to the right in parentheses above, is used for the summary table.
- Outcome (unknown, recovered/resolved, recovering/resolving, not recovered/not resolved, resolved with sequelae, fatal) (only SAF-EU)

  For multiple occurrences of a TEAE in a subject the worst outcome, i.e. the most to the right in parentheses above, is used for the summary table.
- Action taken with IMP (not applicable, unknown, dose not changed, dose reduced, drug withdrawn)

  For multiple occurrences of a TEAE in a subject the most dramatic action taken with IMP, i.e. the most to the right in parentheses above, is used for the summary table. (only SAF-EU)
- Countermeasures (none, others, newly started medication, trial discontinuation)

  For multiple occurrences of a TEAE in a subject the most dramatic countermeasure, i.e. the most to the right in parentheses above, is used for the summary table. (only SAF-EU)
- Time to onset after first IMP intake (categories: ≤1 h, >1-≤4 h, >4-≤12 h, >12-≤24 h, >24-≤48 h, >48-≤72 h, >72 h) (only SAF-EU)

All AEs will be listed together with information on onset, duration, intensity, seriousness, relationship to IMP, outcome, and countermeasure(s) taken.

Additionally, the following listings will be produced for enrolled subjects:

- All deaths
- All serious AEs
- All AEs that lead to discontinuation from the treatment
- All AEs that lead to discontinuation from the trial

Adverse event summaries will only include events up to the Follow-up Visit, i.e. 14 days after first IMP intake. Serious AEs (SAEs) occurring after the Follow-up Visit will be added to the safety database and will be described in the integrated clinical trial report but not considered in any statistical analysis.

The distributions of the time from the first dose of IMP to treatment discontinuation (see Section 16.1.8 for details) due to AE will be summarized descriptively using time-to-event methods (only SAF-EU). Subjects who reach the maximum duration of treatment (72 hours, see Section 16.1.4) will be censored at 72 hours after first IMP intake. Subjects who discontinue during the Treatment Period for reasons other than AE will be censored at the time of the decision to discontinue treatment.

13.2 Laboratory parameters

For subjects aged at least 2 years, laboratory parameters are assessed by a local and central laboratory at baseline. Blood samples taken at the End of Treatment Visit will only be analyzed by a central laboratory. For subjects aged less than 2 years, only the local laboratory analysis will be performed. For summary statistics (SAF-EU), only values obtained from the central laboratory will be used. Laboratory data of subjects <2 years (SAF-US<2) will be summarized based on respective reference ranges as provided by the local laboratory.

All laboratory parameters collected in this trial are continuous variables:

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

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

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

Descriptive statistics will be calculated for each safety laboratory parameter and glomerular filtration rate at baseline, at the End of Treatment Visit, and for the changes from baseline to the End of Treatment Visit. Descriptive statistics will be done for laboratory values from the central laboratory only.

A shift table (changes from normal to abnormal [high, low] and vice versa) will be provided for the changes with respect to the reference range for the laboratory parameters.

Values outside sponsor defined alert ranges (potentially clinically important values) for the laboratory parameters will be assessed based on the classification in Table 8. This applies for all laboratory values recorded. The number of subjects with at least 1 value outside the sponsor defined alert ranges (potentially clinically important values) will be summarized descriptively. A listing of subjects with values outside the sponsor defined alert ranges (potentially clinically important values) will be generated.

13.3 Electrocardiogram

Twelve-lead ECGs will be recorded at baseline and the End of Treatment Visit. The parameters assessed in the ECG are the RR interval, PR interval, QRS interval and QT interval. The corrected QTcF (Fridericia) interval will be calculated as $QTcF = QT/(RR)^{1/3}$. Normal and abnormal ECG parameters are assessed according to the classification in Table 3 and Table 4. Furthermore, the investigator will provide an ECG overall interpretation at the Enrollment Visit and the End of Treatment Visit (“normal”, “abnormal, clinically not relevant” and “abnormal, clinically relevant”).

Table 3: Classification of abnormal ECG parameters

Parameter (unit)	Age class	Abnormally low	Abnormally high
PR (msec)	0-<1 months	<100	>150
	1-<6 months	<100	>150
	7-<12 months	<100	>150
	1-<2 years	<100	>150
	2-<3 years	<100	>150
	3-<12 years	<100	>180
	12-<18 years	<100	>200
QRS (msec)	0-<1 months	<40	>79
	1-<6 months	<40	>79
	7-<12 months	<40	>79
	1-<2 years	<40	>79
	2-<3 years	<40	>79
	3-<12 years	<50	>89
	12-<18 years	<60	>99
QT (msec)	0-<1 month	<320	>450
	1-<6 months	<320	>450
	7-<12 months	<320	>450
	1-<2 years	<320	>450
	2-<18 years	<320	>450
RR (msec)	0-<3 months	<333	>750
	3-<6 months	<400	>860
	7-<12 months	<400	>860
	1-<2 years	<430	>1000
	2-<18 years	<600	>1200

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

Table 4: 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.
QTcF = Corrected QT interval using the Fridericia correction (ECG).

Descriptive statistics of the ECG parameters at baseline, at End of Treatment Visit, and for changes from baseline to End of Treatment Visit will be generated based on measurement from the ECG central reader. Moreover, the classification of abnormal QTcF values (normal, prolonged) and other abnormal ECG parameters (“normal”, “abnormally low/high”) by visit will be summarized

descriptively for each relevant age group. Shift tables will summarize the changes between measurements at the baseline and End of Treatment Visit based on the classification of parameters.

The overall interpretation on ECG findings (“normal”, “abnormal, clinically not relevant”, and “abnormal, clinically relevant”) assessed by the investigator will be summarized by visit and relevant age group.

13.4 Vital signs and oxygen saturation

Vital signs measured in the trial are diastolic and systolic blood pressure (DBP and SBP; mmHg), heart rate (HR; beats per minute), and respiration rate (breaths per minute). Furthermore, oxygen saturation will be measured. Vital signs and oxygen saturation are assessed at the Enrollment Visit, before every administration of IMP and at the End of Treatment Visit. For the analyses the baseline value will be the assessment defined for baseline in Section 7.2.

Descriptive statistics of vital signs and oxygen saturation by time point and also for the changes from baseline to each time point measured will be provided. A shift table with respect to the normal ranges presented in Table 5 will be provided.

Values outside the sponsor defined alert ranges (potentially clinically important values) are assessed according to the classifications in Table 6 depending on the subject’s age. A listing of subjects with values outside these ranges will be generated. The number of subjects regarding values outside the sponsor defined alert range (alert low, non-alert, alert high) will be summarized descriptively and the display will be repeated by age group. Furthermore, the display by individual parameter is repeated separately for subjects with a baseline value or the respective parameter within or outside the normal range.

Furthermore, for subjects with oxygen saturation below 92% for at least 60 seconds, the time that oxygen saturation fell below 92%, the lowest oxygen saturation as well as the corresponding systolic blood pressure, diastolic blood pressure, respiratory rate, and HR will be included in the subject listing.

Table 5: Normal ranges of vital signs and oxygen saturation

	Age class								
Parameter (unit)	**0-<3 months**	**3-<6 months**	**6-<12 months**	**1-<3 years**	**3-<6 years**	**6-<9 years**	**9-<12 years**	**12-<16 years**	**16-<18 years**
Diastolic BP (mmHg)	45-55	50-65	55-65	55-70	50-75	57-71	60-75	64-78	65-81
Systolic BP (mmHg)	65-85	70-90	80-100	90-105	90-105	95-110	101-116	108-121	109-127
Heart rate HR (bpm)	100-150	90-120	80-120	70-110	86-117	74-111	67-103	62-96	58-92
Respiration rate	35-55	30-45	25-40	20-30	21-27	18-24	16-22	15-21	13-19
Oxygen saturation SpO_2 (%)	≥96	≥96	≥96	≥96	≥96	≥96	≥96	≥96	≥96

The ranges of vital signs are based on Fleming et al. 2011 and NIH pediatric blood pressure charts.
BP = blood pressure; NIH = National Institute of Health.

Table 6: Sponsor defined alert values for vital signs and oxygen saturation

		Age class							
Parameter (unit)		**0-<3 months**	**3-<12 months**	**1-<3 years**	**3-<6 years**	**6-<9 years**	**9-<12 years**	**12-<16 years**	**16-<18 years**
Diastolic BP (mmHg)	abnormally low	<35	<40	<40	<45	<42	<45	<49	<50
	abnormally high	>65	>85	>90	>80	>86	>89	>93	>95
Systolic BP (mmHg)	abnormally low	<60	<60	<75	<80	<80	<86	<93	<95
	abnormally high	>110	>110	>120	>110	>125	>130	>135	>140
Heart rate HR (bpm)	abnormally low	<80	<70	<60	<80	<74	<67	<62	<58
	abnormally high	>180	>150	>140	>120	>111	>103	>96	>92
Respiration rate	abnormally low	<25	<20	<18	<17	<12	<12	<12	<12
	abnormally high	>70	>60	>50	>30	>24	>24	>24	>24
Oxygen saturation SpO_2 (%)	abnormally low	<92	<92	<92	<92	<92	<92	<92	<92

BP = blood pressure.

13.5 Additional safety parameters

13.5.1 Physical examination

A general physical examination will be done at the Enrollment Visit by rating each body system as normal or abnormal. An update of the physical status is recorded at the End of Treatment Visit (changed/unchanged).

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

13.5.2 Columbia-Suicide Severity Rating Scale

For the C-SSRS, results of each asked question for suicidal ideation and for suicidal behavior, at children's baseline (questionnaire at Enrollment Visit, but after surgery) as well as since last visit (questionnaire at End of Treatment Visit), will be presented in a subject data listing.

13.5.3 Sedation score

Sedation scores will be summarized descriptively as a categorical variable for each time point indicated in Table 1.

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15 SAP AMENDMENTS

15.1 SAP Amendment 01

This amendment was prepared to include changes of protocol amendment 04, 23rd June 2015 to protocol amendment 06, 19th Aug 2016.

A detailed description of all changes made in amendment 01 of this SAP can be found in Section 5.2.1.

15.2 SAP Amendment 02

This amendment was prepared to further describe how the US objective of analyzing subjects aged between birth and less than 17 years will be implemented.

A detailed description of all changes made in amendment 02 of this SAP can be found in Section 5.2.2.

16 APPENDIX

16.1 Programming specifications

16.1.1 Percentages and decimal places

- Percentages have to be presented to 1 decimal point.
- Percentages equal to 0 or 100 have to be presented as such without any decimal point.
- For descriptive summary statistics, the same number of decimal places as in the raw data should be presented when reporting minimum and maximum values, 1 more decimal place when reporting mean, quartiles and 95% CI and SD.
- P-values will be displayed up to the fourth decimal place.
  - P-values rounded to 0.0000 will be displayed as "<0.0001"
  - P-values rounded to 1.0000 will be displayed as ">0.9999"

16.1.2 Presentation of descriptive statistics

For descriptive statistics of a continuous variable and less than 5 non-missing values the rules of Table 7 apply.

Table 7: Parameters to be calculated for continuous variables

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; min = minimum; max = maximum; SD = standard deviation; Q1 = first quartile; Q3 = third quartile.

16.1.3 Precision of time variables

The precision of time assessments captured in the eCRF is *minutes*, which will be utilized in all calculations. Unless stated otherwise, when summary statistics are applied on time variables, results are illustrated in hours with 2 decimal places. The conversion of minutes to hours is:

$$\frac{time\ [minutes]}{60\ \frac{minutes}{hour}} = time\ [hours]$$

16.1.4 Treatment Period

The Treatment Period start date/time is the date/time of first IMP intake as documented on the eCRF.

The Treatment Period end date/time is assessed by the following formula from eCRF data:

end date/time = min{72 hours after first IMP intake,
date/time captured on End of Treatment page}

Subjects reaching the maximum duration of treatment (72 hours) are identified by the main reason to discontinue treatment on the "End of Treatment" page in the eCRF:

- "Maximum duration of treatment (72 hours) reached"

16.1.5 Bayesian analysis for the EU PDCO population

The primary endpoint for the EU PDCO will also be analyzed within the Bayesian framework, using prior information for the treatment effect from a clinical trial for acute pain in adults [redacted]. This prior information will be incorporated into the analysis using a conditional power prior approach (see, e.g., Neelon and O'Malley 2010), which allows to control the weight of the prior information in the final analysis.

For the EU PDCO, for the primary endpoint, a Bayesian ANOVA that includes treatment, baseline age group, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors will be conducted. In case of fewer than 6 subjects in an age group, age groups will be pooled according to the rules described in Section 7.3. If fewer than 6 subjects received hydromorphone or if fewer than 6 subjects received morphine, the factor supplemental opioid analgesia used will not be included in the ANOVA model.

Non-informative Normal prior distributions with mean 0 and variance 1000 will be assigned to the intercept and the regression coefficients for baseline age group and opioid analgesic used. The prior for the treatment effect will be a Normal distribution with mean equal to the treatment effect derived from the trial in adults (−0.463, see below) and variance equal to the variance of the treatment effect derived from the trial in adults (0.0676^2, see below) divided by δ, where $\delta \in [0,1]$ represents the down-weighting factor of the information from adults; when $\delta = 0$ the prior variance equals infinity and hence an improper flat prior distribution is considered, and when $\delta = 1$ the variance equals that derived from the adults. Finally a non-informative Gamma distribution with parameters shape = 0.001 and rate = 0.001 will be assumed for the residual precision $1/\sigma^2$ (i.e. the inverse of the residual variance).

A value of $\delta = 0.1$ will be considered for the down-weighting factor. This corresponds to down-weighting the information obtained from the trial in adults by 90%.

The posterior distribution has no analytical closed expression. Therefore Markov chain Monte Carlo (MCMC) simulation techniques will be used to obtain a sample of the posterior distribution of all model parameters. This will be done using the SAS Proc MCMC as implemented in SAS v9.3 or later. To this end, a chain of 110 000 iterations will be run, discarding the first 10 000 as burn-in and keeping every 10th. The resulting thinned sample of size 10 000 will be used to summarize the posterior distribution of all the model parameters.

The posterior distribution of the treatment effect will be plotted (density function) and numerically summarized using the mean, quartiles, SD, and 95% credibility interval. In addition the posterior probability for the treatment effect to be below 0 will be presented.

Superiority of tapentadol versus placebo will be considered if the upper limit of the 95% credibility interval is below 0.

Bayesian model details

Let Y_i be the amount of supplemental opioid analgesic medication taken by subject i within the first 24 hours after first IMP intake, T_i the treatment group (0 = placebo, 1 = tapentadol), A_i the age group (categories coded from 1 to K) and O_i the type of opioid analgesic used (0 = hydromorphone, 1 = morphine). Then the Bayesian model is as follows:

$$Y_i \sim \text{Normal}(\mu_i, \sigma^2)$$

$$\mu_i = \beta_0 + \sum_{k=1}^{K} \beta_{1k} I_{(A_i=k)} + \beta_2 O_i + \beta_3 T_i$$

$$\beta_0, \beta_{11}, \ldots \beta_{1K}, \beta_2 \sim \text{Normal}(0, 1000)$$

$$\beta_3 \sim \text{Normal}\left(m_A, \frac{s_A^2}{\delta}\right)$$

$$1/\sigma^2 \sim \text{Gamma}(0.001, 0.001)$$

where $m_A = -0.463$ and $s_A^2 = 0.0676^2$ are respectively the expected value and the variance of the treatment effect β_3 derived from [redacted] (see next section for further details).

Elicitation of the prior distribution for the treatment effect

In [redacted], four different types of rescue medication were used: acetaminophen (1st line), ibuprofen (2 line), ketorolac (2nd line) and Lortab (3rd line). Given the lack of equivalence between these and morphine, it is not feasible to assess the total amount of rescue medication taken in morphine equivalent. However, the combined number of intakes is to some extent informative of the amount of supplemental analgesia used. For subjects in the FAS, the mean (SD) of the number of doses taken of all types of rescue medication combined on Day 2 (the first 24 hours after surgery) was 4.2 (2.2) in the placebo group, 2.3 (1.9) in the tapentadol 58 mg group (HCL salt, corresponding to 50 mg free base as used in the rest of the document) and 1.6 (1.8) in the tapentadol 116 mg group (HCL salt, corresponding to 100 mg free base as used in the rest of the document) based on 67, 67, and 68 subjects, respectively (integrated clinical trial report [redacted], Section [redacted], Table [redacted]).

Adopting a conservative approach, we focus on the difference between placebo and tapentadol 58 mg (the lowest dose of tapentadol). The relative difference between placebo and tapentadol in

the mean number intakes can be roughly estimated as (4.2-2.3)/4.2 = 0.452. That is, subjects in the tapentadol 58 mg group used 45.2% less supplemental analgesia than those in the placebo group. This estimation can be slightly refined using simulation. If we assume that the number of intakes is approximately normally distributed according to Normal(4.2, 2.2^2) for placebo and Normal(2.3, 1.9^2) for tapentadol, both truncated to the interval $[0, +\infty]$, then we can draw n = 67 values from each distribution and compute the relative difference between the sample means. If we repeat this process a large number of times, say 1 000 000, then we get an empirical estimate of the mean and SD for the relative difference of 0.429 and 0.0616, respectively.

Rusy et al (2010) observed a mean (SD) supplemental use of opioid of 1.32 (0.408) mg/kg over 24 hours based on 30 subjects in the placebo group. Rugyte et al (2007) observed in their placebo group a mean (SD) supplemental use of opioid of 0.67 (0.20) mg/kg over 24 hours based on 17 subjects. The pooled mean (SD) of supplemental opioid analgesia for the placebo group in both studies is 1.08 (0.349) mg/kg over 24 hours.

With the distribution of the relative difference between placebo and tapentadol in the intake of rescue medication in adults, a Normal(0.429, 0.0616^2), and the mean amount of supplemental opioid analgesia in pediatric population (1.08 mg/kg), we can derive the prior distribution for the treatment effect (tapentadol – placebo) as Normal($-0.429*1.08$, $(0.0626*1.08)^2$)=Normal(-0.463, 0.0676^2). Therefore the conditional prior given a down-weighting factor δ is Normal(-0.463, $0.0676^2/\delta$).

16.1.6 Analyses of medication intake regarding different trial phases

Baseline characteristics:

The amount of morphine or hydromorphone taken within 24 hours prior to first IMP administration and after surgery will be derived from the following eCRF pages:

- Opioid Background Infusion
- Opioid Analgesics administered by NCA/PCA
- Additional IV Bolus Administration of Opioid Analgesics (clinician bolus, or in case of NCA/PCA failure)
- Other Analgesic Medication (only opioid analgesic medication and only before first IMP intake and after surgery)

The total amounts of non-opioid analgesic medications used within 24 hours prior to first IMP administration and after surgery will be derived from the following eCRF pages:

- Other Analgesic Medication (only non-opioid analgesic medication and only before first IMP intake and after surgery)
- Prior / concomitant medication

Efficacy endpoints:

The amount of supplemental opioid analgesic medication used within the first 12 hours, within the first 24 hours and between 24 hours and 96 hours after first IMP intake will be derived from the following eCRF pages:

- Opioid Analgesics administered by NCA/PCA

- Additional IV Bolus Administration of Opioid Analgesics (clinician bolus, or in case of NCA/PCA failure)
- Other Analgesic Medication (all intraveneous opioid used, added as morphine equivalents (1st IMP to 12h/24h/decision to stop treatment); morphine equivalents of IV opioids will be calculated with respective conversion factors)

The number of subjects taking non-opioid analgesic medications within the first 12 hours and 24 hours after first IMP intake will be derived from the following eCRF pages:

- Other Analgesic Medication (only non-opioid analgesic medication and only after first IMP intake)
- Prior / concomitant medication

Handling of missing/partial information on NCA/PCA administered opioid analgesics

For some subjects the time on the NCA/PCA page was not always related to a push, in some cases the nurse entered the time and the dose administered since the nurse last checked. This means the date/time of the eCRF entry will be used as the end time of an interval over which the recorded dose was given. The start time will be the last NCA/PCA entry before. The dose will be distributed evenly over the time interval. The subjects to be handled this way will be identified using a specific protocol deviation code.

In case only a total dose is available respective start and stop times should be entered into the eCRF (the start time should be associated with a zero dose entry and the end time with the dose) and then the total dose will be analyzed as interval dose.

Subjects who were given oral morphine/hydromorphone instead of using NCA/PCA are handled as zero NCA/PCA dose to be consistent with handling of patients switching to exclusively oral opioid analgesic medication as per protocol amendment 04.

Handling of the individual subjects with missing or only partial information will in addition be described in the final statistical review report.

Prior and concomitant medications:

Analyses of prior and concomitant medication will be based on information of the following eCRF pages:

- Prior / concomitant medication
- Additional therapies / treatments
- Other Analgesic Medication
- Opioid Background Infusion
- Opioid Analgesics administered by NCA/PCA
- Additional IV Bolus Administration of Opioid Analgesics (clinician bolus, or in case of NCA/PCA failure)

16.1.7 Treatment period and trial completer

There are 2 sets of treatment period completers, completing 12 hours and 24 hours of treatment.

For the 12 hours treatment period completer:

- Decision to discontinue treatment is later than 12 hours after first IMP intake

For the 24 hours treatment period completer:

- Decision to discontinue treatment is later than 24 hours after first IMP intake

The time of first IMP intake will be assessed from the "Administration of IMP page" in the eCRF. The time of the decision to discontinue treatment will be assessed from the "End of Treatment" page in the eCRF. If the decision occurs prior to last dose of IMP then the date/time of last IMP dose will be used instead. If the decision is more than 6 hours after the last dose of IMP then the date/time of last dose of IMP + 6 hours will be used instead.

There are 2 sets of trial completers, i.e. 12 hours and 24 hours trial completer.

An X-hours trial completer is an X-hours treatment period completer that completed the Follow-up Visit, i.e. Visit 4.

16.1.8 Time to treatment discontinuation

For all time to treatment discontinuation analyses, the time to treatment discontinuation will be calculated in hours using the following formula:

$$\frac{date}{time}\, of\ decision\ to\ stop\ treatment\ on\ End\ of\ Treatment\ page - \frac{date}{time}\, 1st\ IMP\ intake$$

16.1.9 Determination of FLACC total score

Regarding the FLACC questionnaire, the individual values of the 5 categories as per eCRF will be used to calculate the total score for statistical evaluation. If at least 1 of the 5 categories is missing, the total score will be set to missing as well.

16.1.10 Multiple assessments of pain intensity, vital signs and oxygen saturation

Pain intensity, vital signs and oxygen saturation are assessedbefore each administration of IMP:

- For all these parameters, the corresponding number of IMP administration is captured in the eCRF and will be used for analyses by time point (i.e. administration of IMP) or to identify specific time points.
- Pain intensity is additionally assessed after the first dose and at the End of Treatment visit, which will also be selectable time-points on the eCRF-page for pain intensity.
- Additionally vital signs and oxygen saturation are assessed at the Enrollment visit and End of Treatment visit on different eCRF-pages, enabling clear distinction from assessments prior each administration of IMP for these parameters.

16.1.11 TEAE assignment of AEs in case of (partially) missing dates

Handling of missing or partial missing dates for AEs:

- Let d_{TS} : h_{TS} : m_{TS} denote the date : hour : minute of first IMP intake
- Let d_{TE} : h_{TE} : m_{TE} denote the date : hour : minute of the end of the therapeutic reach of the last IMP administration (derived variable, not directly assessable from eCRF data)
- Let d_{AS} : h_{AS} : m_{AS} denote the date : hour : minute of the start of the AE
- Let d_{AE} : h_{AE} : m_{AE} denote the date : hour : minute of the end of the AE

1. d_{AS} : h_{AS} : m_{AS} non-missing
    a. d_{AS} : h_{AS} : $m_{AS} \in [d_{TS} : h_{TS} : m_{TS}, d_{TE} : h_{TE} : m_{TE}]$ → TEAE
    b. d_{AS} : h_{AS} : $m_{AS} \notin [d_{TS} : h_{TS} : m_{TS}, d_{TE} : h_{TE} : m_{TE}]$ → non-TEAE
2. d_{AS} : h_{AS} available, m_{AS} missing
    c. d_{AS} : $h_{AS} \in [d_{TS} : h_{TS}, d_{TE} : h_{TE}]$ → TEAE
    d. d_{AS} : $h_{AS} \notin [d_{TS} : h_{TS}, d_{TE} : h_{TE}]$ → non-TEAE
3. d_{AS} available, h_{AS} missing, m_{AS} availability irrelevant
    e. $d_{AS} \in [d_{TS}, d_{TE}]$ → TEAE
    f. $d_{AS} \notin [d_{TS}, d_{TE}]$ → non-TEAE
4. d_{AS} missing, h_{AS}, m_{AS} availability irrelevant
    g. d_{AE} : h_{AE} : m_{AE} non-missing
        i. $d_{AE} : h_{AE} : m_{AE} \geq d_{TS} : h_{TS} : m_{TS}$ → TEAE
        ii. $d_{AE} : h_{AE} : m_{AE} < d_{TS} : h_{TS} : m_{TS}$ → non-TEAE
    h. d_{AE} : h_{AE} available, m_{AE} missing
        i. $d_{AE} : h_{AE} \geq d_{TS} : h_{TS}$ → TEAE
        ii. $d_{AE} : h_{AE} < d_{TS} : h_{TS}$ → non-TEAE
    i. d_{AE} available, h_{AE} missing, m_{AE} availability irrelevant
        i. $d_{AE} \geq d_{TS}$ → TEAE
        ii. $d_{AE} < d_{TS}$ → non-TEAE
    j. d_{AE} missing, h_{AE}, m_{AE} availability irrelevant → TEAE

16.1.12 Compliance algorithm

All information is based on the "Administration of IMP" page of the eCRF.

- Let $t_0, \dots, t_m$ be the times of administration of IMP
- Let $s_1, \dots, s_m$ be the sleeping indicator respective to $t_1, \dots, t_m$ with
- $s_i = 1$ if "subject sleeping" is ticked
- $s_i = 0$ otherwise (i.e. if no entry or "other" is ticked)
- Let T be the time of decision to discontinue the treatment on the "End of Treatment" page
- For information on time calculation will be done in hours (x.xx h) and for dosing information unit is milligram (x.xx mg)

For the 24-hour compliance

Let $\tilde{T}$ the sleep adjusted treatment time (hours) be defined as

$$\tilde{T} = \min\{T - t_0, 24\}\,[\text{h}] - \sum_{i=1}^{m} s_i\, D_i\, \mathbf{1}_{\{t_i - t_0 \leq 24\}}[\text{h}]$$

With the delay of treatment (hours) as

$$D_i = \min\{t_i - t_{i-1} - 4.25, 1.75\}\ [\text{h}]$$

C_j the compliance of subject j as percent of *actual intake* is defined as:

- $C_j = \frac{Actual\ intake\ [mg]}{(\lfloor \tilde{T}/4.25 \rfloor + 1) * \min\{1.25 * w_j, 100\}\ [mg]} * 100\%$,
  if actual intake < floor $\left(\frac{\tilde{T}}{4.25} + 1\right) * \min\{1.25 * w_j, 100\}$
- $C_j = 100\%$,
- if floor $\left(\frac{\tilde{T}}{4.25} + 1\right) * \min\{1.25 * w_j, 100\}$ < actual intake < floor $\left(\frac{\tilde{T}}{3.75} + 1\right) * \min\{1.25 * w_j, 100\}$
- $C_j = \frac{Actual\ intake\ [mg]}{(\lfloor \tilde{T}/3.75 \rfloor + 1) * \min\{1.25 * w_j, 100\}\ [mg]} * 100\%$,
- if actual intake > floor $\left(\frac{\tilde{T}}{3.75} + 1\right) * \min\{1.25 * w_j, 100\}$

Where w_j is the weight of subject in kg j and "actual intake" is the actual intake of IMP of subject j (mg). Note that the maximum single dose a patient is permitted to receive is 100 mg and the dose for the first 24 hours is 1.25 mg/kg. The dosing interval is 4 hours with a range of $\pm$0.25 hours. The floor function returns the largest integer that is less than or equal to the argument.

12-hour compliance

Repeat the above algorithm by substituting "24" by "12" in the above definition of $\tilde{T}$.

Actual intake derivation

For *actual intake* of IMP of subject j, use the sum of the amount of IMP of each administration of IMP of subject j up to the time of discontinuation/ at 12 hours/ at 24 hours (inclusive).

For each administration of IMP use the following calculation procedure to obtain the amount of IMP intake:

Check if "Was dose completely administered" is ticked "Yes" or "No"

a. If "Yes": Use the value in "Total dose planned for administration" [mg]
b. If "No": take the entry in "approximate volume administered" [ml] and multiply by "dose strength", i.e. either by 4 if "4 mg/ml" is ticked or by 20 if "20 mg/ml" is ticked

Compliance for subjects below 6 month will be based on dosing recommendations as per protocol amendment 07 but will be done according to same algorithm.

16.2 Sponsor defined alert ranges for laboratory parameters

Table 8: Sponsor defined alert ranges for laboratory parameters

	Parameter	Age class (years)	Abnormally low	Abnormally high	Comment
Chemistry	ALT	2-10	-/-	>2.0 ULN	
		>10-<18		>3.0 ULN	
	AST	2-7	-/-	>2.0 ULN	
		>7-<18		>3.0 ULN	
	AP	2-<18	-/-	>2.0 ULN	
	Total bilirubin	2-<18	-/-	>1.5 ULN	
	Total protein	2-<18	<0.5 LLN	>1.1 ULN	
	Bicarbonate	2-<4	<12 mmol/l	>28 mmol/l	
		4-<18	<17 mmol/l	>30.6 mmol/l	
	Estimated GFR based on serum creatinine as offered by central lab (see also Schwartz et al. 2009)	2-<18	GFR <90 ml/min/1.7 m^2	-/-	
	Triglycerides (male)	0-<10	<0.34 mmol/l	>1.13 mmol/l	
		10-<15	<0.36 mmol/l	>1.41 mmol/l	
		15-<18	<0.42 mmol/l	>1.67 mmol/l	
	Triglycerides (female)	0-<10	<0.4 mmol/l	>1.24 mmol/l	
		10-<15	<0.42 mmol/l	>1.48 mmol/l	
		15-<18	<0.44 mmol/l	>1.40 mmol/l	
	Chloride	0-<18	<94 mmol/l	>112 mmol/l	
	Urea	2-<18	-/-	>2.0 ULN	
	Sodium	2-<18	<0.95 LLN	>1.05 ULN	
	Potassium	2-<18	<0.9 LLN	>1.1 ULN	
	Calcium	2-<18	<0.8 LLN	>1.2 ULN	
	Phosphorous	2-<18	<0.8 LLN	>1.2 ULN	
	Glucose (random)	2-<18	<0.8 LLN	>2.5 ULN	
	Uric Acid	2-<18	-/-	>1.5 ULN	
	Creatinine	2-<18	-/-	>1.5 ULN	
	CK	2-7	-/-	>6 ULN	
		>7-10		>2.5 ULN	
		Female >10-<18		>5 ULN	

	Parameter	Age class (years)	Abnormally low	Abnormally high	Comment
		Male >10-<18		>2.5 ULN	
	LDH	2-<18	-/-	>2.0 ULN	
	Lipase	2-<18	-/-	>2.0 ULN	
Hematology	Haematocrit	2-<18	<30%	>55%	
	Haemoglobin (female)	2-<6	<100 g/l	>160 g/l	
		6-<18	<110 g/l	>180 g/l	
	Haemoglobin (male)	2-<6	<100 g/l	>160 g/l	
		6-<18	<110 g/l	>190 g/l	
	MCV	2-<6	<74 fl		
		6-<18	<76 fl	>98 fl	
	MCH (male)	2-<3	<25 pg	>29 pg	
		3-<6	<25 pg	>30 pg	
		6-<12	<24 pg	>34 pg	
		12-<18	<26 pg	>34 pg	
	MCH (female)	2-<3	<25 pg	>28 pg	
		3-<6	<25 pg	>30 pg	
		6-<12	<24 pg	>34 pg	
		12-<18	<26 pg	>34 pg	
	MCHC	0-<18	<310 g/l	>380 g/l	
	WBC	2-<18	<3000/µl	>15 000/µl	
	RBC (male)	2-<3	<4.1/µl	>5.1/µl	
		3-<6	<4.1/µl	>5.3/µl	
		6-<12	<3.7/µl	>6.0/µl	
		12-<18	<4.5/µl	>6.4/µl	
	RBC (female)	2-<3	<4.4/µl	>5.0/µl	
		3-<6	<4.1/µl	>5.2/µl	
		6-<12	<3.7/µl	>6.0/µl	
		12-<18	<4.1/µl	>5.6/µl	
	Platelets	2-<18	<110*109/l	>600*109/l	

The values are still to be determined for subjects aged from birth to <2 years old.

-/- = No sponsor-defined alert ranges defined.

ALT = alanine transaminase; AST = aspartate transaminase; AP = alkaline phosphatase; GFR = glomerular filtration rate; CK = creatine kinase; LDH = lactic acid dehydrogenase; LLN = lower limit normal; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; ULN = upper limit normal; WBC = white blood cell.

16.3 List of statistical output documentation

The statistical output documentation to be included integrated clinical trial report Section 16.1.9 will contain the original SAS output for the analyses (including sensitivity analyses) of the primary endpoint.