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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203794 and NDA 022304
Supplement #:	S-10 for NDA203794 and S-24 for NDA022304
Drug Name:	NUCYNTA® (Tapentadol) Oral Tablets and NUCYNTA® (Tapentadol) Oral Solution
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1 EXECUTIVE SUMMARY

This supplement NDA (sNDA) seeks to update the label of both NDA022304 and NDA203794 to include information for pediatric patients.

One randomized, double-blinded, multi-center, and placebo-controlled study (Study KF5503/65) was conducted to support Tapentadol oral solution (OS) in the treatment of post-operative acute pain requiring opioid treatment in pediatric subjects aged from birth to less than 18 years old. This trial was performed to meet the requirements for pediatric development plans agreed with authorities in 2 regions (Paediatric Committee of the European Medicines Agency [EU PDCO] and United States Food and Drug Administration [US FDA]). One hundred seventy-five (175) eligible subjects from birth to < 18 years old were randomized at 2:1 ratio to Tapentadol OS or placebo at 30 sites across EU and 14 sites in the US. The randomization was stratified by age groups (birth to less than 30 days, 30 days to less than 6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years, and 17 years to <18 years) and by use of morphine or hydromorphone as supplemental opioid analgesia.

Among the 160 randomized and treated subjects aged 2 to < 18 years old (the protocol-defined primary efficacy analysis set):

- For the FDA-requested primary efficacy endpoint of the amount of supplemental opioid analgesic medication used during the first 12 hours after the first dose of investigational medicinal product (IMP) (this was the first secondary efficacy endpoint for the EU PDCO), Tapentadol OS demonstrated statistical significance in children and adolescents compared to placebo. The estimated [least square] mean (SE) difference of Tapentadol minus Placebo was -0.05 (0.02) mg/kg bodyweight of morphine equivalents (95% confidence interval [CI] [-0.09, -0.00], p-value=0.404).
- For the EU-requested primary efficacy endpoint of the amount of supplemental opioid analgesic medication used during the first 24 hours after the first dose of IMP (this was the first secondary efficacy endpoint for the Agency), Tapentadol OS also demonstrated statistical significance in children and adolescents compared to placebo. The estimated [least square] mean (SE) difference of Tapentadol minus Placebo was -0.1 (0.04) mg/kg bodyweight of morphine equivalents (95% CI [-0.18, -0.02], p-value=0.0154).

Based on these efficacy results, I recommend the approval of Tapentadol OS for the management of acute pain severe enough to require an opioid analgesic in pediatric subjects.

Table 1: Amount of supplemental opioid analgesic medication (mg/kg) used within the first 12/24 hours after first IMP intake (all randomized and treated subjects aged 2 years to <18 years old)

	12 Hours		**24 Hours**	
Statistic	**Placebo N = 52**	**Tapentadol OS N = 108**	**Placebo N = 52**	**Tapentadol OS N = 108**
Mean (SD)	0.14 (0.19)	0.09 (0.11)	0.25 (0.35)	0.16 (0.20)
LS Mean (SE)	0.13 (0.02)	0.08 (0.01)	0.24 (0.03)	0.14 (0.03)
LS Mean Difference Tapentadol-placebo (95% CI)		-0.05 (-0.09, -0.00)		-0.10 (-0.18, -0.02)
p-value		0.0404		0.0154

p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance (ANOVA). The ANOVA model included treatment, baseline age group and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Supplemental opioid analgesia was expressed in mg/kg of morphine IV-equivalents.
N = number of subjects in analysis set; n = number of subjects; SD = standard deviation; SE = standard errors; LSmean = least square mean; CI = confidence interval; ANOVA = analysis of variance; IV = intravenous; OS = oral solution.
Source: Tables 27 and 28 of Study KF5503/65 CSR.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Tapentadol hydrochloride is a centrally acting opioid analgesic agent. Nucynta® (Tapentadol) immediate-release (IR) tablets were first approved by the FDA in 2008, under NDA 022304 (Sponsor, Janssen Research and Development [JRD]) for the relief of moderate to severe acute pain in patients 18 years of age or older. The extended-release (ER) formulation of Nucynta, Nucynta ER®, was approved by the FDA on 25 August 2011, under NDA 200533. Subsequently, an alternative IR formulation of Nucynta, Nucynta OS, was approved on 15 October 2012, under NDA 203794, for the management of moderate to severe acute pain in adults. NDA 22304 for Nucynta IR tablets was approved with a requirement for 2 pediatric assessments (355-1 and 355-2) in children from birth to <17 years of age per the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). The Nucynta OS (NDA 203794) approval letter of 15 Oct 2012 also required 2 pediatric assessments (1937-1 and 1937-2).

2.1.2 History of Drug Development

NDA 22304 for Nucynta (Tapentadol) IR tablets was approved with a requirement for 2 pediatric assessments (355-1 and 355-2) in children from birth to <17 years of age per the Pediatric Research Equity Act (PREA). NDA203794 for Nucynta OS approval letter of 15 Oct 2012 also required 2 pediatric assessments (1937-1 and 1937-2). However, the pediatric studies required under the PREA were deferred because the product was ready for approval for use in adults, and the pediatric studies had not yet been completed.

On 12 December 2012, a Proposed Pediatric Study Request (PPSR) was submitted to Nucynta IR, OS and ER NDAs to receive a Pediatric Written Request (PWR) under the Best Pharmaceuticals for Children Act (BPCA). Following the pediatric study request submission, the Division provided a formal PWR to Janssen Research & Development, LLC (the Sponsor at the time) on 08 July 2013 pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the FDA Amendments Act of 2007, to obtain needed (b) (4)

(b) (4)

Upon receiving a formal PWR, (b) (4)

2.1.3 Studies Reviewed

To fulfill (b) (4) PREA requirements, the following clinical studies are included in this submission: one multiple-dose confirmatory Phase 3 safety and efficacy trial (KF5503/65) and three (3) supportive open-label single-dose pharmacokinetic (PK) trials. This review focuses on the Phase 3 Study KF5503/65. Table 2 below contains a summary of this study.

Table 2: Summary of Efficacy Study to be assessed in the Statistical Review

Study No	Design	Objective	Treatment / Sample Size	Study Population	Endpoints
KF5503/65	Multi-center, randomized, double-blinded, parallel group, placebo-controlled	To evaluate 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	Tapentadol OS/ 119 Placebo / 56	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	Primary: The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the **first 12** hours after first IMP* intake Secondary (Primary for the EU): The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the **first 24** hours after first IMP* intake

* IMP = Investigational medicinal product
Source: Statistical Reviewer's Summary.

2.2 Data Sources

This sNDA was initially submitted on December 20, 2021 but was refused to file since for the studies included, the applicant did not submit the electronic datasets, any raw datasets, and a few other essential documents.

In this resubmission, the applicant included electronic datasets in ADaM format and raw datasets in STDM format, along with description for each dataset.

The data sources for this review include clinical study reports, protocols, statistical analysis plan (SAP), and datasets. The study reports, protocols and SAP were electronic submitted and located at:
\\CDSESUB1\evsprod\NDA203794\0077\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5351-stud-rep-contr\kf550365

All data sources were electronic submitted and located at
\\CDSESUB1\evsprod\NDA203794\0083\m5\datasets\kf550365

The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours after first IMP intake were included in the "adsoam.xpt" dataset with the identifying value of "IMPUTE12" of the variable "PARAMCD" and the variable name "AVAL" for the supplemental opioid analgesic medication outcomes. The treatment variable, given both as numeric (TRTPN) and character (TRTP), was also included in the "adsoam.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be verified with minor data manipulation. The statistical analyses were primarily based on the analysis datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study KF5503/65 was a randomized, double-blinded, multi-center, and placebo-controlled study to the efficacy and safety of Tapentadol OS in the treatment of post-operative acute pain requiring opioid treatment in pediatric subjects aged from birth to less than 18 years old.

Subjects in the study underwent surgery and were started on nurse-controlled analgesia (NCA) or patient-controlled analgesia (PCA) with morphine or hydromorphone. After surgery, when the subject was able to tolerate liquids, the subject was allocated to either Tapentadol OS or placebo (randomized 2:1), given every 4 hours for up to 48 hours. The maximum duration of the treatment was 72 hours. The dose of Tapentadol OS was 1.25 mg/kg, which could be reduced after 24 hours if there is a reduced need for analgesia according to the investigator's judgment, as follows:

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

The allocation to IMP was stratified by age groups (birth to less than 30 days, 30 days to less than 6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <17 years, and 17 years to <18 years) and by use of morphine or hydromorphone as supplemental opioid analgesia.

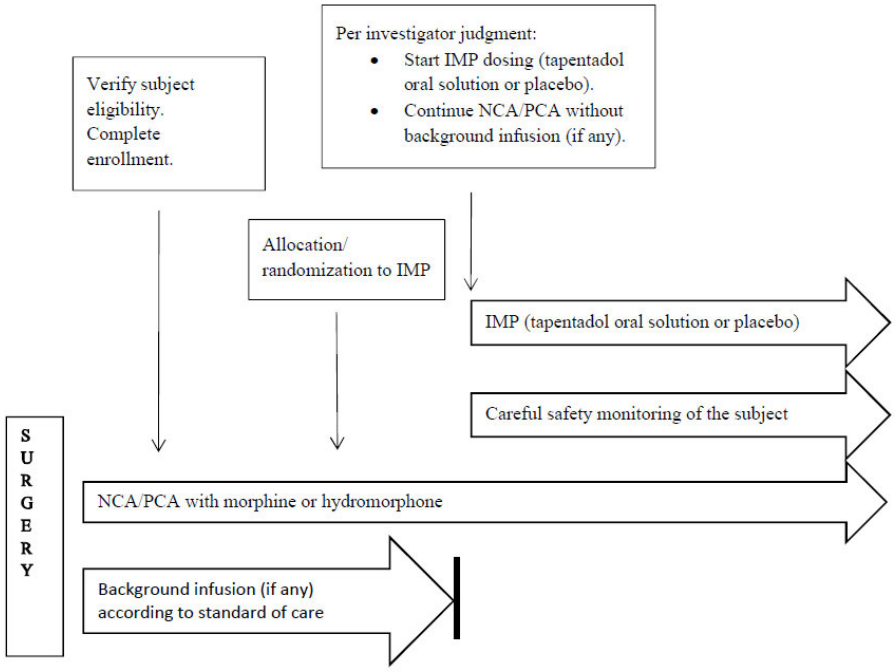
After the first dose of IMP, NCA/PCA was continued with the same opioid as used previously (i.e., morphine or hydromorphone, defined as supplemental opioid analgesia), according to investigator judgment and standard of care. At the time of the first investigational medicinal product (IMP) administration, the background opioid infusion (if any) was discontinued.

Dosing with IMP was stopped if:

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

The study flow chart displays in the following figure.

Figure 1: Study KF5503/65 Flow Chart



NCA = Nurse controlled analgesia; PCA = Patient controlled analgesia; IMP = investigational medicinal product.
Source: Figure 1 of the KF5503/65 Clinical Study Report (CSR).

The key inclusion criteria were:

1) Informed consent, and if applicable assent, given according to local regulations
2) Male or female subject aged from birth (>37 weeks gestational age) to less than 18 years
3) Subject has undergone surgery (other than brain surgery or gastrointestinal surgery expected to affect the absorption of Tapentadol [in the investigator's judgment]) that, in the investigator's opinion, would reliably produce moderate to severe pain requiring opioid treatment for at least 24 hours after first dose of IMP. Subjects must remain hospitalized until the End of Treatment Visit
4) Subject has received post-operative morphine or hydromorphone by NCA/PCA, with or without a background infusion of the same opioid, according to standard of care prior to allocation/randomization to IMP and subject is expected to require this morphine or hydromorphone by NCA/PCA after starting IMP.
5) Subject is able to tolerate liquids at the time of allocation/randomization to IMP.

The primary endpoint was the total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 12 hours after first IMP intake.

The secondary efficacy endpoints were:

- The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within the first 24 hours after first IMP intake (this was the primary efficacy endpoint for the EU PDCO).

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

3.2.2 Statistical Methodologies

It is noted that FDA required the study population included all subjects aged from birth (>37 weeks gestational age) to less than 18 years, while EU requirement was different that included subjects (as defined in the protocol) from 2 years to <18 years. During the study design discussion process, it was agreed with the Division that the applicant reported all analyses using the EU PDCO populations complemented by the respective population of subjects <2. Therefore, the following applicant-defined analysis sets had four different categories defined as follows:

- Enrolled Set: The Enrolled Set (denoted by Enrolled-All) includes all enrolled subjects (as defined in the protocol) of the trial; Enrolled-EU included all enrolled subjects (as defined in the protocol) from 2 years to <18 years of age; while Enrolled-US included all enrolled subjects (as defined in the protocol) from birth to <17 years of age; in addition, Enrolled-US <2, which denotes those subjects <2 years old and is identical to Enrolled-All <2.
- Allocated Set: The overall Allocated Set includes all enrolled subjects that are allocated (randomized) to IMP. This set is denoted by Allocated-All. Similar as for the enrolled set, there were Allocated-EU (subjects from 2 years to <18 years of age), Allocated-US (subjects from birth to <17 years of age), and Allocated-US<2 (those subjects <2 years old and is identical to the Allocated-All <2).
- Safety Set: The overall SAF includes all treated subjects of the trial. This set is denoted by SAF-All. Similar as for the enrolled set, there were SAF-EU, SAF-US (subjects from birth to <17 years of age), and SAF-US<2 (those subjects <2 years old and is identical to the SAF-All <2).
- Full Analysis Set (FAS): The overall FAS includes all subjects that are allocated and treated. This set is denoted by FAS-All. Similar as for the enrolled set, there were FAS-EU, FAS-US (subjects from birth to <17 years of age), and FAS-US<2 (those subjects <2 years old and is identical to the FAS-All <2).
- Per Protocol Set: 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 led to the exclusion of a subject from the PPS(s) were decided

during blinded data review meetings held before locking and unblinding the data for the EU PDCO set and before database lock and unblinding for subjects aged <2 years.

The primary analysis set was the FAS-EU set, which included all allocated (randomized) and treated subjects aged 2 years to <18 years old.

The primary efficacy endpoint for the US FDA/ EU PDCO was the amount of supplemental opioid analgesic medication used within the first 12 hours/24 hours after first IMP intake. Supplemental opioid analgesia was expressed in mg/kg of morphine-equivalents. Hydromorphone doses were multiplied by 5 to obtain the morphine equivalent. Supplemental opioid analgesic medications included in the analysis were opioids given via NCA/PCA, clinician bolus, and other intravenously administered opioids.

The primary null hypothesis was tested using an ANOVA which included treatment, baseline age group (2 to < 6 years, 6 to < 12 years, and 12 to <18 years), and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Treatment effects were estimated based on least squares means of the difference. The 95% confidence interval and p-value were presented for the difference in least squares means.

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 12/24 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

As part of the sensitivity analyses, two 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), were 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 used 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.
2. Treatment mean imputation rule: The treatment mean imputation rule used 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.

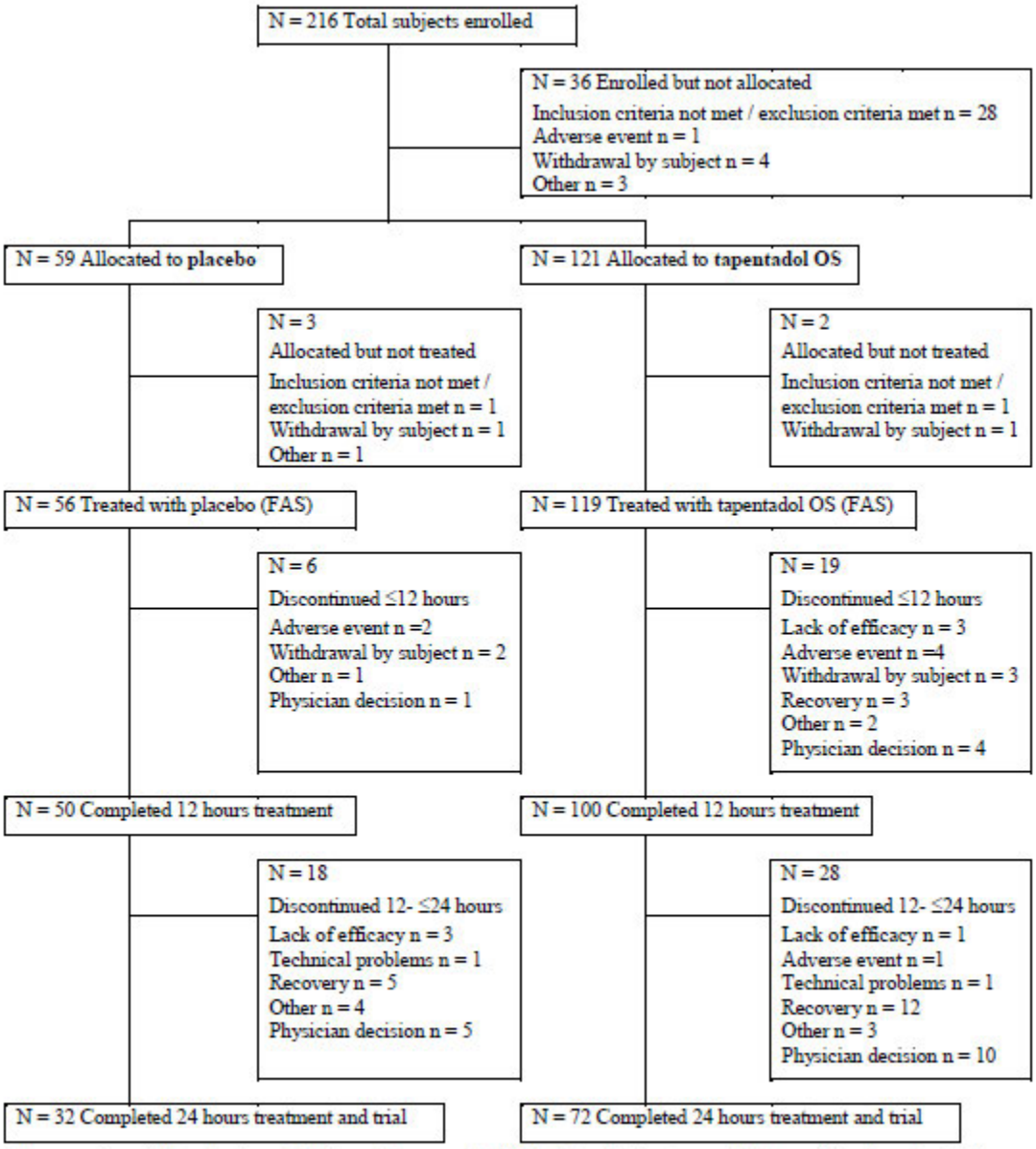
Other than the two primary endpoints (use of supplemental opioid over 24 hours [EU PDCO primary endpoint] / 12 hours [US FDA primary endpoint]), all non-descriptive analyses of secondary endpoints were conducted at a significance level of $\alpha = 0.05$ and the applicant regarded them as exploratory. Therefore, no adjustment for multiplicity for any of the analyses of the secondary endpoints was made.

The sample size calculation was based on results from previously conducted trials in post-surgical pediatric subjects where supplemental opioid was measured. The assumption for the between-treatment difference was 0.20 mg/kg in 24 hours (0.10 mg/kg in 12 hours) and the standard deviation (SD) was 0.42 mg/kg in 24 hours (0.21 mg/kg in 12 hours). Assuming $\alpha = 0.05$ (two-sided), 80% power ($\beta = 0.2$), and a randomization ratio of 2:1 (Tapentadol to placebo) resulted in a sample size of 106 Tapentadol-treated subjects and 53 placebo-treated subjects, i.e., 159 subjects in the EU PDCO Set and 159 subjects in the US FDA Set. Due to the overlapping age groups as per regulatory requirements, it was expected that approximately 168 subjects would be treated with IMP overall.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 216 subjects were enrolled, 180 (83.3%) of these subjects were allocated to IMP and 175 (81.0%) subjects received IMP (56 subjects on placebo and 119 subjects on Tapentadol OS) (Figure 2). The subject disposition by age group in the safety set is summarized in Table 3: Subject disposition by age group – Safety SetTable 3.

Figure 2: Subjects Disposition



Recovery is opioid analgesic medication no longer needed. Physician decision is a switch to exclusively oral opioid analgesic medication indicated according to the local standard of care.

N = number of subjects; OS = oral solution.

Source: Tables 15.1.1.1.1, 15.1.1.2.2, 15.1.1.1.5, 15.1.1.3.1 of Study KF5503/65 CSR.

Table 3: Subject disposition by age group – Safety Set

	Placebo n (%)	Tapentadol OS n (%)	Overall n (%)
Safety Set (from birth to < 18 years)	56	119	175
Safety Set US analysis (from birth to <2 years)	4	11	15
From birth to <30 days	1	2	3

From 30 days to <6 months	1	2	3
From 6 months to <2 years	2	7	9
Safety Set EU analysis (from 2 years to <18 years)	52	108	160
From 2 years to <6 years	12	23	35
From 6 years to <12 years	15	32	47
From 12 years to <17 years	22	45	67
From 17 years to <18 years	3	8	11

Source: Table 3 of Study KF5503/65 CSR.

In this study, the FAS set was the same as the safety set, which means that all randomized and treated subjects were included in the FAS set.

Of the 175 subjects receiving IMP, 150 subjects (50 [89.3%] subjects on placebo and 100 [84%] subjects on Tapentadol OS) completed 12 hours of treatment with IMP; and 148 of these subjects (49 [87.5%] subjects on placebo and 99 [83.2%] subjects on Tapentadol OS) attended the follow up visit thereby completing the trial.

Overall, 32 of 56 subjects (57.1%) on placebo and 72 of 119 subjects (60.5%) on Tapentadol OS completed 24 hours of treatment with IMP (i.e., 24 hours treatment period completers). All of these subjects attended the follow up visit and completed the trial (Table 4). As per protocol, subjects could stop treatment due to recovery (opioid analgesic medication no longer needed) or physician decision (switch to exclusively oral opioid analgesic medication) even if they had not yet completed 24 hours:

- Among the 24 (42.9%) placebo subjects who discontinued before 24 hours (hence didn't complete the trial), 5 (8.9%) discontinued due to recovery (opioid analgesic medication no longer needed) and 6 (10.7%) discontinued due to physician decision (switch to exclusively oral opioid analgesic medication); 3 (5.4%) subjects discontinued due to lack of efficacy and 2 (3.6%) discontinued due to adverse events.
- Among the 47 (39.5%) Tapentadol OS subjects who discontinued before 24 hours (hence didn't complete the trial), 15 (12.5%) discontinued due to recovery (opioid analgesic medication no longer needed) and 14 (11.8%) discontinued due to physician decision (switch to exclusively oral opioid analgesic medication); 4 (3.4%) subjects discontinued due to lack of efficacy and 5 (4.2%) discontinued due to adverse events.

Table 4: Subject Disposition (FAS-ALL Subjects)

	Placebo n (%)	**Tapentadol OS n (%)**	**Overall n (%)**
FAS-All	56 (100)	119 (100)	175 (100)
12 hours treatment period completers [a]	50 (89.3)	100 (84)	150 (85.7)
Treatment discontinuation before 12 hours	6 (10.7)	19 (16.0)	25 (14.3)
Reason for treatment discontinuation			
Lack of efficacy	0	3 (2.5)	3 (1.7)
Adverse Event	2 (3.6)	4 (3.4)	6 (3.4)
Withdrawal by Subject	2 (3.6)	3 (2.5)	5 (2.9)
Recovery	0	3 (2.5)	3 (1.7)
Other	1 (1.8)	2 (1.7)	3 (1.7)
Physician Decision [c]	1 (1.8)	4 (3.4)	5 (2.9)

24 hours treatment period completers [a]	32 (57.1)	72 (60.5)	104 (59.4)
Treatment discontinuation before 24 hours	24 (42.9)	47 (39.5)	71 (40.6)
After 12 hours but before or at 24 hours after first IMP	18 (32.1)	28 (23.5)	46 (26.3)
Reason for treatment discontinuation			
Lack of efficacy	3 (5.4)	1 (0.8)	4 (2.3)
Adverse Event	0	1 (0.8)	1 (0.6)
Technical Problems	1 (1.8)	1 (0.8)	2 (1.1)
Recovery	5 (8.9)	12 (10.1)	17 (6.3)
Other	4 (7.1)	3 (2.5)	7 (0.4)
Physician Decision [c]	5 (8.9)	10 (8.4)	15 (8.6)
12 hours trial completers [a]	49 (87.5)	99 (83.2)	148 (84.6)
12 hours trial non-completers [b]	7 (12.5)	20 (16.8)	27 (15.4)
24 hours trial completers [a]	32 (57.1)	72 (60.5)	104 (59.4)
24 hours trial non-completers [b]	24 (42.9)	47 (39.5)	71 (40.6)

a) 12/24 hours treatment period completers are subjects with a decision to discontinue treatment later than 12/24 hours after first IMP intake, respectively. 12/24 hours trial completers are 12/24 hours treatment period completers that completed the Follow-up Visit, respectively.
b) Treatment discontinued before 12 (or 24) hours or follow-up visit not performed.
c) Physician decision is a switch to exclusively oral opioid analgesic medication indicated according to the local standard of care.
Source: Table 5 of Study KF5503/65 CSR.

Demographic and baseline characteristics were generally balanced between treatment groups in this study (Table 5 and Table 6).

Table 5: Demographic and Baseline Characteristics (FAS-EU)

	Placebo N=52 n (%)	**Tapentadol OS N=108 n (%)**	**Overall N=160 n (%)**
Gender			
Male	29 (55.8)	55 (50.9)	84 (52.5)
Female	23 (44.2)	53 (49.1)	76 (47.5)
Ethnicity			
Hispanic or Latino	9 (17.3)	21 (19.4)	30 (18.8)
Not Hispanic or Latino	38 (73.1)	80 (74.1)	118 (73.8)
Not Reported	5 (9.6)	7 (6.5)	12 (7.5)
Race			
American Indian or Alaska Native	0	0	0
Asian	2 (3.8)	3 (2.8)	5 (3.1)
Black or African American	7 (13.5)	7 (6.5)	14 (8.8)
White	40 (76.9)	91 (84.3)	131 (81.9)
Mixed Race	0	2 (1.9)	2 (1.3)
Not Reported	3 (5.8)	5 (4.6)	8 (5.0)
Age Group (eCRF)			
2 years to < 6 years	12 (23.1)	23 (21.3)	35 (21.9)
6 years to < 12 years	15 (28.8)	32 (29.6)	47 (29.4)
12 years to < 18 years	25 (48.1)	53 (49.1)	78 (48.8)
Height (m)			

Mean (SD)	143.3 (29.5)	145.0 (27.7)	144.4 (28.2)
Median (Q1, Q3)	45.10 (127.0, 163.0)	152.5 (124.0, 165.5)	152.5 (124.5,165.0)
Min – Max	72 – 193	87 - 185	72 - 193
Weight (kg)			
Mean (SD)	42.22 (19.88)	43.09 (21.72)	42.80 (21.08)
Median (Q1, Q3)	45.10 (24.35,56.60)	43.90 (23.40,58.55)	45.00 (23.75,57.30)
Min – Max	10.7 - 89.1	11.0 - 98.2	10.7 - 98.2
BMI (kg/m^2)			
Mean (SD)	19.12 (3.84)	18.83 (4.13)	18.92 (4.03)
Median (Q1, Q3)	18.70 (15.90,21.15)	18.15 (15.70,21.75)	18.35 (15.85,21.45)
Min – Max	13.9 - 31.4	9.5 - 29.7	9.5 - 31.4
Amount of morphine or hydromorphone taken prior to IMP [mg/kg] [a]			
Mean (SD)	0.45 (0.71)	0.59 (0.12)	0.55 (1.07)
Median	0.20	0.21	0.21
Min – Max	0.0 - 3.7	0.0 - 8.8	0.0 - 8.8
Duration of Surgery			
Mean (SD)	203.94 (155.79)	186.03 (110.51)	191.85 (126.79)
Median	147.50	170.50	169.00
Min – Max	30.0 - 947.0	26.0 - 494.0	26.0 - 947.0
Time between end of surgery and intake of first IMP [minutes]			
Mean (SD)	795.92 (552.98)	1018.92 (1483.84)	946.45 (1261.25)
Median	470.10	729.00	567.60
Min – Max	90.0 - 2473.8	90.0 - 10977.0	90.0 - 10977.0

SD = Standard Deviation; N = number of subjects; BMI = Body Mass Index; eCRF = electronic case report form; OS = oral solution.
Source: Tables 11 and 13 of Study KF5503/65 CSR.

Table 6: Demographic and Baseline Characteristics (FAS-US <2 years)

	Placebo N=4 n (%)	**Tapentadol OS N=11 n (%)**	**Overall N=15 n (%)**
Gender			
Male	2 (50.0)	6 (54.5)	8 (53.3)
Female	2 (50.0)	5 (45.5)	7 (46.7)
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3 (75.0)	10 (90.9)	13 (86.7)
Not Reported	1 (25.0)	1 (9.1)	2 (13.3)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	1 (9.1)	1 (6.7)
Black or African American	0	0	0

White	4 (100)	10 (90.9)	14 (93.3)
Age Group (eCRF)			
Birth to < 30 days	1 (25.0)	2 (18.2)	3 (20.0)
30 days to <6 months	1 (25.0)	2 (18.2)	3 (20.0)
6 months to <2 years	2 (50.0)	7 (63.6)	9 (60.0)
Amount of morphine or hydromorphone taken prior to IMP [mg/kg] [a]			
Mean (SD)	0.3	0.26 (0.26)	0.28 (0.22)
Median	0.3	0.20	0.24
Min – Max	0.2 - 0.4	0.0 – 0.8	0.0 – 0.8
Duration of Surgery			
Mean (SD)	139.3	93.7 (39.1)	105.9 (40.5)
Median	136.0	105.0	110.0
Min – Max	115 - 170	30 - 151	30 - 170
Time between end of surgery and intake of first IMP [minutes]			
Mean (SD)	2296.5	956.95 (733.70)	1314.16 (1061.52)
Median	2365.5	511.80	1234.20
Min – Max	1020.0 - 3435.0	259.8 - 2059.8	259.8 - 3435.0

SD = Standard Deviation; N = number of subjects; BMI = Body Mass Index; eCRF = electronic case report form; OS = oral solution.
Source: Table 12 of Study KF5503/65 CSR.

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint

Table 7 presents the efficacy results for the primary endpoint in the FAS-EU Population. Statistically significantly more supplemental opioid analgesic medication was used by subjects in the placebo group than in the Tapentadol OS group during the first 12 hours after the first administration of IMP (p = 0.0404). The estimated [least square] mean (SE) difference between Tapentadol and placebo was -0.05 (0.02) mg/kg bodyweight of morphine equivalents with a 95% CI of [-0.09, -0.00].

For the EU requested primary endpoint of supplemental opioid analgesic medication used during the first 24 hours, Tapentadol OS group (observed mean (SD) of 0.16 (0.20) mg/kg) also demonstrated statistical significance compared with placebo (observed mean (SD) of 0.25 (0.35) mg/kg) (p = 0.0154). The estimated [least square] mean (SE) difference between Tapentadol and placebo -0.10 (0.04) mg/kg bodyweight of morphine equivalents with a 95% CI of [-0.18, -0.02].

Table 7: Amount of supplemental opioid analgesic medication used (mg/kg) within 12 hours and within 24 hours after first IMP intake (FAS-EU)

	Placebo N=52	Tapentadol OS N=108
12 Hours		
Mean (SD)	0.14 (0.19)	0.09 (0.11)
Median	0.08	0.05
Min – Max	0.0 – 0.9	0.0 – 0.5
LS Mean (SE)	0.13 (0.02)	0.08 (0.01)
LS Mean Difference Tapentadol-placebo (95% CI)		-0.05 (-0.09, -0.00)
p-value		0.0404
24 Hours		
Mean (SD)	0.25 (0.35)	0.16 (0.20)
Median	0.13	0.07
Min – Max	0.0 - 1.7	0.0 - 0.9
LS Mean (SE)	0.24 (0.03)	0.14 (0.03)
LS Mean Difference Tapentadol-placebo (95% CI)		-0.10 (-0.18, -0.02)
p-value		0.0154

p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance (ANOVA). The ANOVA model included treatment, baseline age group and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Supplemental opioid analgesia was expressed in mg/kg of morphine IV-equivalents.
N = number of subjects in analysis set; n = number of subjects; SD = standard deviation; SE = standard errors; LSmean = least square mean; CI = confidence interval; ANOVA = analysis of variance; IV = intravenous; OS = oral solution.
Source: Tables 27 and 28 of Study KF5503/65 CSR.

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Error! Reference source not found. Sensitivity analyses results using the per protocol analysis set, the placebo mean imputation and treatment mean imputation to impute values for the FAS-EU analysis set were presented in Table 8. The results are consistent with the primary analysis results.

Table 8: Sensitivity Analyses of the Amount of supplemental opioid analgesic medication used within 12 hours and within 24 hours after first IMP intake (FAS-EU)

		Placebo	Tapentadol OS
12 Hours			
Per Protocol Set	**N**	46	94
	LS Mean (SE)	0.13 (0.02)	0.08 (0.02)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.05 (-0.09, -0.00)
	p-value		0.0492
Placebo Mean Imputation	**N**	52	108
	LS Mean (SE)	0.12 (0.02)	0.08 (0.01)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.04 (-0.08, 0.00)
	p-value		0.0613
Treatment Mean Imputation	**N**	52	108
	LS Mean (SE)	0.12 (0.02)	0.08 (0.01)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.04 (-0.08, -0.00)
	p-value		0.0424

24 Hours			
Per Protocol Set	**N**	46	94
	LS Mean (SE)	0.25 (0.33)	0.16 (0.20)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.10 (-0.18, -0.01)
	p-value		0.0209
Placebo Mean Imputation	**N**	52	108
	LS Mean (SE)	0.21 (0.03)	0.14 (0.02)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.08 (-0.15, -0.01)
	p-value		0.0253
Treatment Mean Imputation	**N**	52	108
	LS Mean (SE)	0.21 (0.03)	0.12 (0.02)
	LS Mean Difference Tapentadol-placebo (95% CI)		-0.09 (-0.16, -0.02)
	p-value		0.0108

p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance (ANOVA). The ANOVA model included treatment, baseline age group and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Supplemental opioid analgesia was expressed in mg/kg of morphine IV-equivalents.
N = number of subjects in analysis set; n = number of subjects; SD = standard deviation; SE = standard errors; LSmean = least square mean; CI = confidence interval; ANOVA = analysis of variance; IV = intravenous; OS = oral solution.
Source: Tables 29, 15.2.2.1.1, and 15.2.2.1.2 of Study KF5503/65 CSR and Statistical Reviewer's Analyses.

The following table is the statistical reviewer's summary of treatment discontinuation. For subjects discontinued study treatment before 12 hours:

- Among the six (6) placebo subjects who discontinued, one (1) discontinued due to physician decision (switch to exclusively oral opioid analgesic medication); the other 5 (9.6%) discontinued due to adverse events (2), withdrawal by subject (2), or other (1), hence their opioid use data in the primary analysis were imputed.
- Among the 18 Tapentadol OS subjects, 7 discontinued due to recovery (3, opioid analgesic medication no longer needed) and physician decision (4, switch to exclusively oral opioid analgesic medication); 12 (11.1%) subjects discontinued due to lack of efficacy (3), adverse event (4), withdrawal by subject (3), or other (2), hence their opioid use data in the primary analysis were imputed.

For subjects discontinued study treatment between 12 hours and 24 hours:

- Among the 18 placebo subjects who discontinued, 10 discontinued due to recovery (5, opioid analgesic medication no longer needed) and physician decision (5, switch to exclusively oral opioid analgesic medication); the other 8 (15.4%) discontinued due to lack of efficacy (3), technical problem (1), or other (4), hence their opioid use data in the EU-designated primary analysis were imputed. Along with the 5 subjects discontinued before 12 hours, a total of 13 (25%) placebo-treated subjects had opioid use data imputed in the EU-designated primary analysis.
- Among the 28 Tapentadol OS subjects, 22 discontinued due to recovery (12, opioid analgesic medication no longer needed) and physician decision (10, switch to exclusively oral opioid analgesic medication); 6 (5.6%) subjects discontinued due to lack of efficacy (1), adverse event (1), technical problem (1), or other (3), hence their opioid use data in the EU-designated primary analysis were imputed. Along with the 12 subjects discontinued

before 12 hours, a total of 18 (16.7%) Tapentadol OS-treated subjects had opioid use data imputed in the EU-designated primary analysis.

Table 9: Subject Disposition (FAS-EU Subjects)

	Placebo n (%)	Tapentadol OS n (%)	Overall n (%)
FAS-EU	52 (100)	108 (100)	160 (100)
12 hours treatment period completers [a]	46 (89.3)	90 (84)	150 (85.7)
Treatment discontinuation before 12 hours	6 (10.7)	18 (16.0)	24
Reason for treatment discontinuation			
Lack of efficacy	0	3	3
Adverse Event	2	4	6
Withdrawal by Subject	2	3	5
Recovery	0	2	3
Other	1	2	2
Physician Decision	1	4	5
24 hours treatment period completers [a]	32 (57.1)	72 (60.5)	104 (59.4)
Treatment discontinuation before 24 hours	24 (42.9)	47 (39.5)	71 (40.6)
After 12 hours but before or at 24 hours after first IMP	18 (32.1)	28 (23.5)	46 (26.3)
Reason for treatment discontinuation			
Lack of efficacy	3 (5.4)	1 (0.8)	4 (2.3)
Adverse Event	0	1 (0.8)	1 (0.6)
Technical Problems	1 (1.8)	1 (0.8)	2 (1.1)
Recovery	5 (8.9)	12 (10.1)	17 (6.3)
Other	4 (7.1)	3 (2.5)	7 (0.4)
Physician Decision	5 (8.9)	10 (8.4)	15 (8.6)

Source: Statistical Reviewer's Analyses.

The statistical reviewer summarized the descriptive statistics of different imputation approaches for these subjects who discontinued study treatments before 12 or 24 hours.

Table 10: Descriptive statistics of different imputation approaches for these subjects who discontinued study treatments before 12 or 24 hours (FAS-EU)

	Primary Imputation		Placebo Mean Imputation		Treatment Mean Imputation	
	Placebo	**Tapentadol OS**	**Placebo**	**Tapentadol OS**	**Placebo**	**Tapentadol OS**
12 Hours	**N=5**	**N=12**	**N=5**	**N=12**	**N=5**	**N=12**
Mean (SD)	0.24 (0.26)	0.15 (0.16)	0.16 (0.11)	0.14 (0.09)	0.16 (0.11)	0.11 (0.09)
Median	0.18	0.12	0.14	0.13	0.14	0.09
Min – Max	0 – 0.65	0 – 0.47	0.07 – 0.34	0.03 – 0.31	0.07 – 0.34	0.02 – 0.30
24 Hours	**N=13**	**N=18**	**N=13**	**N=18**	**N=13**	**N=18**
Mean (SD)	0.38 (0.35)	0.25 (0.27)	0.28 (0.15)	0.23 (0.10)	0.28 (0.15)	0.17 (0.10)
Median	0.36	0.17	0.25	0.20	0.25	0.15
Min – Max	0 – 1.29	0 – 0.94	0.03 – 0.61	0.04 – 0.41	0.03 – 0.61	0.02 – 0.39

Source: Statistical Reviewer's Analyses.

These summary statistics indicate that among the three imputation approaches, the placebo mean imputation (used 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) could be viewed as the most conservative approach,

where the observed mean for those who discontinued study treatment and hence had post-discontinuation supplemental opioid analgesia imputed were similar. As presented in Table 8, the results of the placebo mean imputation are consistent with the primary analysis results. This indicates the robustness of the primary efficacy analysis results.

3.2.4.2 Exploratory Endpoints

The following table summarized the total amount of supplemental opioid analgesic medication received, assessed in 12-hour intervals from 24 hours to 72 hours after the first dose of IMP in subjects from 2 years to <18 years. From 24 hours to 36 hours, the mean (SD) amount of supplemental opioid analgesic medication used in subjects from 2 years to <18 years in the Tapentadol OS group (0.08 [0.09] mg/kg) was numerically better than subjects in the placebo group (0.14 [0.21] mg/kg). For each of the 12-hour periods between 36 hours and 60 hours, there was no difference in use between the placebo group (0.03 [0.07] mg/kg to 0.06 [0.12] mg/kg) and Tapentadol OS group (0.05 [0.10] mg/kg to 0.06 [0.09] mg/kg). From 60 hours to 72 hours, the mean (SD) amount of supplemental opioid analgesic medication used in subjects from 2 years to <18 years in the placebo group (0.03 (0.07)) was numerically better than subjects in the Tapentadol OS group (0.06 (0.08) mg/kg). However, it should be noted that there were too few subjects in both groups after 36 hours for a meaningful conclusion.

Table 11: Summary of amount of supplemental opioid analgesic medication used (mg/kg) after 24 hours after first IMP intake (FAS-EU)

	Placebo N=52	**Tapentadol OS N=108**
24 to 36 Hours		
n	19	38
Mean (SD)	0.14 (0.21)	0.08 (0.09)
Median	0.07	0.05
Min – Max	0.0 – 0.7	0.0 – 0.4
36 to 48 Hours		
n	12	30
Mean (SD)	0.06 (0.12)	0.06 (0.09)
Median	0.00	0.02
Min – Max	0.0 – 0.4	0.0 – 0.4
48 to 60 Hours		
n	8	20
Mean (SD)	0.06 (0.14)	0.05 (0.10)
Median	0.00	0.00
Min – Max	0.0 – 0.4	0.0 – 0.4
60 to 72 Hours		
n	6	10
Mean (SD)	0.03 (0.07)	0.06 (0.08)
Median	0.00	0.00
Min – Max	0.0 – 0.2	0.0 – 0.2

Source: Table 15.2.4.1.3 of Study KF5503/65 CSR.

The following table presents the summary of the area under the pain curve (AUPC) of changes from baseline in pain intensity over up to 12 hours and up to 24 hours using age-appropriate pain scales (Face, Legs, Activity, Cry, Consolability [FLACC] scale for ages birth to less than 6 years or in older children who are not able to report their pain using the other scales, Faces Pain Scale-Revised [FPS-R] for ages 6 years to <12 years, and Visual analog scale [VAS] for ages 12 years to <18 years). In this analysis, a larger AUPC reflects a higher improvement of pain values.

There was no notable difference between the placebo group and the Tapentadol OS group for the FLACC at up to 12 hours and up to 24 hours. For the FPS-R and the VAS, a numerically larger improvement of AUPC was observed in the Tapentadol OS group compared with the placebo group at both up to 12 hours and up to 24 hours.

Table 12: Area under the pain curve based on the change from baseline up to 12 hours and 24 hours after first IMP intake (FAS-EU)

		Placebo		**Tapentadol OS**	
		AUPC12	**AUPC24**	**AUPC12**	**AUPC24**
FLACC	n	13	13	23	23
	Mean (SD)	17.60 (19.86)	37.25 (42.76)	16.31 (19.80)	34.94 (39.79)
	Median	16.83	29.49	11.75	35.98
	Min – Max	-1.6 – 70.8	-4.8 – 142.8	-19.4 – 54.3	-31.4 – 97.0
FPS-R	n	14	14	31	31
	Mean (SD)	1.51 (23.43)	4.60 (43.37)	12.69 (20.87)	26.20 (41.26)
	Median	0.00	3.73	11.15	24.54
	Min – Max	-36.9 – 47.0	-83.4 – 72.2	-19.3 – 61.8	-39.7 – 114.0
VAS	n	25	25	53	53
	Mean (SD)	64.77 (182.42)	118.84 (381.75)	100.36 (222.39)	217.01 (446.49)
	Median	40.83	62.74	60.29	152.38
	Min – Max	-406.5 – 449.0	-617.1 – 918.9	-365.2 – 819.7	-574.3 – 1601.1

Intermediate missing pain values are not imputed, missing pain scores at End of Treatment Visit will be imputed by the mean of non-missing pain scores on respective pain intensity scale.
AUPC12 = Area under the pain curve based on the change to baseline up to 12 hours after 1st IMP intake.
AUPC24 = Area under the pain curve based on the change to baseline up to 24 hours after 1st IMP intake.
FLACC = Face, Legs, Activity, Cry, Consolability (scale); FAS = Full Analysis Set; FPS-R = Faces Pain Scale–Revised; n = subjects in population reporting on respective pain intensity scale; SD = standard deviation; min = minimum; max = maximum; VAS = visual analog scale.
Source: Table 37 of Study KF5503/65 CSR.

In addition, there were no difference observed between Tapentadol OS and placebo for the percentage of responders (defined as responses of “very much improved” and “much improved”) of clinical global impression of change (CGIC) and the patient global (overall) impression of change (PGIC).

Overall, the exploratory endpoints didn’t reveal any information that contradict the results of the primary analysis.

3.2.4.3 Conclusion

In Study KF5503/65, Tapentadol OS demonstrated statistical superiority to placebo in the amount of supplemental opioid used during the first 12/24 hours after first IMP intake for pediatric subjects between 2 and < 18 years old.

3.3 Evaluation of Safety

Among subjects from 2 years to < 18 years of age, 26 (50%) subjects in placebo group and 62 (57.4%) subjects in Tapentadol OS group experienced at least one treatment emergent adverse events (TEAE) overall during the study; 11 subjects (21.2%) in the placebo group and 29 subjects (26.9%) in the Tapentadol OS group with at least 1 TEAE that was considered to be related to the administration of IMP by the investigator.

For a comprehensive review of safety, please refer to Dr. Lisa Wiltrout's clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race, Region, and Administration Type (NCA or PCA)

The applicant did the subgroup analyses for supplemental opioid analgesic medication used within the first 24 hours, while subgroup analyses based on gender, age, race, region, and administration type (NCA or PCA) within the first 12 hours were performed by the statistical reviewer.

More supplemental opioid analgesic medication was used within the first 12 and the first 24 hours in the older age groups, both in the placebo and Tapentadol OS groups. The difference in supplemental opioid analgesic medication uses between the placebo and Tapentadol OS groups was more pronounced in females than in males. White subjects comprised most of the subjects in the trial, and subgrouping by race resulted in too few subjects in the other groups for a meaningful conclusion. Except for the analyses by age group, and in the African American subgroup, the results of these analyses were consistent with the results of the primary analysis. It should be noted that all these analyses are descriptive in nature given the small number of subjects by subgroup category.

Table 13: Subgroup Analyses of Supplemental Opioid Analgesic Medication Use by Gender, Age, Race, Region, and Administration Method (FAS-EU)

	Placebo		**Tapentadol OS**		**Difference (95% CI)[1]**
	n	**LS Mean[1]**	**n**	**LS Mean[1]**	
12 hours					
Overall	52	0.129	108	0.082	-0.047 (-0.091, -0.002)
Age					
2 to <6 years	12	0.044	23	0.046	0.002 (-0.038, 0.042)
6 to < 12 years	15	0.111	32	0.064	-0.047 (-0.105, 0.012)
12 to <18 years	25	0.212	53	0.142	-0.070 (-0.155, 0.014)
Gender					

Male	29	0.076	55	0.071	-0.004 (-0.041, 0.031)
Female	23	0.193	53	0.087	-0.106 (-0.188, -0.024)
Race					
African American or Black	7	0.216	7	0.267	0.051 (-0.107, -0.209)
Asian	2	0.076	3	0.183	N/A
White	40	0.122	91	0.077	-0.045 (-0.088, -0.001)
Region					
Europe	26	0.096	63	0.056	-0.040 (-0/096, 0.015)
USA	26	0.139	45	0.088	-0.051 (-0.126, 0.024)
NCA or RCA Administration					
NCA	19	0.067	40	0.066	-0.001 (-0.044, 0.042)
RCA	33	0.147	64	0.077	-0.070 (-0.139, -0.002)
24 hours					
Overall	52	0.237	108	0.139	-0.097 (-0.176, -0.019)
Age					
2 to <6 years	12	0.066	23	0.082	0.016 (-0.049, 0.080)
6 to < 12 years	15	0.196	32	0.122	-0.074 (-0.185, 0.037)
12 to <18 years	25	0.406	53	0.239	-0.167 (-0.311, -0.022)
Gender					
Male	29	0.156	55	0.139	-0.018 (-0.088, 0.053)
Female	23	0.403	53	0.201	-0.202 (-0.361, -0.043)
Race					
African American or Black	7	0.269	7	0.275	0.006 (-0.307, 0.319)
Asian	2	0.116	3	0.333	N/A
White	40	0.229	91	0.157	-0.072 (-0.152, 0.007)
Region					
Europe	26	0.195	63	0.107	-0.088 (-0.195, 0.020)
USA	26	0.316	45	0.228	-0.088 (-0.223, 0.047)
NCA or RCA Administration					
NCA	19	0.142	40	0.133	-0.009 (-0.092, 0.074)
RCA	33	0.275	64	0.130	-0.145 (-0.265, -0.026)

[1] The LS Mean and the 95% CI was based on the ANOVA (analysis of variance) model included treatment, and the supplemental opioid analgesic used (morphine versus hydromorphone) as factors. Supplemental opioid analgesia was expressed in mg/kg of morphine IV-equivalents.
Source: Tables 32, 15.2.3.1.4, 15.2.3.1.5, 15.2.3.1.6, and 15.2.3.1.7 of Study KF5503/65 CSR, and statistical reviewer's analyses.

4.2 FAS-US < 2 Years

In the age group of subjects <2 years, low mean amounts of supplemental opioid analgesic medication were used in the first 24 hours when compared to subjects from 6 years to <18 years. However, it should be noted that there were too few subjects in this subgroup for a meaningful conclusion.

Table 14: Amount of supplemental opioid analgesic medication (mg/kg) used within the first 12/24 hours after first IMP intake (FAS-US <2 years)

	12 Hours		24 Hours	
Statistic	**Placebo N = 4**	**Tapentadol OS N = 11**	**Placebo N = 4**	**Tapentadol OS N = 11**
Mean (SD)	0.01 (NA)	0.03 (0.04)	0.016	0.054 (0.090)
Median	0.01	0.00	0.013	0.016

Min-Max	0.0 – 0.0	0.0 – 0.1	0.00 – 0.04	0.00 – 0.30

FAS = Full Analysis Set; NA = not available; n = number of subjects; SD = standard deviation; OS = oral solution.
Source: Tables 15.2.4.2.1 and 15.2.4.2.2 of Study KF5503/65 CSR.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for this NDA submission.

5.2 Collective Evidence

For the primary efficacy endpoint of the amount of supplemental opioid analgesic medication used during the first 12 hours after the first dose of investigational medicinal product (IMP), Tapentadol OS demonstrated statistically superiority to placebo in children and adolescents aged 2 to <18 years old. The estimated mean is 0.13 mg/kg for the placebo group, and 0.08 mg/kg for the Tapentadol OS group; the estimated treatment difference between Tapentadol OS and placbo is -0.05 with a 95% CI of (-0.09, -0.00), the p-value is < 0.0404.

For the secondary efficacy endpoint of the amount of supplemental opioid analgesic medication used during the first 24 hours after the first dose of investigational medicinal product (IMP) (the primary efficacy endpoint required by EU PDCO), Tapentadol OS also demonstrated statistically superiority to placebo in children and adolescents aged 2 to <18 years old. The estimated mean is 0.24 mg/kg for the placebo group, and 0.14 mg/kg for the Tapentadol OS group; the estimated treatment difference between Tapentadol OS and placebo is -0.10 with a 95% CI of (-0.18, -0.02), the p-value is < 0.0154.

Results of sensitivity analyses using different approaches to impute missing values were consistent with the results of the primary analysis.

For the subgroup of subjects between 2 to < 6 years of age (Table 13), it appeared that the amount of supplemental opioid analgesic medication use was similar between Tapentadol OS and placebo during the first 12 hours and the first 24 hours after the first dosing of IMP. From statistical perspective, these subgroup analyses are descriptive and were not planned for making statistical inference of a particular age subgroup. Partially due to this finding, the clinical reviewer had concerns for approving Tapentadol OS in this age subgroup (2 to < 6 years). Therefore, I would like to defer the decision of including this age group to the clinical review team based on their overall clinical evaluation (such as safety, benefit-risk, dose-response, etc.) for children aged 2 to < 6 years.

5.3 Conclusions and Recommendations

In conclusion, the study provided sufficient evidence to support the treatment effect of Tapentadol OS over placebo in the amount of supplemental opioid analgesic medication used during the first

12 and 24 hours after the first dose of IMP for pediatric subjects. Therefore, I recommend the approval of Tapentadol OS for pediatric subjects.

5.4 Labeling Recommendations

In Section 14.3 Pediatric Clinical Study of the label, only p-values were reported in the applicant's proposal. I recommend the details of the treatment effect (such as a table includes the estimated treatment means, the estimated treatment difference along with its 95% CI, and the p-value) be presented in this section.

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/s/

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