CLINICAL PHARMACOLOGY REVIEW

NDA: 203794 NDA: 22304	Submission Date: 10/03/2022 Filing meeting: 11/17/2022 Filing date: 12/2/2022 PDUFA date: 7/3/23 (Clock extension; DARRTS dated 3/29/23)
Submission Type; Code:	[redacted] (b) (4) N 203794 Supplement 10 (oral solution) N 22304 Supplement 24 [oral immediate release (IR) tablets] - Efficacy Supplement to meet a PREA PMR 1973-3 and 355-5: Pharmacokinetic, efficacy, and safety study or studies of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to less than 17 years. [redacted] (b) (4)
Location	Noted that the following studies, with tapentadol concentration data pertinent to clinical pharmacology, were submitted in both supplements, S-10 and S-24. • KF5503/59 (also designated as R331333PAI2005): Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years • KF5503/68 (also designated as R331333PAI2006): Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years • KF5503/72 (also designated as R331333PAI2007): Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years N 203794 Supplement 10 Label: \\CDSESUB1\EVSPROD\NDA203794\0083\m1\US\114-

	labeling Study reports, including the bioanalytical methods: \\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr Population PK reports: For PBPK: \\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poppk\poppk-study-report-1.pdf For Population PK: \\CDSESUB1\EVSPROD\NDA203794\0086\NDA203794\0086\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poppk\poppk-study-report.pdf Bioanalytical method for Study KF5503/59 R331333PAI2005 only: \\CDSESUB1\EVSPROD\NDA203794\0085\NDA203794\0085\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\r331333pai2005 Response to clinical information request (IR) regarding the efficacy of 1.25 mg/kg in pediatrics \\CDSESUB1\EVSPROD\NDA203794\0094 N 22304 Supplement 24 Label: \\CDSESUB1\EVSPROD\NDA022304\0163\m1\us\114-labeling Study reports, including the bioanalytical methods: \\CDSESUB1\EVSPROD\NDA022304\0163\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr See above for the discussion on the population PK and bioanalytical information for KF5503/59 R331333PAI2005.
Brand/Code Name:	Nucynta Oral Solution; Nucynta IR Tablet

Generic Name:	Tapentadol HCl oral solution; Tapentadol HCl IR tablet
Pharmacometrics Primary Reviewer:	Michael Bewernitz, Ph.D.
Pharmacometrics Team Leader:	Atul Bhattaram, Ph.D.
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	DNP
OND Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Sponsor:	Collegium Pharmaceutical, Inc.
Relevant NDA(s)	-
Relevant IND(s):	-
Formulation; Strength(s):	Oral Solution: 20 mg/mL; Tablets: 50 mg, 75 mg, 100 mg
Applicant's Proposed Indication:	NUCYNTA (tapentadol) oral solution NUCYNTA (tapentadol) oral solution is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adults and pediatric patients aged (b) (4) years and older with a body weight of at least 16 kg. --- NUCYNTA (tapentadol) tablets NUCYNTA (tapentadol) tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adults and pediatric patients aged (b) (4) years or older with a body weight of at least 40 kg.
Applicant's Proposed Dosage Regimen:	NUCYNTA (tapentadol) oral solution Solution (Highlights of Applicant's proposed Prescribing Information): • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (b) (4) • For adults, initiate treatment with NUCYNTA oral

	solution with or without food at a dose of 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. • For pediatric patients, aged (b) (4) years and older with a body weight of at least 16 kg, initiate treatment with NUCYNTA oral solution at a dose of 1.25 mg per kg body weight every 4 hours. The maximum daily dose is 7.5 mg per kg body weight (i.e., equivalent to six 1.25 mg/kg doses over a 24-hour period). • NUCYNTA oral solution can be taken with or without food. • Moderate Hepatic Impairment: Initiate treatment with 50 mg no more than once every 8 hours (maximum of three doses in 24 hours). Monitor closely for respiratory and central nervous system depression. • Do not abruptly discontinue NUCYNTA oral solution in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. • Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with NUCYNTA Oral Solution. Consider prescribing naloxone based on the patient's risk factors for overdose. ---------- <u>NUCYNTA (tapentadol) tablets</u> Tablet (Highlights of Applicant's proposed Prescribing Information): • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. • Discuss availability of naloxone with the patient and

	caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with NUCYNTA tablets. Consider prescribing naloxone based on the patient's risk factors for overdose. • For adults, initiate treatment with NUCYNTA tablets at a dose of 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. • For pediatric patients aged (b) (4) years or older with body weight of at least 40 kg, initi e treatment with NUCYNTA tablets (b) (4) [redacted] • Moderate Hepatic Impairment: Initiate treatment with 50 mg no more than once every 8 hours (maximum of three doses in 24 hours). Monitor closely for respiratory and central nervous system depression. • Do not abruptly discontinue NUCYNTA tablets in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide.

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information resubmitted in the current Supplemental applications on 10/03/2022, N 203794 Supplement 10 and N 22304 Supplement 24 for Nucynta Oral Solution and IR Tablets, respectively, to meet:

1) A PREA PMR 1973-3 and 355-5: Pharmacokinetic, efficacy, and safety study or studies of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to less than 17 years; and,

(b) (4)

In addition, the Applicant proposes the following labeling changes based on the data derived from the submitted studies:

1) Section 1. Indications and Usage (to include pediatric patients);
2) Section 2. Dosage and Administration (to include pediatric dosing based on body weight, and pediatric dosing related to impairments);
3) Section 6. Adverse Reactions (to include pediatric clinical trials experience);
4) Section 8. Use in Specific Populations (to update the pediatric use section);
5) Section 12. Clinical Pharmacology [to include/update pharmacokinetic (PK) information derived from the population PK (PPK) assessments]; and,
6) Section 14. Clinical Studies (to describe the results from a pediatric clinical safety and efficacy study).

Noted that the following studies, with tapentadol concentration data pertinent to clinical pharmacology, were submitted in both supplements, S-10 and S-24:

1) KF5503/59 (also designated as R331333PAI2005): Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years;
2) KF5503/68 (also designated as R331333PAI2006): Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years;
3) KF5503/72 (also designated as R331333PAI2007): Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years.

Noted in tapentadol label, its exact mechanism of action is unknown. Tapentadol is a centrally acting synthetic analgesic. Preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Therefore, the efficacy of tapentadol may not be extrapolated from adults to pediatrics based on comparable systemic drug exposure. The Applicant submitted the results from a safety and efficacy multiple dose clinical trial, Study KF5503/65 (also designated as Study R331333PAI3037), in pediatric patients age from birth to 18 years old (a Phase 3, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution) (b) (4)

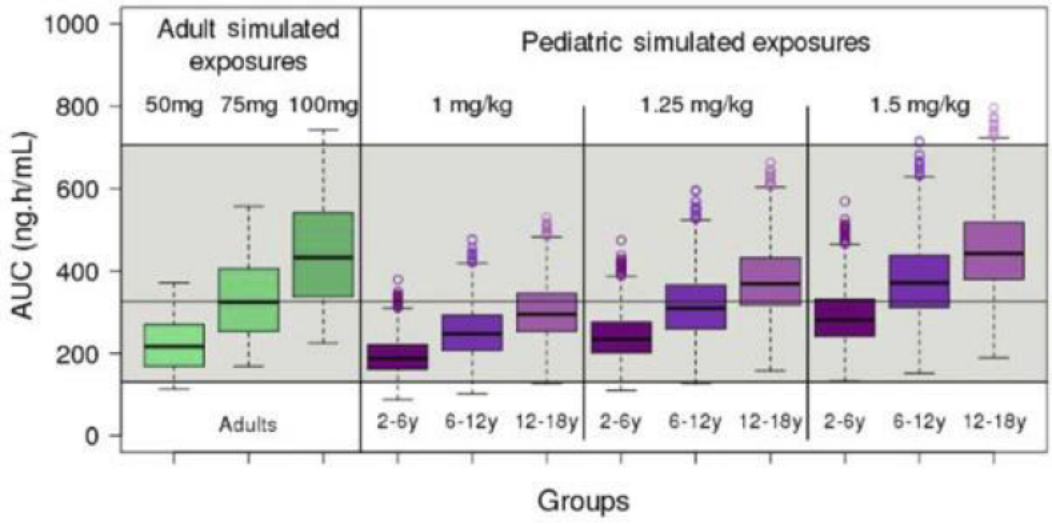
The proposed dosing recommendations (Section 2. Dosage and Administration) and updates to PK information (Section 12. Clinical Pharmacology) were partially based on the results from the PPK assessment. The Applicant selected the pediatric dose tested in study KF5503/65 based on comparable systemic drug exposure between pediatrics and adults, and use the results from this study as pivotal evidence to support the pediatric indication. In this study, patients from 6 months to less than 18 years of age were administered NUCYNTA (tapentadol) oral solution 1.25 mg/kg body weight (maximum single dose 100 mg) or the same volume of placebo every four hours for the first 24 hours with dose reduction to 1.0 mg/kg body weight after 24 hours if there was a reduced need for analgesia at the investigator's discretion.

The integrity of tapentadol concentration data presented in the pediatric PK studies appear to be acceptable, e.g., individual concentration-time values, bioanalytical information, values presented in tables, etc., and, there are no concerns identified.

The Applicant utilized pediatric tapentadol exposure information obtained from tapentadol oral 1.0 mg/kg in modeling and simulation analyses. Pediatric modeling and simulation predicted a

dose of 1.25 mg/kg was found to be similar to adult exposures from tapentadol 50 to 100 mg doses (Figure 1).

Figure 1: Boxplots of the simulated AUCs of tapentadol in adults receiving 50, 75, and 100 mg q4h and pediatric subjects by age group receiving 1.0, 1.25, and 1.5 mg/kg q4h of tapentadol. (Noted this figure is from Figure 4 of Watson, et al., J Pain Res 2019:12;2835-2850)



Boxplot of the simulated area under the curve over tau (dosing interval) at steady-state (AUCss) of tapentadol in adults and pediatric subjects 2 to <18 years of age receiving 1.0 mg/kg, 1.25 mg/kg, and 1.5 mg/kg of tapentadol every 4 hrs. The gray shaded area represents the 2.5th and the 97.5th percentile of the AUCss in adults receiving 50 mg and 100 mg tapentadol every 4 hrs, respectively. The central black line indicates the 50th percentile (median) of the AUC in adults receiving 75 mg tapentadol every 4 hrs

(source: Response to clinical information request (IR) regarding the efficacy of 1.25 mg/kg in pediatrics \\CDSESUB1\EVSPROD\NDA203794\0094)

From the OCP/DNP's perspective, based on the totality of the submitted clinical pharmacology data, the clinical pharmacology information contained in the Supplement applications is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling. Based on the discussion in the wrap-up meeting, (b) (4) the product will be approved in pediatric subjects 6 years and above. Refer to the clinical and statistical review for more discussion on the clinical efficacy trial.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	With respect to clinical pharmacology, the Applicant proposes the following labeling changes based on the data derived from the submitted tapentadol concentrations [Studies KF5503/59 (also designated as R331333PAI2005), KF5503/68 (also designated as R331333PAI2006), and KF5503/72 (also designated as R331333PAI2007)], and PPK assessment:

	1. Section 2. Dosage and Administration (to include pediatric dosing based on body weight, and pediatric dosing related to impairments); 2. Section 8. Use in Specific Populations (to update the pediatric use section); 3. Section 12. Clinical Pharmacology [to include/update PK information derived from the PPK assessments]. Based on the PPK assessment, the systemic exposure of 1.25 mg/kg dose in pediatric subjects ages 2 to less than 18 was found to be similar to adult exposures from tapentadol 50 to 100 mg doses.
General dosing instructions	There are proposed changes to pediatric dosing instructions for both tapentadol oral solution and IR tablets. See below, Section 3. Detailed Labeling Recommendation, for further discussions.
Dosing in patient subgroups (intrinsic and extrinsic factors)	See above.
Labeling	See below, Section 3. Detailed Labeling Recommendation, for further discussions. It is recommended to include half-life and Cmax by age group in the Label alongside the estimates of AUC in Table 2. The final label language will reflect additional discussions that may occur after this review has been archived.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.
Other (specify)	Not applicable.

1.2 Phase IV Commitments – Not applicable

1.3 Summary of Clinical Pharmacology Findings

The current submissions, i.e., Supplements 10 and 24, are a Resubmission of N 203794, Nucynta oral solution, Supplement 10, and, N 22304, Nucynta IR tablet, Supplement 24, after a Refuse-

to-File (RTF) letter was sent to the Applicant (Collegium Pharmaceutical, Inc.) on 02/18/2022 (DARRTS date). The RTF letter contained concerns related to clinical and biometrics.

Regulatory Background: Initial Supplements 10 and 24 submissions (12/20/2021)

Initially the Applicant has submitted, on 12/20/2021, N 203794, Nucynta oral solution, Supplement 10, and N 22304, Nucynta IR tablet, Supplement 24, which included the pediatric final clinical study reports (KF5503/59, KF5503/68 and KF5503/72; tapentadol and tapentadol-O-glucuronide concentration-time data), physiologically based pharmacokinetic (PBPK) and PPK modeling reports, and the proposed labeling changes in pediatric population.

The proposed Labeling language seeks approval of tapentadol in adults and pediatric patients aged (b) (4) years and older with a body weight of at least 16 kg and 40 kg for tapentadol solution and tablets, respectively.

In addition to the forementioned studies above, the Applicant submitted a safety and efficacy multiple dose clinical trial, Study KF5503/65 (also designated as R331333PAI3037), in pediatric patients age from birth to 18 years old (a Phase 3, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution).

The Applicant made reference to (b) (4) New Post marketing Requirements (PMR) 1973-3 and 355-5 issued on 6/23/2015 to NDAs 203794 and 22304, respectively, which the pharmacokinetic, efficacy, and safety of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to less than 17 years were requested.

The same information obtained from the pediatric studies (b) (4) and PPK modeling reports were submitted in both supplements, except for some body weight related dosing specifics under Section 2.5, Dosage and Administration, of the Prescribing Information, due to one formulation being a solution and the other being a tablet.

(b) (4)

The Applicant stated that a modeling and simulation approach was taken to define the pediatric initial doses. Specifically, PPK model was first developed using adult data (adults AUCs that is "generally associated with efficacy and good tolerability, i.e., 50 mg to 100 mg.") Simulations were performed to identify tapentadol doses that would produce exposures in pediatric subjects that were similar to those reported in adults following administration of 50, 75 and 100 mg tapentadol IR tablets.

From the developed PPK model, the doses were predicted for children in the trials KF5503/59 and KF5503/68. Doses of approx. 0.7 mg/kg and 1.4 mg/kg of tapentadol were expected to produce exposures in children similar to those observed in adults. A dose of 1.0 mg/kg, the average of the predicted dose range, was selected for use in the two pediatric trials KF5503/59 (6 to less than 18 years old) and KF5503/68 (2 to less than 18 years old).

As pediatric patients were recruited in the decreasing age strata of the trials, the serum concentration data was used to validate the model, and then to generate a pediatric PPK model. This PPK model was then used to select the doses for the confirmatory efficacy and safety multiple dose trial, KF5503/65 (efficacy and safety from birth to less than 18 years old with multiple oral doses).

Note in tapentadol label, its exact mechanism of action is unknown. Tapentadol is a centrally acting synthetic analgesic. Preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Therefore, the efficacy of tapentadol may not be extrapolated from adults to pediatrics based on comparable systemic drug exposure. The Applicant submitted the results from the safety and efficacy multiple dose clinical trial, Study KF5503/65 (also designated as Study R331333PAI3037), in pediatric patients age from birth to 18 years old (a Phase 3, randomized, multi-site, double-blind, placebo-controlled, parallel group, multiple oral dose trial of tapentadol oral solution) as pivotal evidence to support the pediatric indication of tapentadol.

Current Resubmission (10/03/2022)

It is noted that the clinical pharmacology filed the initial Supplements with comments (PPK comments) to be forwarded to the Applicant in the 74-day letter 02/10/2022 (DARRTS date). The reader is referred to the Clinical Pharmacology Filing Form dated 02/10/2022 (DARRTS date).

After a cursory review of the current Resubmission, it appeared that **no** new clinical pharmacology information was submitted. Therefore, the information submitted in the initial submission (12/20/2021) will be essentially reviewed for this current Resubmission:

1) KF5503/59 (also designated as R331333PAI2005): Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years;

2) KF5503/68 (also designated as R331333PAI2006): Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years;

3) KF5503/72 (also designated as R331333PAI2007): Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years.

Information Request (IR) communicated:

In this Resubmission, after a cursory review of the submissions, the following IRs were sent to the Applicant.

1. Study KF5503/59 bioanalytical information IR on 11/2/2022

"We have requested the following during the initial Supplement submission (submission date 12/20/21): "For Study KF5503/59, submit all pertinent bioanalytical information. Submit the requested information by no later than 2/1/2022." If you have submitted the requested bioanalytical information in the Resubmission, please direct us to the location in the submission. Otherwise, submit the requested information by no later than 11/11/22."

Applicant's response: The Applicant responded and submitted the requested information dated 11/14/22.

Comments: No further commnunication is needed with the Applicant at this juncture.

2. Population Pharmacokinetics information IR on 11/16/2022

"When attempting to open the population PK analysis report file poppk-study-report-2.pdf (submitted to 0083\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\poppk\), we receive the following error message from Adobe Acrobat "There was an error opening this document. The file is damaged and could not be repaired." Re-submit a functioning version of this report by Friday November 18th, 2022."

Applicant's response: The Applicant responded and submitted the poppk-study-report-2.pdf file dated 11/18/2022.

Comments: No further commnunication is needed with the Applicant at this juncture.

3. Population Pharmacokinetics information IR on 5/9/23

"You provide PK simulation results in the document *response-to-fda-information-request-16feb2023.pdf* submitted to sequence 0094 on March 7th 2023. The PK simulations in presented in Figure 1 on page 2 of *response-to-fda-information-request-16feb2023.pdf* appear to differ from the PK simulations presented in Figure 33 on page 83 of *poppk-study-report.pdf* (sequence 0086). For example:

- In Figure 1 of *response-to-fda-information-request-16feb2023.pdf*, the median $AUC_{tau,ss}$ for the 1.25 mg/kg dose in the 6-12 year group is closer to the median $AUC_{tau,ss}$ for 75 mg in adults (rather than the hinges of the adult boxplot).
- In Figure 33 on page 83 of *poppk-study-report.pdf*, the median $AUC_{tau,ss}$ for the 1.25 mg/kg dose in the 6-12 year group is closer to the lower hinge of the $AUC_{tau,ss}$ boxplot for 75 mg in adults (rather than the median or upper hinge of the adult boxplot).
- Similarly, the $AUC_{tau,ss}$ in the 12-18 year group appears to be greater in Figure 1 than in Figure 33 despite a constant dose of 1.25 mg/kg.

It is not clear how to interpret the two PK simulation results which appear to use the same dose (1.25 mg/kg), same age groups (6-12 years and 12-18 years), and same PK metric ($AUC_{tau,ss}$) yet produce noticeably different $AUC_{tau,ss}$ values. We note that the simulations presented in *response-to-fda-information-request-16feb2023.pdf* cite a PK model from Watson et al. 2019 which appears to differ from the PPK model used for simulations in *poppk-study-report.pdf*.

You may consider responding in one of the two following ways:

a) If you intend for only one of these figures to be considered for supporting dose selection in subjects age 6-12 years and 12-18 years (i.e. only Figure 1 in *response-to-fda-information-request-16feb2023.pdf* or only Figure 33 in *poppk-study-report.pdf*), please clarify which figure is the most appropriate.
b) If you believe both Figure 1 and Figure 33 are both worth considering for informing dose selection, then please clarify what factors are contributing to the apparent $AUC_{tau,ss}$ differences between these figures for 1.25 mg/kg in patients age 6-12 years and 12-18 years (i.e. differing aspects of simulation methodology, differing adult population, differing pediatric population(s), differing boxplot generation procedure, etc.) and provide your rationale for why both Figure 1 and Figure 33 should be considered.

Please provide you response, no later than Friday May 12th 2023."

Applicant's response: The Applicant responded dated 5/12/2023.

"The Figure 1 on page 2 of response-to-fda-information-request-16feb2023.pdf is from the Watson et al. 2019 article as noted by the FDA pharmacometrics review team. In the Watson

et al. article the analysis dataset included tapentadol concentrations obtained from 92 pediatric patients receiving a single tapentadol oral solution (OS) dose of 1.0 mg/kg bodyweight in two single-dose PK clinical trials. These two studies are Study KF5503/59 and Study KF5503/68:

1. Study KF5503/59 - Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years.
2. Study KF5503/68 - Open-label Evaluation of the Pharmacokinetic Profile, Safety, and Efficacy of Tapentadol Oral Solution for the Treatment of Post-surgical Pain in Children and Adolescents Aged From 2 Years to Less Than 18 Years.

Population PK analysis as noted in the Watson et al. article was performed using nonlinear mixed effects modeling. Simulations were performed to identify tapentadol OS doses in pediatric subjects (2 to <18 years) that would produce exposures similar to those in adults receiving safe and efficacious doses of tapentadol IR (50–100 mg every 4 h).

The PopPK report submitted with SN0086 to NDA 203794 was created with the aim to characterize the PK profile of tapentadol and its major metabolites, tapentadol-O-glucuronide and tapentadol-O-sulfate, in terms of CL/F and V/F, following a single oral administration of tapentadol solution to children aged from birth to less than 2 years (Study KF5503/72), administered following a surgical procedure that routinely produces moderate to severe acute post- surgical pain requiring opioid treatment. The PK simulation results in the document response-to-fda-information-request-16feb2023.pdf submitted with SN0094 updated the current pediatric PopPK model which includes children aged 2 years to < 18 years old (KF5503/68 & 59) based on Watson et al.

[redacted] (b) (4) the only Figure 1 in response-to-fda-information-request-16feb2023.pdf based on Study 59 and 68 (Watson, et al.) is to be considered for supporting dose selection in subjects aged 6-12 years and 12-18 years."

Comments: No further commnunication is needed with the Applicant at this juncture.

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*Noted:

The following tables provide snapshots of the [redacted] (b) (4), PMRs and the descriptions of the pediatric studies.

Table 1 PWR#3 and PMR timelines

NDA	Issued on 7/10/2019	Issued on 6/23/2015	Studies	Type and population	Submitted in the supplements
203794	PWR	[redacted] (b) (4)			

		1937-3		[redacted] (b) (4)	[redacted] (b) (4) and a request to fulfill PMRs 1937-3 and 355-5.
022304		New Postmarketing Requirement 355-5		Noted: -PREA require efficacy study from birth to 17 years old; -Nucynta efficacy is not extrapolated from adults based on PK.	

Table 2 PMRs

NDA	Issued on 6/23/2015	Previously released on 6/23/2015	Replacement on 6/23/2015
203794	New Postmarketing Requirement 1937-3	1937-1. A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to less than 1 7 years. 1937-2. A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to 5 years.	1937-3. PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to less than 17 years. *Reason: To combine the safety, PK, and efficacy studies of all age cohorts into a single trial*
022304	New Postmarketing Requirement 355-5	355-3. Same as 1937-1 355-4. Same as 1937-2	355-5. Same as 1937-3 *Reason: Same as above*

Table 3 Pediatric studies

NDA	Issued on 7/10/19	Study	Description
203794 and 022304	PWR	[redacted] (b) (4)	

Noted:
1. NDA 22304 for NUCYNTA® (tapentadol) Immediate-Release Tablet approved on 11/20/2008;
2. NDA 203794 for NUCYNTA® (tapentadol) Oral Solution approved on 10/15/2012;
3. NDA 200533 for Nucynta ER® Tablet, approved on 8/25/2011

Clinical pharmacology results

PK/Population PK modeling and simulation exposure information:

Pediatric tapentadol exposure (mean±SD) information following Nucynta oral solution in pediatric studies mentioned above is presented in a tabulated formats in Section 2.3.1. For bioanalytical methodology information from pediatric studies, see Section 2.6.1.

As previously stated, the pediatric tapentadol exposure information was utilized in tapentadol modeling and simulation analyses with tapentadol 1.0 mg/kg in studies KF5503/59 and KF5503/68.

Based on the Applicant's Response (dated 5/12/23) to the Agency's IR (dated 5/9/23), the Applicant stated that the figure presented in the literature by Watson, et al. is "…to be considered for supporting dose selection in subjects aged 6-12 years and 12-18 years." Pediatric PPK model predicted a dose of 1.25 mg/kg in pediatrics ages 2 to less than 18 will have similar exposure to adult exposures from tapentadol 50 to 100 mg doses. See Section 1.1 Recommendations for Figure 1 from Watson et al.

2 QBR

2.1 General Attributes of the Drug

The reader is referred to Nucynta's original Clinical Pharmacology Review, N 22304 (DARRTS dated 9/30/08).

2.2 General Clinical Pharmacology

The reader is referred to Nucynta's original Clinical Pharmacology Review, N 22304 (DARRTS dated 9/30/08).

2.3 Intrinsic Factors

2.3.1 Pediatric tapentadol exposure information following Nucynta oral solution or IR tablets

Study KF5503/59 (R331333PAI2005)

Study KF5503/59 was a multicenter, open-label, single-dose study that evaluated the PK, safety, and tolerability of tapentadol 1 mg/kg in children and adolescents aged 6 years to <18 years with a maximum body weight of 85 kg and body mass index (BMI) <95th percentile.

Each eligible subject who entered the study received a single oral dose of tapentadol 1 mg/kg after a scheduled surgical procedure that routinely produce acute, moderate to severe postsurgical pain.

The study consisted of a screening phase (≤30 days, including the pre- and postoperative evaluations, the surgical procedure and its post-recovery period), a treatment phase (Day 1), and end-of-treatment phase assessments upon completion of the 15-hour postdose evaluation. All subjects underwent 15-hour postdose evaluations with PK blood sampling at predefined timepoints. Safety assessment was based on adverse events (AEs), clinical laboratory tests, vital signs measurements, and physical and electrocardiogram (ECG) findings.

A summary of the concentrations of tapentadol and tapentadol-O-glucuronide in serum are summarized in the table below (Table 1).

Table 1 Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum Following Single-Dose Administration of Tapentadol to Pediatric Subjects

a) Tapentadol Concentrations (ng/ mL)

Interval	N	Mean	Standard Deviation	Minimum	Median	Maximum	CV%
>5 min to <30 min	10	10.9	13.8	0.87	4.04	38.6	126.5
30 min to <45 min	19	39.1	32.4	0.33	34.6	109	82.7
45 min to <1 h	10	59.2	26.7	23.8	53.3	111	45.1
1 h to <1.5 h	16	51.5	26.3	0.23	56.0	96.2	51.1
1.5 h to <2 h	1	66.8	-	66.8	66.8	66.8	-
2 h to <3 h	12	47.1	21.9	4.27	43.6	97.0	46.6
3 h to <4 h	10	34.4	8.46	25.0	31.4	47.8	24.6
4 h to <5 h	17	30.1	13.6	6.52	29.8	67.7	45.3
5 h to <6 h	6	26.5	9.39	16.2	23.6	42.8	35.5
6 h to <8 h	9	18.0	7.88	9.05	14.6	30.9	43.9
8 h to <12 h	22	6.97	3.89	1.75	6.19	14.7	55.9
>12 h	22	4.26	2.95	0.490	3.51	15.0	69.3

b) Tapentadol-O-Glucuronide Concentrations (ng/mL)

Interval	N	Mean	Standard Deviation	Minimum	Median	Maximum	CV%
>5 min to <30 min	8	203	183	15.4	155	512	90.1
30 min to <45 min	18	834	706	30.4	594	2400	84.7
45 min to <1 h	10	1250	460	346	1200	1800	36.8
1 h to <1.5 h	15	1033	441	393	1070	1810	42.7
1.5 h to <2 h	1	1840	-	1840	1840	1840	-
2 h to <3 h	12	1241	489	99.7	1190	1790	39.4
3 h to <4 h	10	1110	359	407	1070	1580	32.3
4 h to <5 h	17	769	287	140	746	1270	37.3
5 h to <6 h	6	714	237	365	771	1040	33.1
6 h to <8 h	9	402	210	170	368	893	52.3
8 h to <12 h	22	167	91.8	55.8	145	390	54.9
>12 h	21	93.7	66.9	43.3	75.9	359	71.4

CV= Co-efficient of variation; N=number of subjects per interval
Note: Intervals in the table represent the time since the dose of tapentadol was administered.
Cross reference: Appendix 17 and Attachment LSIPK01.]
(Source: \\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\r331333pai2005\r331333pai2005-study-report.pdf; p. 33/113)

Study KF5503/68 (R331333PAI2006)

Study KF5503/68 was a non-randomized, single-site, open-label, single-arm, single-dose, oral administration of 1 mg/kg tapentadol oral solution in pediatric male and female subjects aged 2 years to less than 18 years, who had completed either dental surgery or a tonsillectomy and subjects aged 2 years to less than 3 years who had undergone ear, nose, or throat surgery.

A summary of the concentrations of tapentadol and tapentadol-O-glucuronide in serum are summarized in the table below (Tables 2-5).

Table 2 Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 1 (12 years to <18 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)

+15 minutes	n = 19	n = 18
	23.2 (34.0)	404 (581)
+30 minutes	n = 18	n = 17
	45.6 (33.0)	855 (672)
+1 hour	n = 18	n = 17
	49.4 (21.2)	1424 (542)
+2 hours	n = 18	n = 18
	43.1 (14.2)	1202 (366)
+4 hours	n = 17	n = 17
	32.8 (10.8)	824 (191)
+6 hours	n = 18	n = 18
	22.3 (11.9)	497 (138)
+11 hours	n = 18	n = 18
	8.14 (6.35)	150 (69.0)
+15 hours	n = 17	n = 17
	3.66 (3.26)	66.9 (35.4)

SD = standard deviation; n = number of subjects with observed values.
Source: Table 15.2.3.1-1, Table 15.2.3.1-2.

Table 3 Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 2 (6 years to <12 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+15 minutes – 1 hour	n = 22	n = 20
	36.5 (21.8)	676 (343)
+1 hour – 4 hours	n = 22	n = 22
	36.5 (15.7)	900 (330)
+4 hours – 11 hours	n = 22	n = 22
	13.5 (6.52)	321 (123)
+11 hours – 15 hours	n = 22	n = 22
	3.71 (1.96)	86.3 (37.8)

SD = standard deviation; n = number of subjects with observed values.
Source: Table 15.2.3.3-1, Table 15.2.3.3-2.

Table 4 Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 3 (3 years to <6 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+15 minutes – 1 hour	n = 11	n = 10
	30.1 (19.2)	494 (377)
+4 hours – 11 hours	n = 11	n = 11
	26.4 (10.7)	504 (112)

SD = standard deviation; n = number of subjects with observed values.
Source: Table 15.2.3.3-1, Table 15.2.3.3-2.

Table 5 Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 4 (2 years to <3 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+1.25 hours	n = 4	n = 4
	19.9 (13.2)	497 (513)
+3 hours	n = 4	n = 4
	37.7 (18.2)	938 (407)
+5 hours	n = 3	n = 3
	23.4 (6.36)	624 (235)
+8 hours	n = 4	n = 4
	10.0 (4.33)	253 (103)

SD = standard deviation; n = number of subjects with observed values.
Source: Table 15.2.3.4-1, Table 15.2.3.4-2.

(Source: \\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550368\ kf5503_68-study-report.pdf; p. 75-76/1190)

Study KF5503/72 (R331333PAI2007)

Study KF5503/72 was a Phase 2, non-randomized, multiple-site, open-label, single oral dose trial in pediatric subjects aged from birth to less than 2 years after a surgical procedure that routinely produced moderate to severe acute post-surgical pain requiring opioid treatment. The doses were 0.75 mg/kg in subjects aged 6 months to <2 years, 0.60 mg/kg in subjects aged 1 month to <6 months, and 0.50 mg/kg in subjects aged birth to <1 month.

A summary of the concentrations of tapentadol and tapentadol-O-glucuronide in serum are summarized in the table below (Table 6).

Table 6 Serum concentrations of tapentadol, tapentadol-O-glucuronide, and tapentadol sulfate - Pharmacokinetic Set [subgroup 1: 6 months to <2 years; - subgroup 2: 1 month to <6 months; - subgroup 3: 0 months to <1 month]

		Age subgroup 1 N = 7	Age subgroup 2 N = 6	Age subgroup 3 N = 5
Tapentadol	+30 minutes	n = 3 [a]	n = 2	n = 1 [a]
Mean (standard deviation)		9.8 (5.21)	8.3 (6.30)	26.62
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		18.79	35.27	43.63
	+2 hours	n = 2 [c]	n = 3	n = 2

		32.2 (14.92)	27.3 (0.81)	19.9 (7.67)
	+4 hours	n = 3	n = 2 [c]	n = 2
		11.1 (5.97)	25.9 (10.33)	15.0 (8.92)
	+6 hours	n = 1	n = 1	n = 1 [c]
		14.85	32.75	18.82
	+8 hours	n = 2 [c]	n = 2	n = 2
		10.7 (4.15)	5.6 (1.81)	14.6 (6.26)
		[a]	[a]	[a]
Tapentadol-O-glucuronide	+30 minutes	n = 3 [a]	n = 1 [a]	n = 1 [a]
Mean (standard deviation)		105.7 (125.00)	128.8	74.38
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		430.7	136.3	209
	+2 hours	n = 2 [c]	n = 3	n = 2
		468.0 (248.41)	324.9 (116.61)	98.5 (2.62)
	+4 hours	n = 3	n = 2 [c]	n = 2
		348.7 (228.22)	449.7 (7.42)	147.6 (53.74)
	+6 hours	n = 1	n = 1	n = 1 [c]
		370.2	253.3	224.8
	+8 hours	n = 2 [c]	n = 2	n = 2
		285.1 (107.06)	92.2 (63.83)	174.1 (11.03)
		[b]		[a]
Tapentadol-O-sulfate	+30 minutes	n = 2 [b]	n = 2	n = 1 [a]
Mean (standard deviation)		22.1 (20.83)	14.6 (8.98)	72.54
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		33.2	26.1	52.69
	+2 hours	n = 2 [c]	n = 3	n = 2
		50.3 (6.97)	24.9 (6.10)	36.4 (3.92)
	+4 hours	n = 3	n = 2 [c]	n = 2
		10.1 (10.21)	22.6 (4.70)	27.7 (3.52)
	+6 hours	n = 1	n = 1	n = 1 [c]
		15.76	20.78	12.39
	+8 hours	n = 2 [c]	n = 2	n = 2
		8.7 (0.69)	4.0 (3.17)	20.7 (12.64)

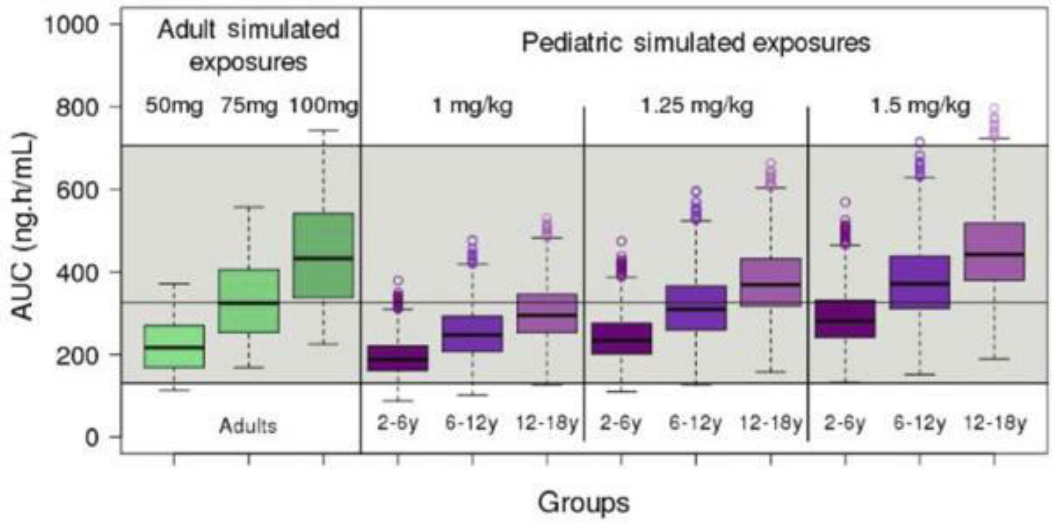
Age subgroups:
- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months
- subgroup 3: 0 months to <1 month

a) One sample was below the limit of quantification.
b) Two samples were below the limit of quantification.
c) 1 sample was taken outside the defined time window.
N = number of subjects; n = number of subjects included in the calculation of descriptive statistics (where n = 1 no descriptive statistics were calculated)
Source: Table 15.2.2.1.1, Table 15.2.2.1.2, Table 15.2.2.1.3, Table 15.2.2.2.1, Table 15.2.2.2.2, Table 15.2.2.2.3, Table 15.2.2.3.1, Table 15.2.2.3.2, Table 15.2.2.3.3
(Source: \\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550372\kf550372-study-report.pdf ; p.60-61/1057)

2.3.2 Pediatric population pharmacokinetic information of Nucynta

The Applicant applied a population pharmacokinetic model to predict steady-state tapentadol plasma exposure in pediatric patients. Figure **2** shows the predicted steady-state AUC tau for 1.00, 1.25, and 1.5 mg/kg every four hours in pediatric patients age 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years as well as in adults for 50, 75, and 100 mg every four hours.

Figure 2: Simulated tapentadol AUCτ,ss in children age birth to < 18 years old and adults following tapentadol administration every 4 hours



Boxplot of the simulated area under the curve over tau (dosing interval) at steady-state (AUCss) of tapentadol in adults and pediatric subjects 2 to <18 years of age receiving 1.0 mg/kg, 1.25 mg/kg, and 1.5 mg/kg of tapentadol every 4 hrs. The gray shaded area represents the 2.5th and the 97.5th percentile of the AUCss in adults receiving 50 mg and 100 mg tapentadol every 4 hrs, respectively. The central black line indicates the 50th percentile (median) of the AUC in adults receiving 75 mg tapentadol every 4 hrs.

Source: sequence 0094, response-to-fda-information-request-16fedb2023.pdf, page 2

The simulations indicate that the 1.25 mg/kg q4h regimen is expected to produce steady-state AUC tau values in subjects 6-12 years and 12 to <18 years consistent with the steady-state AUC tau values in adults receiving 50 mg q4h and 75 mg q4h. From PK perspective, the simulations presented in **Figure 2** support the proposed 1.25 mg/kg q4h regimen for subjects age 6 to 12 years and age 12 to <18 years. Additional details on the simulations can be found in the section of the appendix titled **Pharmacokinetic Simulation (Section 4.3) in this review**. Please refer to the Clinical review for details on the rationale the dose in subjects age 6 to <18 years.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 What active moieties were measured in the plasma in the clinical pharmacology studies and what bioanalytical methods are used to assess concentrations?

Tapentadol and tapentadol glucuronide serum levels were determined using the LC-MS/MS method in accordance with the study protocols and validation reports. There were no issues identified for Studies KF5503/59, KF5503/68 and KF5503/72.

Study KF5503/59

Tapentadol and tapentadol glucuronide serum levels were determined using the LC-MS/MS method, as validated in PBRL-RD-1132/JJP334EL-093343-B/ BA1539. The method for serum, as applied during the study, is described in the Assay Instructions PBRL-BV-1132 "Determination of tapentadol and tapentadol glucuronide in human serum by LC-MS/MS (API 4000) " (Date: 28 June 2011), attached as Addendum 3. Procedural details as applied to this study are recorded in the raw data of JJP560EL-115603-A.

The standard curves for tapentadol and tapentadol glucuronide were 0.200, 0.400, 1.00, 2.00, 4.00, 10.0, 20.0, 40.0, 100 and 200 ng/mL and 10.0, 20.0, 50.0, 100, 200, 500, 1000, 2000, 5000 and 10000 ng/mL, respectively. Tapentadol's inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 0.8 – 2.6 and -7.5 – 6.0, respectively. Tapentadol glucuronide's inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 1.1 – 5.3 and -8.1 – 4.0, respectively. The lower limit
of quantifications for tapentadol and tapentadol glucuronide were 0.2 and 10 ng/mL, respectively.

Quality Control samples for tapentadol (0.6, 10, 160 ng/mL) inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 1.5 – 5.2 and -6.3 – 2, respectively.
Quality Control samples for tapentadol glucuronide (30, 500, 8000 ng/mL) inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 3.3 – 4.3 and -5.6 – 1.8, respectively.

Study KF5503/68

Tapentadol and tapentadol glucuronide serum levels were determined using the LC with tandem mass in accordance with the study plan PK1477A and the validation report PK1352.

The values for the overall accuracy (expressed as percent of nominal value) and the overall precision (expressed as coefficient of variation; CV) for quality control samples assayed during analysis of study samples are shown in Table 7 and Table 8.

[Standard range: 0.20, 0.20, 0.40, 1.00, 2.00, 5.00, 7.50, 15.0, 20.0 and 10.0, 20.0, 50.0, 100, 250, 375, 750, 1000 ng/mL for tapentadol and tapentadol glucuronide, respectively.

QCs: 0.4, 10.0, 20.0 and 20.0, 500, 1000 ng/mL for tapentadol and tapentadol glucuronide, respectively.

Table 7: Study performance of tapentadol

Calibration range	0.200 – 20.0 ng/mL
Lower limit of quantification (LLOQ)	0.200 ng/mL
Coefficient of determination	≥ 0.9986
Mean accuracy [%] at LLOQ (n = 32)	99.9
Mean precision [%] at LLOQ (n = 32)	7.7
Mean accuracy [%] of QC samples (n = 105)	96.3 - 102.2
Mean precision [%] of QC samples (n = 105)	2.9 - 8.3

Table 8: Study performance of tapentadol glucuronide

Calibration range	10.0 – 1000 ng/mL
Lower limit of quantification (LLOQ)	10.0 ng/mL
Coefficient of determination	≥ 0.9981
Mean accuracy [%] at LLOQ (n = 34)	93.7
Mean precision [%] at LLOQ (n = 34)	3.6
Mean accuracy [%] of QC samples (n = 102)	96.0 - 101.3
Mean precision [%] of QC samples (n = 102)	1.9 - 5.0

Study KF5503/72

Tapentadol and tapentadol glucuronide serum levels were determined using the LC-MS/MS method in accordance with the study protocol PK1563A, the standard operating procedure HQ-PK-131-6028 and the validation report PK1562.

The values for the overall accuracy (expressed as percent of nominal value) and the overall precision (expressed as coefficient of variation; CV) for quality control samples assayed during analysis of study samples are shown in Tables 9 - 11.

Standard range: 0.20, 0.20, 0.40, 1.00, 2.00, 5.00, 7.50, 15.0, 20.0 and 10.0, 20.0, 50.0, 100, 250, 375, 750, 1000 ng/mL for tapentadol and tapentadol glucuronide, respectively.

QCs: 0.4, 10.0, 20.0 and 20.0, 500, 1000 ng/mL for tapentadol and tapentadol glucuronide, respectively.

Table 9 Study performance of tapentadol (CG5503 base) in human serum

Calibration range [ng/mL]	0.200 - 20.0
Lower limit of quantification (LLOQ) [ng/mL]	0.200
Coefficient of determination	≥0.9962
Mean accuracy at LLOQ [%]	100.4
Mean precision at LLOQ [%]	8.8
Mean accuracy of QC samples [%]	96.0 - 99.7
Mean precision of QC samples [%]	3.2 - 7.9

Table 10 Study performance of tapentadol glucuronide (GRTE1472) in human serum

Calibration range [ng/mL)	10.0 - 1000
Lower limit of quantification (LLOQ) [ng/mL]	10.0
Coefficient of determination	≥0.9935
Mean accuracy at LLOQ [%]	91.9
Mean precision at LLOQ [%]	6.4
Mean accuracy of QC samples [%]	95.2 - 102.8
Mean precision of QC samples [%]	3.2 - 6.5

Table 11 Study performance of tapentadol sulfate (GRT3793H) in human serum

Calibration range [ng/mL)	1.00 - 100
Lower limit of quantification (LLOQ) [ng/mL)	1.00
Coefficient of determination	≥0.9961
Mean accuracy at LLOQ [%]	94.7
Mean precision at LLOQ [%]	7.3
Mean accuracy of QC samples [%]	96.7 - 100.1
Mean precision of QC samples [%]	4.9 - 8.7

3 Detailed Labeling Recommendations

The following revisions (deleted and revised in red fonts) are recommended from the clinical pharmacology perspective.

N 203794 Supplement 10 (oral solution)

Section	Proposed	Recommended
2.5	(b) (4)	Currently, Labeling negotiations are

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

4 Appendices

4.1 Proposed Package Insert (Original and Annotated)

Use the following link to see the proposed Labels by the Applicant.

N 203794 Supplement 10

Label: \\CDSESUB1\EVSPROD\NDA203794\0083\m1\US\114-labeling

N 22304 Supplement 24

Label: \\CDSESUB1\EVSPROD\NDA022304\0163\m1\us\114-labeling

4.2 Individual Study Review

4.2.1 Study KF5503/59 R331333PAI2005: Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the Treatment of Postsurgical Pain in Children and Adolescents Aged From 6 to Less Than 18 Years

The study synopsis can be found here:

\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\r331333pai2005\r331333pai2005-study-report.pdf

For individual concentration-time values for tapentadol and tapentadol glucuronide according to the ***bioanalytical report***, see pages 43-55/152:

\\CDSESUB1\EVSPROD\NDA203794\0085\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\r331333pai2005\r331333pai2005-method.pdf

Noted that the same study reports were submitted in N 22304.

Reviewer's note: Pertinent additional information from the study report body:

The eligible subjects received a single oral dose of tapentadol OS 1 mg/kg, up to a maximum of 75 mg, followed by 15 hours of PK sampling, and safety and pain intensity assessments on Day 1. Subjects weighing between 75 kg to 85 kg received the maximum dose of 75 mg.

Tapentadol OS Dosing Regimen

A 1-mg/kg tapentadol dose was considered an appropriate dose (with a maximum dose of 75 mg), allowing characterization of the exposure and disposition of the drug without compromising the safety of the pediatric subjects. Subjects weighing between 75 kg to 85 kg received the maximum dose of 75 mg. Selection of the tapentadol dose for pediatric subjects was based largely upon PK considerations: (1) the PK of tapentadol in pediatric subjects and adults would be similar after adjusting for body size, and (2) underlying pain mechanisms and the exposure-effect curve of tapentadol would be similar in adults and children >2 years of age. A nonlinear mixed effects modeling (NONMEM) population PK model and a 2-compartment model described the serum PK of tapentadol after oral administration of IR formulations. Evaluations demonstrated that oral clearance and central volume of distribution of tapentadol increased with an increase in body weight. Simulations showed that 0.7 mg/kg and 1.4 mg/kg doses of tapentadol in children were expected to produce exposures similar to those after administration of 50 mg and 100 mg tapentadol IR in adults. The safety and efficacy of tapentadol in adults have been demonstrated during a completed Phase 3 program in acute pain. Based on efficacy and tolerability data derived in adults, 50 mg to 100 mg of tapentadol (as an IR formulation administered 4 to 6 times daily) has been selected as the therapeutic dose range in adults. The maximum tapentadol dose of 75 mg was intended to reduce the risk of excessive exposure in the pediatric subjects with an accurate estimation of the PK parameters.

Dosage and Administration

After the surgical procedure, the subjects received a dose of tapentadol OS, based on the predetermined dose and concentration of tapentadol OS based on their body weight.

Subjects remained in fasting condition until 2 hours after tapentadol administration and in an upright position from the time of tapentadol administration until 4 hours after tapentadol administration. Drinking of water was allowed ad libitum from 1 hour after dosing onwards, and intake of food was allowed ad libitum from 2 hours after dosing onwards.

Table 2: Dose and Formulation

(Study R331333PAI2005)

Weight	Dose[a]	Tapentadol Oral Solution	Formulation number
<20 kg	1 mg/kg	4 mg/mL	F041
≥20 kg to 75 kg	1 mg/kg	20 mg/mL	F038
>75 kg to 85 kg	75 mg[b]	20 mg/mL	F038

[a] The single dose of tapentadol was not to exceed 75 mg for any subject.
[b] Fixed dose.

Bioanalytical Procedures

Serum samples were analyzed for tapentadol and tapentadol-O-glucuronide concentrations using a validated bioanalytical method at (b) (4) The quantification range was 0.2 ng/mL to 200 ng/mL for tapentadol and 10.0 to 10,000 ng/mL for tapentadol-O-glucuronide.

Table 4: Demographic and Baseline Characteristics

Safety Analysis Set (Study R331333PAI2005)

	Group 1 (12-<18 yrs)	Group 2 (6-<12 yrs)	Overall (6-<18 yrs)
All Safety Subjects	30	14	44
Sex			
N	30	14	44
Male	14 (46.7%)	6 (42.9%)	20 (45.5%)
Female	16 (53.3%)	8 (57.1%)	24 (54.5%)
Race			
N	30	14	44
White	27 (90.0%)	10 (71.4%)	37 (84.1%)
Asian	0	0	0
Black or African American	2 (6.7%)	1 (7.1%)	3 (6.8%)
Native Hawaiian or Other Pacific Islander	1 (3.3%)	0	1 (2.3%)
Other	0	3 (21.4%)	3 (6.8%)
Age (years)			
N	30	14	44
Mean (SD)	14.9 (1.68)	8.7 (1.68)	13.0 (3.37)
Median	14.5	8.5	14.0
Range	(12, 17)	(6, 11)	(6, 17)
Baseline Weight (kg)			
N	30	14	44
Mean (SD)	59.2 (11.89)	33.9 (12.32)	51.1 (16.82)
Median	58.5	29.2	51.5
Range	(36, 85)	(20, 58)	(20, 85)
Baseline Height (cm)			
N	30	14	44
Mean (SD)	166.3 (9.17)	135.3 (11.97)	156.5 (17.69)
Median	166.7	133.1	160.2
Range	(147, 183)	(114, 158)	(114, 183)
Baseline BMI (kg/m^2)			
N	30	14	44
Mean (SD)	21.3 (3.73)	18.0 (3.64)	20.3 (3.99)
Median	20.4	16.3	20.0
Range	(16, 33)	(14, 26)	(14, 33)

BMI: body mass index; N: number of subjects, SD: standard deviation; yrs: years
Attachment TSIDEM01.rtf [JNJ-26120211\PAI2005\DBR_FINAL\RE_CSR\tsidem01.sas] 02DEC2013, 20:36

Table 5: Concentrations of Tapentadol and Tapentadol-O-Glucuronide in Serum Following Single-Dose Administration of Tapentadol to Pediatric Subjects

Study R331333PAI2005

Tapentadol Concentrations (ng/ mL)

Interval	N	Mean	Standard Deviation	Minimum	Median	Maximum	CV%
>5 min to <30 min	10	10.9	13.8	0.87	4.04	38.6	126.5

30 min to <45 min	19	39.1	32.4	0.33	34.6	109	82.7
45 min to <1 h	10	59.2	26.7	23.8	53.3	111	45.1
1 h to <1.5 h	16	51.5	26.3	0.23	56.0	96.2	51.1
1.5 h to <2 h	1	66.8	-	66.8	66.8	66.8	-
2 h to <3 h	12	47.1	21.9	4.27	43.6	97.0	46.6
3 h to <4 h	10	34.4	8.46	25.0	31.4	47.8	24.6
4 h to <5 h	17	30.1	13.6	6.52	29.8	67.7	45.3
5 h to <6 h	6	26.5	9.39	16.2	23.6	42.8	35.5
6 h to <8 h	9	18.0	7.88	9.05	14.6	30.9	43.9
8 h to <12 h	22	6.97	3.89	1.75	6.19	14.7	55.9
>12 h	22	4.26	2.95	0.490	3.51	15.0	69.3

Tapentadol-O-Glucuronide Concentrations (ng/mL)

Interval	N	Mean	Standard Deviation	Minimum	Median	Maximum	CV%
>5 min to <30 min	8	203	183	15.4	155	512	90.1
30 min to <45 min	18	834	706	30.4	594	2400	84.7
45 min to <1 h	10	1250	460	346	1200	1800	36.8
1 h to <1.5 h	15	1033	441	393	1070	1810	42.7
1.5 h to <2 h	1	1840	-	1840	1840	1840	-
2 h to <3 h	12	1241	489	99.7	1190	1790	39.4
3 h to <4 h	10	1110	359	407	1070	1580	32.3
4 h to <5 h	17	769	287	140	746	1270	37.3
5 h to <6 h	6	714	237	365	771	1040	33.1
6 h to <8 h	9	402	210	170	368	893	52.3
8 h to <12 h	22	167	91.8	55.8	145	390	54.9
>12 h	21	93.7	66.9	43.3	75.9	359	71.4

CV= Co-efficient of variation; N=number of subjects per interval
Note: Intervals in the table represent the time since the dose of tapentadol was administered.
Cross reference: Appendix 17 and Attachment LSIPK01.]

BIOANALYTICAL STUDY SUMMARY

Comp. No(s): JNJ-26120211 and JNJ-27646138

Title: LC-MS/MS determination of tapentadol and tapentadol glucuronide in human serum samples originating from clinical trial R331333-PAI2005.

Authors: [redacted] (b) (4)

Test Facility: [redacted] (b) (4)

Sponsor: Janssen Research & Development, a division of Janssen Pharmaceutica N.V., B-2340 Beerse, Belgium

Analytical method

Tapentadol and tapentadol glucuronide serum levels were determined using the LC-MS/MS method, as validated in PBRL-RD-1132/JJP334EL-093343-B/ BA1539. The method for serum, as applied during the study, is described in the Assay Instructions PBRL-BV-1132 " Determination of tapentadol and tapentadol glucuronide in human serum by LC-MS/MS (API 4000) " (Date: 28 June 2011), attached as Addendum 3.

Procedural details as applied to this study are recorded in the raw data of JJP560EL-115603-A.

The standard curves for tapentadol and tapentadol glucuronide were 0.200, 0.400, 1.00, 2.00, 4.00, 10.0, 20.0, 40.0, 100 and 200 ng/mL and 10.0, 20.0, 50.0, 100, 200, 500, 1000, 2000, 5000 and 10000 ng/mL, respectively. Tapentadol's inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 0.8 – 2.6 and -7.5 – 6.0, respectively. Tapentadol glucuronide's inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 1.1 – 5.3 and -8.1 – 4.0, respectively. The lower limit of quantifications for tapentadol and tapentadol glucuronide were 0.2 and 10 ng/mL, respectively.

Quality Control samples for tapentadol (0.6, 10, 160 ng/mL) inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 1.5 – 5.2 and -6.3 – 2, respectively. Quality Control samples for tapentadol glucuronide (30, 500, 8000 ng/mL) inter-run precision (%CV) and % inter-run bias values for the (and) ranged from 3.3 – 4.3 and -5.6 – 1.8, respectively.

4.2.2 Study KF5503/68 R331333PAI2006: Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years

The study synopsis can be found here:

\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550368\kf5503_68-study-report.pdf

For individual concentration-time values for tapentadol and tapentadol glucuronide according to the ***bioanalytical report***, see pages 1104 - 1121/1190:

\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550368\kf5503_68-study-report.pdf

For individual concentration-time profiles, see pages 206 - 309 /1190.

\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550368\kf5503_68-study-report.pdf

Noted that the same study reports were submitted in N 22304.

Reviewer's note: Pertinent additional information from the study report body:

From the Study report body: “Subjects were encouraged to take a small drink (approximately 25 mL) of water after dosing to ensure all medication was cleared and swallowed from the mouth.”

“9.4.4 Selection of doses in the trial

The selection of the tapentadol dose to be evaluated in pediatric subjects was based largely upon pharmacokinetic considerations. The key assumptions were that, in children aged 2 years and older, the underlying pain mechanisms are similar to those in adults, the pharmacokinetics of tapentadol is similar to that in adults after adjusting for the body size (e.g., body weight), and the exposure-effect curves of tapentadol are similar in adults and in children 2 years and older. In addition, tapentadol IR 50 mg to 100 mg administered 4 times to 6 times daily had been shown to be efficacious and safe in adults, and the bioequivalence of the tapentadol oral solution used in this trial and tapentadol IR had been demonstrated.

Nonlinear mixed effects modeling (using NONMEM®) was performed to develop a population pharmacokinetic model using pooled data from 1833 adults enrolled in Phase I, Phase II, and Phase III trials in the tapentadol acute pain program. Simulations were performed to identify tapentadol doses that would produce total exposures (i.e., serum AUC) in pediatric subjects that are similar to those reported in adults. The approved adult therapeutic dose range that is generally associated with efficacy and good tolerability in adults, 50 mg to 100 mg, was used for comparison.

Doses of approximately 0.7 mg/kg and 1.4 mg/kg of tapentadol oral solution in children were expected to produce exposures similar to those following administration of 50 mg and 100 mg, respectively, given as an immediate-release formulation in adults.

Based on the simulation results, the tapentadol dose was set to 1 mg/kg, an average of the predicted dose range (0.7 mg/kg to 1.4 mg/kg). This dose was expected to produce exposures within the range observed following administration of 50 mg to 100 mg of tapentadol in adults and thus expected to be efficacious without compromising the safety of the trial subjects.

The maximum tapentadol dose of 75 mg was intended to reduce the risk of excessive exposure in the pediatric patients to be tested, while enabling an accurate estimation of the pharmacokinetic parameters in this population.”

Note: blood sampling timepoints organized in a table format:

Group	Age	
1	12 years to less than 18 years	15 ±5 min, 30 ±5 min, and 1, 2, 4, 6, 11, and 15 h (±10 min)
2	6 years to less than 12 years	15 min and 1 h, between 1 h and 4 h, between 4 h and 11 h, and between 11 h and 15 h, with at least 1 h between samples
3	3 years to less than 6 years	15 mins and 1 h, and between 4 h and 11 h
4	2 years to less than 3 years	1.25, 3, 5, and 8 h (±10 minutes)

Demographic Data:

Table 9: Descriptive statistics for demographic data - Safety Set

	Group 1 (12-<18 y) N (%)	Group 2 (6-<12 y) N (%)	Group 3 (3-<6 y) N (%)	Group 4 (2-<3 y) N (%)	Group 3+4 (2-<6 y) N (%)	Total N (%)
Total	21 (100)	28 (100)	12 (100)	5 (100)	17 (100)	66 (100)
Sex						
Female	9 (42.9)	17 (60.7)	4 (33.3)	4 (80.0)	8 (47.1)	34 (51.5)
Male	12 (57.1)	11 (39.3)	8 (66.7)	1 (20.0)	9 (52.9)	32 (48.5)
Race						
White	21 (100)	27 (96.4)	10 (83.3)	5 (100)	15 (88.2)	63 (95.5)
Black or African American	0	1 (3.6)	0	0	0	1 (1.5)
Other	0	0	2 (16.7)	0	2 (11.8)	2 (3.0)
Ethnicity						
Hispanic Or Latino	0	2 (7.1)	1 (8.3)	1 (20.0)	2 (11.8)	4 (6.1)
Not Hispanic Or Latino	21 (100)	26 (92.9)	11 (91.7)	4 (80.0)	15 (88.2)	62 (93.9)
Age (years)						
Mean (SD)	15.5 (1.6)	8.3 (1.6)	3.9 (0.8)	2.0 (0.0)	3.4 (1.1)	9.3 (4.9)
Median	16.0	8.0	4.0	2.0	3.0	8.0
Range (Min;Max)	(12;17)	(6;11)	(3;5)	(2;2)	(2;5)	(2;17)
Height (cm)						
Mean (SD)	170.6 (10.7)	132.9 (11.1)	105.6 (5.7)	92.4 (4.7)	101.7 (8.1)	136.9 (28.3)
Median	170.0	134.5	106.0	92.0	102.0	135.5
Range (Min;Max)	(150;196)	(113;152)	(94;115)	(86;99)	(86;115)	(86;196)
Weight (kg)						
Mean (SD)	61.30 (9.78)	28.85 (5.89)	17.22 (1.83)	14.24 (1.54)	16.34 (2.20)	35.95 (19.36)
Median	60.80	28.80	17.50	13.60	16.40	29.95
Range (Min;Max)	(43.5;79.7)	(19.5;44.9)	(13.2;19.5)	(12.7;16.3)	(12.7;19.5)	(12.7;79.7)
Body Mass Index (kg/m^2)						
Mean (SD)	20.99 (2.31)	16.19 (1.34)	15.43 (0.88)	16.66 (1.28)	15.79 (1.13)	17.61 (2.85)
Median	20.70	16.15	15.20	16.60	15.60	16.75
Range (Min;Max)	(17.7;25.6)	(13.7;19.4)	(14.1;17.0)	(15.3;18.4)	(14.1;18.4)	(13.7;25.6)

N = number of subjects; y = years; SD = standard deviation; Min = Minimum; Max = Maximum.

Source: Table 15.1.2.1, Table 15.1.2.2.

Mean concentrations of tapentadol and tapentadol-O-glucuronide:

Table 14: Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 1 (12 years to <18 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+15 minutes	n = 19	n = 18
	23.2 (34.0)	404 (581)
+30 minutes	n = 18	n = 17
	45.6 (33.0)	855 (672)
+1 hour	n = 18	n = 17
	49.4 (21.2)	1424 (542)
+2 hours	n = 18	n = 18
	43.1 (14.2)	1202 (366)
+4 hours	n = 17	n = 17
	32.8 (10.8)	824 (191)
+6 hours	n = 18	n = 18
	22.3 (11.9)	497 (138)
+11 hours	n = 18	n = 18
	8.14 (6.35)	150 (69.0)
+15 hours	n = 17	n = 17
	3.66 (3.26)	66.9 (35.4)

SD = standard deviation; n = number of subjects with observed values.

Source: Table 15.2.3.1-1, Table 15.2.3.1-2.

Table 15: Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 2 (6 years to <12 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+15 minutes – 1 hour	n = 22	n = 20
	36.5 (21.8)	676 (343)
+1 hour – 4 hours	n = 22	n = 22
	36.5 (15.7)	900 (330)
+4 hours – 11 hours	n = 22	n = 22
	13.5 (6.52)	321 (123)
+11 hours – 15 hours	n = 22	n = 22
	3.71 (1.96)	86.3 (37.8)
+15 minutes – 1 hour	n = 11	n = 10
	30.1 (19.2)	494 (377)
+4 hours – 11 hours	n = 11	n = 11
	26.4 (10.7)	504 (112)

SD = standard deviation; n = number of subjects with observed values.

Source: Table 15.2.3.3-1, Table 15.2.3.3-2.

Table 16: Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 3 (3 years to <6 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+15 minutes – 1 hour	n = 11	n = 10
	30.1 (19.2)	494 (377)
+4 hours – 11 hours	n = 11	n = 11
	26.4 (10.7)	504 (112)

SD = standard deviation; n = number of subjects with observed values.

Source: Table 15.2.3.3-1, Table 15.2.3.3-2.

Table 17: Mean (SD) serum concentrations of tapentadol and tapentadol-O-glucuronide for Group 4 (2 years to <3 years) - Pharmacokinetic Set

Timepoint	Tapentadol (ng/mL)	Tapentadol-O-glucuronide (ng/mL)
+1.25 hours	n = 4	n = 4
	19.9 (13.2)	497 (513)
+3 hours	n = 4	n = 4
	37.7 (18.2)	938 (407)
+5 hours	n = 3	n = 3
	23.4 (6.36)	624 (235)
+8 hours	n = 4	n = 4
	10.0 (4.33)	253 (103)

SD = standard deviation; n = number of subjects with observed values.

Source: Table 15.2.3.4-1, Table 15.2.3.4-2.

The exposure parameters (Cmax and AUC0-t) for tapentadol observed in subjects 12 years to less than 18 years were similar to those observed in an adult population within the therapeutic dose range of 50 mg to 100 mg. For tapentadol-O-glucuronide, descriptive parameters were generally lower in this adolescent group than observed in the adult population.

BIOANALYTICAL STUDY SUMMARY

Title: DETERMINATION OF TAPENTADOL AND TAPENTADOL GLUCURONIDE IN HUMAN SERUM SAMPLES FROM THE STUDY KF5503/68 BY LC-MS/MS

Study no.: PK1477A
Date of report: 09 Jul 2014
Organization unit: Department of Pharmacokinetics (GI-GPR-P-PK)
Clinical study no.: KF5503/68

Title clinical study: Open-label evaluation of the pharmacokinetic profile, safety, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to less than 18 years
Test facility: Grünenthal GmbH, Zieglerstr. 6, 52078 Aachen, Germany
Study director: Dr. Klaus Pusecker
Bioanalytics starting date: 22 Jan 2013
Bioanalytics completion date: 07 Mar 2014

Analytical method
Tapentadol and tapentadol glucuronide serum levels were determined using the LC with tandem mass in accordance with the study plan PK1477A and the validation report PK1352.

The values for the overall accuracy (expressed as percent of nominal value) and the overall precision (expressed as coefficient of variation; CV) for quality control samples assayed during analysis of study samples are shown in Table 1 and Table 2.

4.2.3 Study KF5503/72 R331333PAI2007: Open-label evaluation of the population pharmacokinetic profile, safety, tolerability, and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years

The study synopsis can be found here:

\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550372\kf550372-study-report.pdf For individual concentration-time points overlay and mean profiles of subjects, see 151- 164/1057.

For individual concentration-time values for tapentadol and tapentadol glucuronide according to the ***bioanalytical report***, see pages 779 - 981/1057:
\\CDSESUB1\EVSPROD\NDA203794\0083\m5\53-clin-stud-rep\535-rep-effic-safety-stud\relief-of-moderate-to-severe-acute-pain\5352-stud-rep-uncontr\kf550372\kf550372-study-report.pdf

Noted that the same study reports were submitted in N 22304.

Reviewer's note: Pertinent additional information from the study report body:

"9.4.4 Selection and timing of dose for each subject
Modeling and simulation was performed to estimate the dose required in this trial (Section 8.5 of the protocol). The median steady state simulated AUCs after a 50 mg, 75 mg, and 100 mg dose in adults were 217 ng.h/mL, 325 ng.h/mL, and 433 ng.h/mL, respectively. The median simulated AUCs in subjects aged from birth to less than 2 years old receiving doses of tapentadol oral solution as specified in Table 1 were estimated to target the 217 ng.h/mL to 433 ng.h/mL exposure range."

12.3.1 Blood sampling for pharmacokinetics:

There will be 2 samples taken per subject. The sampling times are 0.5 hours and 4 hours (6 subjects, 2 per age subgroup), 2 hours and 8 hours (6 subjects, 2 per age subgroup) and 1 hour and 6 hours (3 subjects, 1 per age subgroup). The investigators will be informed of the times to use for individual subjects.

Concentrations were determined using validated liquid chromatography-tandem mass spectrometry bioanalytical assays. Details are provided in the bioanalytical report (Appendix 16.1.13)."

Demographics

Table 6: Descriptive statistics for demographic parameters – Safety Set, Full Analysis Set

		Age subgroup 1 N = 8	Age subgroup 2 N = 6	Age subgroup 3 N = 5	Overall N = 19
Parameter	**Category**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Sex	Female	4 (50.0)	2 (33.3)	3 (60.0)	9 (47.4)
	Male	4 (50.0)	4 (66.7)	2 (40.0)	10 (52.6)
Race [a]	White	7 (87.5)	3 (50.0)	4 (80.0)	14 (73.7)
	American Indian or Alaska Native	0	0	0	0
	Asian	1 (12.5)	1 (16.7)	0	2 (10.5)
	Black or African American	1 (12.5)	0	1 (20.0)	2 (10.5)
	Native Hawaiian or other Pacific Islander	0	0	0	0
	Other	0	2 (33.3)	0	2 (10.5)
Ethnicity	Hispanic or Latino	2 (25.0)	3 (50.0)	0	5 (26.3)
	Not Hispanic or Latino	6 (75.0)	3 (50.0)	5 (100)	14 (73.7)
Age [days]	Mean (SD)	420.0 (147.8)	92.8 (37.9)	14.6 (8.5)	210.0 (209.0)
	Median	435.0	90.0	10.0	120.0
	Range (Min - Max)	270 - 690	47 - 150	8 - 28	8 - 690
Height [cm]	Mean (SD)	73.3 (5.2)	62.0 (4.3)	53.4 (4.4)	64.5 (9.5)
	Median	72.0	61.0	54.0	63.0
	Range (Min - Max)	66 - 82	58 - 70	48 - 59	48 - 82
Weight [kg]	Mean (SD)	9.21 (1.50)	5.92 (1.18)	3.78 (0.66)	6.74 (2.59)
	Median	8.70	5.55	4.10	6.30
	Range (Min - Max)	7.5 - 11.4	4.9 - 8.1	2.8 - 4.4	2.8 - 11.4
Body Mass Index [kg/m^2]	Mean (SD)	17.11 (1.36)	15.28 (1.31)	13.36 (2.49)	15.55 (2.24)
	Median	17.05	15.30	14.00	15.90
	Range (Min - Max)	15.2 - 18.8	13.3 - 16.7	9.8 - 16.4	9.8 - 18.8
Body temperature [°C]	Mean (SD)	37.10 (0.44)	37.03 (0.32)	36.64 (0.53)	36.96 (0.45)
	Median	37.00	36.95	36.70	37.00
	Range (Min - Max)	36.4 - 37.9	36.6 - 37.5	36.0 - 37.2	36.0 - 37.9

Age subgroups:

- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months
- subgroup 3: 0 months to <1 month

a) One subject was reported in 2 race categories.

Min = minimum; Max = maximum; N = number of subjects; n = number of subjects in a specified category; SD = standard deviation.

Source: Table 15.1.2.1, Table 15.3.5.1, Listing 16.2.4.1

11.1.1 Bioanalytics

All pharmacokinetic samples taken during the clinical trial were analyzed for tapentadol, tapentadol-O-glucuronide, and tapentadol sulfate.

The number of samples analyzed and the details of assay performance including overall accuracy and overall precision are described in the bioanalytical report PK1563A.

Protocol amendment 01 allowed the possibility of measuring other tapentadol metabolites than tapentadol-O-glucuronide.

Table 14: Serum concentrations of tapentadol, tapentadol-O-glucuronide, and tapentadol sulfate - Pharmacokinetic Set

	Time point	Age subgroup 1 N = 7	Age subgroup 2 N = 6	Age subgroup 3 N = 5
Tapentadol	+30 minutes	n = 3 [a]	n = 2	n = 1 [a]
Mean (standard deviation)		9.8 (5.21)	8.3 (6.30)	26.62
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		18.79	35.27	43.63
	+2 hours	n = 2 [c]	n = 3	n = 2
		32.2 (14.92)	27.3 (0.81)	19.9 (7.67)
	+4 hours	n = 3	n = 2 [c]	n = 2
		11.1 (5.97)	25.9 (10.33)	15.0 (8.92)
	+6 hours	n = 1	n = 1	n = 1 [c]
		14.85	32.75	18.82
	+8 hours	n = 2 [c]	n = 2	n = 2
		10.7 (4.15)	5.6 (1.81)	14.6 (6.26)
Tapentadol-O-glucuronide	+30 minutes	n = 3 [a]	n = 1 [a]	n = 1 [a]
Mean (standard deviation)		105.7 (125.00)	128.8	74.38
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		430.7	136.3	209
	+2 hours	n = 2 [c]	n = 3	n = 2
		468.0 (248.41)	324.9 (116.61)	98.5 (2.62)
	+4 hours	n = 3	n = 2 [c]	n = 2
		348.7 (228.22)	449.7 (7.42)	147.6 (53.74)
	+6 hours	n = 1	n = 1	n = 1 [c]
		370.2	253.3	224.8
	+8 hours	n = 2 [c]	n = 2	n = 2
		285.1 (107.06)	92.2 (63.83)	174.1 (11.03)
Tapentadol-O-sulfate	+30 minutes	n = 2 [b]	n = 2	n = 1 [a]
Mean (standard deviation)		22.1 (20.83)	14.6 (8.98)	72.54
[ng/mL]	+1 hour	n = 1	n = 1	n = 1
		33.2	26.1	52.69
	+2 hours	n = 2 [c]	n = 3	n = 2
		50.3 (6.97)	24.9 (6.10)	36.4 (3.92)
	+4 hours	n = 3	n = 2 [c]	n = 2
		10.1 (10.21)	22.6 (4.70)	27.7 (3.52)
	+6 hours	n = 1	n = 1	n = 1 [c]
		15.76	20.78	12.39
	+8 hours	n = 2 [c]	n = 2	n = 2
		8.7 (0.69)	4.0 (3.17)	20.7 (12.64)

Summary statistics were only calculated when there were 2 or more samples.
Age subgroups:
- subgroup 1: 6 months to <2 years
- subgroup 2: 1 month to <6 months
- subgroup 3: 0 months to <1 month
a) One sample was below the limit of quantification.
b) Two samples were below the limit of quantification.
c) 1 sample was taken outside the defined time window.
N = number of subjects; n = number of subjects included in the calculation of descriptive statistics (where n = 1 no
descriptive statistics were calculated)

Source: Table 15.2.2.1.1, Table 15.2.2.1.2, Table 15.2.2.1.3, Table 15.2.2.2.1, Table 15.2.2.2.2, Table 15.2.2.2.3,
Table 15.2.2.3.1, Table 15.2.2.3.2, Table 15.2.2.3.3

BIOANALYTICAL STUDY SUMMARY

Study no.: PK1563A
Study title: Determination of tapentadol, tapentadol glucuronide and tapentadol sulfate in human serum samples from the study KF5503-72 by LC-MS/MS
Clinical study no.: KF5503-72
Clinical study title: Open-label evaluation of the population pharmacokinetic profile, safety, tolerability and efficacy of tapentadol oral solution for the treatment of post-surgical pain in children aged from birth to less than 2 years
Test facility: Grünenthal GmbH, Zieglerstr. 6 52078 Aachen, Germany
Number of samples: 35 human serum samples
Number of runs analyzed: 20
Study director: Dr Jörg Diekmann
Bioanalytics starting date: 21 Jan 2015
Bioanalytics completion date: 02 Nov 2016

4.3 Population Pharmacokinetic Analyses

4.3.1 Pharmacokinetic Modeling

(b) (4)

The Watson PPK model used to generate the updated PK simulations is similar to a PPK model that OCP previously reviewed (clinical pharmacology review of NDA 022304 archived on 08/27/2013). Both the Watson PPK model and the model from the 2013 clin pharm review were built using PK data from two studies; KF5503/59 and KF5503/68. Details on these studies is found below.

KF5503/59: Study 59 is a multicenter, open-label, study to evaluate the PK, safety, and tolerability of a single dose of 1 mg/kg tapentadol oral solution in children and adolescent subjects age 6 to 17 years recovering from postsurgical pain. PK data are available from n=36 subjects. Study 59 is also referred to as R331333PAI2005, PAI-2005, and NCT01134536.

KF5503/68: Study 68 is an open-label, non-randomized, single-site, single-dose evaluation of the pharmacokinetics, safety, and efficacy of a single administration of 1 mg/kg (no more than 75 mg) tapentadol oral solution for the treatment of post-surgical pain in children and adolescents aged from 2 years to 17 years. PK data were provided from n=56 subjects. Study 68 is identified in the Watson 2019 publication as NCT01729728.

The model described the 2013 clin pharm review includes PK data from these studies only including subjects age 6 to 17 years. The model described in the Watson PPK model builds on the model previously reviewed by OCP by expanding the PK dataset to include subjects age 2 to 17 years. The same structural model was preserved, and similar estimates are provided for structural parameters (i.e. CL/F is 174 L/h in the 2013 Clin pharm review and 170 L/h in the Watson et al., 2019 publication; V/F is 719 L in the 2013 clin pharm review and 685 L in Watson et al., 2019). The parameter estimates for the Watson PPK model are shown in the table below.

Table 1: Tapentadol PK Parameter Estimates for Pediatric Patients from Watson et al., 2019

Parameter	Estimate	RSE (%)	95% Confidence interval	
			NONMEM	Bootstrap (n=500)
CL/F (L/h)	170	3.3	159.06–180.94	162.08–182.94
V/F (L)	685	4.5	624.83–745.17	653.55–777.96
Ka (h^{-1})	2.03	16.5	1.373–2.687	1.599–3.263
TLAG (h)	0.247	0.7	0.243–0.251	0.245–0.273
Exponent CL-WT	0.638	11.1	0.499–0.777	0.515–0.766
Exponent V-WT	0.847	10.2	0.678–1.016	0.718–1.029
Additive error (ng/mL)	0.181	39.1	0.042–0.32	0.036–0.415
Proportional error (σ)	0.329	8.7	0.273–0.385	0.269–0.365
IIV CL/F (ω^2)	0.048	32.1	0.018–0.078	0.025–0.088
IIV V/F (ω^2)	0.024	61.5	−0.005–0.053	0.012–0.081
IIV Ka (ω^2)	1.99	32.2	0.734–3.246	1.042–3.673
Cov CL/F-V/F	0.03	46.1	0.003–0.057	0.012–0.071
Cov CL/F-Ka	0.009	614.5	−0.107–0.126	−0.090–0.155
Cov V/F-Ka	−0.072	93.6	−0.203–0.060	−0.219–0.080

Abbreviations: CL/F, apparent clearance after OS administration; Cov, covariance; σ, standard deviation; ω2, variance; IIV, inter-individual variability; Ka, first-order absorption rate constant; RSE, relative standard error (derived from the covariance matrix of the estimates reported by NONMEM); TLAG, absorption lag-time; V/F, apparent volume of distribution after OS administration; WT, weight.
Source: Watson et al., 2019.

[*Reviewer comment: The Watson PPK model, which is an update of the model previously accepted by OCP, is acceptable for use in the PK simulations.*]

Overall, the Applicant's proposal to use the PPK model from Watson et al., 2019 for simulations is acceptable.

4.3.2 Pharmacokinetic Simulation

The Applicant conducted PK simulations to support the proposed dosing. For this task the Applicant used the PK model described in the Watson et al. 2019 publication (see section the section **Pharmacokinetic Modeling** for details on the model). The Applicant simulated steady-state AUC tau for virtual adults receiving 50, 75 or 100 mg every four hours, as well as virtual pediatric patients (grouped as 2 to < 6 years, 6 to < 12 years, and 12 to 18 years) receiving a 1, 1.25, or 1.5 mg/kg every 4 hours. Applicant's simulations are presented in **Figure 2**. The Applicant also proposes label statements based on the simulated PK data. **Table 2** shows summary statistics of steady-state AUC tau for these age groups.

Table 2: Simulated median steady-state tapentadol area under the curve (AUCtau,ss) in pediatric and adult subjects receiving tapentadol every 4 hours (q4h) for 5 days

Simulated AUC Group	Pediatric Dose (1.25 mg/kg)			Adult Doses		
	2 to <6y	6 to <12y	12 to <18y	50 mg	75 mg	100 mg
AUC (ng·h/mL) Median	234	309	369	217	325	434
$2.5^{th} – 97.5^{th}$ PCT	(148-383)	(197 – 487)	(233 – 563)	(131 – 353)	(196 – 529)	(262 – 706)]

AUC = area under the curve tau at steady-state, PCT = percentile
Source: sequence 0094, response-to-fda-information-request-16fedb2023.pdf, page 3

[*Reviewer comment: The methodology for the PK simulations is acceptable.*

The PK simulations described in ***Figure 2*** *provide support for the proposed dosing from a PK perspective. Please refer to the review for the Clinical team for additional details regarding the dose selection.*

OCP recommends removing (b) (4) *The final label language will reflect additional discussions that may occur after this review has been archived.*]

4.4 Cover Sheet and OCP Filing/Review Form

The reader is referred to Office of Clinical Pharmacology Filing Form, DARRTS dated 12/02/22, for additional information.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID J LEE
06/08/2023 06:36:46 PM

MICHAEL A BEWERNITZ
06/09/2023 09:52:53 AM

VENKATESH A BHATTARAM
06/09/2023 10:03:03 AM

YUN XU
06/09/2023 10:04:24 AM