Combined Clinical, Cross-Discipline Team Leader, and Division Director Summary Review

Application Type	Pediatric Efficacy Supplements to fulfill PREA Post-Marketing Requirement (b) (4)
NDA/Supplement Numbers	022304/S-024 and 203794/S-010
Priority or Standard	Priority (3-month PDUFA clock extension for major amendments submitted to both supplements on March 20, 2023)
Submit Date	October 3, 2022
PDUFA Goal Date	July 3, 2023 (includes a 3-month clock extension)
Division/Office	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/Office of Neuroscience/CDER
Reviewer Names	Lisa Wiltrout, MD, DAAP Alla Bazini, MD, Associate Director for Therapeutic Review, Anesthesiology, DAAP Rigoberto Roca, MD, Division Director, DAAP
Review Completion Date	June 27, 2023
Established or Proper Name	Tapentadol oral tablet (immediate-release) Tapentadol oral solution
Proprietary Name	Nucynta tablet Nucynta oral solution
Applicant	Collegium Pharmaceutical, Inc.
Dosage Forms	Oral tablet (NDA 022304) - 50 mg, 75 mg, and 100 mg Oral solution (NDA 203794) - 20 mg per 1 mL in 100 mL and 200 mL fill bottles
Applicant Proposed Dosing Regimens	Oral tablet - (b) (4)
Dosing Regimens to be Approved with this Action	Oral tablet - For pediatric patients who are at least 6 years old, weigh at least 40 kg, and are able to swallow tablets:

	• For patients weighing 40 to 59 kg, administer 50 mg every 4 hours. Do not exceed a maximum single dose of 50 mg. If adequate analgesia is not achieved with a 50 mg NUCYNTA tablet every 4 hours, do not increase to a 75 mg NUCYNTA tablet. Instead consider use of another NUCYNTA product that allows for more flexible dosing, such as NUCYNTA oral solution. • For patients weighing 60 to 79 kg, initiate treatment with 50 mg every 4 hours. Increase the dose if needed to 75 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. Do not exceed a maximum single dose of 75 mg. If adequate analgesia is not achieved with a 75 mg NUCYNTA tablet every 4 hours, do not increase to a 100 mg NUCYNTA tablet. Instead consider use of another NUCYNTA product that allows for more flexible dosing, such as NUCYNTA oral solution. • For patients weighing greater than or equal to 80 kg, initiate treatment with 50 mg every 4 hours. Increase the dose if needed to 75 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. If adequate pain relief is not attained with a 75 mg NUCYNTA tablet every 4 hours, increase the dose to 100 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. Do not exceed a maximum single dose of 100 mg. Oral solution - For pediatric patients who are at least 6 years old and weigh at least 16 kg: • For patients weighing 16 kg to less than 40 kg, administer 1.25 mg/kg every 4 hours. Do not exceed the maximum single dose of 1.25 mg/kg. • For patients weighing greater than or equal to 40 kg, start with 50 mg (2.5 mL) every 4 hours. If adequate pain relief is not attained with a 50 mg dose of NUCYNTA oral solution every 4 hours, adjust the dose as needed to a maximum of 1.25 mg/kg every 4 hours to maintain adequate analgesia with acceptable tolerability. Do not exceed the maximum single dose of 100 mg.
Applicant Proposed Indications/Populations	Oral tablet - 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. Oral solution - 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.
Indications/Populations to be Approved with this Action	Oral tablet - Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults and pediatric patients aged 6 years and older with a body weight of at least 40 kg. Oral solution - Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults and pediatric patients aged 6 years and older with a body weight of at least 16 kg.
Regulatory Action	Oral tablet (NDA 022304 S-024) - Approval Oral solution (NDA 203794 S-010) - Approval

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
API	active pharmaceutical ingredient
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DMC	data monitoring committee
DMEPA	Division of Medication Error and Prevention Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
EU	European Union
EU PDCO	Pediatric Committee (of the European Medicines Agency)
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FLACC	Faces, Legs, Activity, Cry, Consolability (scale)
FPS-R	Faces Pain Scale-Revised
GCP	good clinical practice
GRMP	good review management practice
HR	heart rate
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NCA	nurse-controlled analgesia
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCA	patient-controlled analgesia
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PPK	population pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SGE	special government employee
SOAM	supplemental opioid analgesic medication
SOC	standard of care
TEAE	treatment emergent adverse event
URRA	Use-related risk analysis
VAS	Visual Analog Scale
US FDA	Food and Drug Administration of the United States of America

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Nucynta Oral Solution (OS) and Nucynta tablets are two immediate-release (IR) formulations of tapentadol. Nucynta OS and Nucynta tablets are bioequivalent. Both products are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults. The Applicant proposes the addition of pediatric (b) (4) to 17 years of age to the indication for both Nucynta OS and Nucynta tablets. The clinical team recommends addition of pediatric patients 6 to 17 years of age to the indication for both products and approval of both pediatric efficacy supplements.

Tapentadol hydrochloride (HCl) is the active pharmaceutical ingredient (API) in both Nucynta products. Tapentadol is a centrally acting, synthetic analgesic agent. Its exact mechanism of action is unknown. Preclinical studies have shown that tapentadol is a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. Both factors contribute to the analgesic effects of the compound.

Pain is the most common reason people seek medical care. Pain has been misunderstood and undertreated in children and remains an unmet medical condition in the pediatric population. There are fewer FDA-approved pharmacologic treatment options for pain management in children than in adults. Opioid analgesics alone or in combination with non-opioid analgesics are the primary treatment option for moderate to severe acute pain in children. Given the limited availability of FDA-approved drugs to treat pain in children, healthcare providers have historically used opioid analgesics off-label for acute pain management in the pediatric population.

The Agency has determined that the analgesic efficacy of tapentadol may not be extrapolated from efficacy data in adults because tapentadol has a different mechanism of action than traditional opioids. The Applicant submitted pediatric efficacy data from one adequate and well-controlled, multiple-dose study using tapentadol OS in pediatric patients from birth to 17 years of age to support the addition of pediatric (b) (4) to 17 years of age to the indication for both Nucynta OS and Nucynta tablets. These data demonstrate that tapentadol OS is efficacious in pediatric patients ages 6 years and older with acute post-operative pain, but do not demonstrate the efficacy of tapentadol OS in pediatric patients less than 6 years of age with acute post-operative pain.

The Applicant submitted pediatric safety data from one adequate and well-controlled, multiple-dose study and three open-label, uncontrolled, single-dose pharmacokinetic (PK) studies using tapentadol OS in pediatric patients from birth to 17 years of age. After review of the submitted safety data, there are no new safety signals with use of tapentadol OS in pediatric patients ages 2 years and older. The most common adverse events in pediatric patients 2 years and older from the multiple-dose study were vomiting, nausea, constipation, pyrexia, somnolence, and pruritus. The safety data demonstrate that tapentadol OS has a safety profile that is comparable to the safety profile of other IR opioid analgesics. Given the known increased risk of misuse, abuse, addiction, overdose, and death associated with use of opioid analgesics, the Agency has required a Risk Evaluation and Mitigation Strategy (REMS) for all IR opioid analgesics. The clinical team recommends the same REMS for pediatric labeling as is required for adults in the currently approved prescribing information for Nucynta OS and Nucynta tablets.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is defined as mild, moderate, or severe pain of sudden onset that is usually the result of a disease, injury, or inflammation and lasts less than three months in duration. • Pain is the most common reason people seek medical care. • Untreated pain has a significant impact on quality of life with physical, social, and economic ramifications. • Pain has been misunderstood, underdiagnosed, and undertreated in children. • It is now understood that pain in pediatric patients must be managed to minimize the development of hyperalgesia, to decrease morbidity and mortality, and to prevent long-term negative consequences.	Pain is the most common reason people seek medical care. Untreated pain has a significant impact on quality of life with physical, social, and economic consequences. Pain has been misunderstood and undertreated in children and remains an unmet medical condition in the pediatric population.
Current Treatment Options	• A multimodal approach to pain management, using a combination of non-pharmacologic and pharmacologic strategies, is most appropriate for both adults and children. • Non-pharmacologic approaches to pain management include rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, and relaxation techniques. • Pharmacologic approaches to pain management are escalated as pain intensity increases. • Mild to moderate pain is primarily managed with non-opioid analgesics, such as acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs). • Moderate to severe pain is managed with lower potency opioid analgesics alone or in combination with non-opioid analgesics. • Moderate to severe pain that is not responsive to lower potency opioid analgesics is managed with higher potency opioid analgesics. • Most of the opioid analgesics available in the United States are not approved for use in children. • Some analgesics with FDA approval for use in the pediatric population include APAP (oral and intravenous), ibuprofen (oral and intravenous), codeine/APAP, hydrocodone/APAP, morphine sulfate oral solution and morphine tablets, buprenorphine (intravenous), and fentanyl (intravenous and transdermal). • Given the limited availability of FDA-approved drugs to treat pain in children, many drug products are used off-label for pain management in the pediatric population.	Many FDA-approved pharmacologic treatment options exist for pain management in adults; however, the selection of FDA-approved pharmacologic treatment options for pain management in the pediatric population is more limited. Given the limited availability of FDA-approved drugs to treat pain in children, healthcare providers have historically used opioid analgesics off-label for acute pain management in the pediatric population. Therefore, it is imperative to assess the safety and effectiveness of opioid analgesics in the pediatric population and provide healthcare providers with correct dosing instructions for each pediatric age group for which an opioid analgesic has been determined to be safe and effective.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The analgesic efficacy of tapentadol in the pediatric population may not be extrapolated from efficacy data in the adult population because tapentadol has a different mechanism of action (mu-opioid agonism and norepinephrine reuptake inhibition) than traditional opioids. • Substantial evidence of effectiveness for tapentadol OS in pediatric patients ages 6 years and older was provided with data from one adequate and well-controlled efficacy and safety study in pediatric patients from birth to 17 years of age, Study KF5503/65. • The efficacy data from Study KF5503/65 did not provide substantial evidence of effectiveness for tapentadol OS in pediatric patients less than 6 years of age. • A descriptive analysis of supplemental opioid analgesic medication use by age subgroup demonstrated no numerical difference in supplemental opioid analgesic medication use between the tapentadol and placebo groups at 12 hours after first dose of study drug and numerically more supplemental opioid analgesic medication use in the tapentadol group as compared to the placebo group at 24 hours after first dose of study drug for pediatric patients in the two to less than six years age group. • Pharmacokinetic modeling and simulation data demonstrated that a tapentadol OS dose of 1.25 mg/kg every 4 hours in pediatric patients ages 2 to less than 6 years yields a pharmacokinetic (PK) exposure that is lower than the PK exposure in pediatric patients ages 6 to less than 18 years. • The benefits of treating pediatric patients two to less than 6 years of age with a potentially subtherapeutic dose of tapentadol OS do not outweigh the known risks associated with use of opioid analgesics. • The sample size of pediatric patients from birth to less than 2 years of age was too small to make any meaningful conclusions about the efficacy of tapentadol OS in this population.	The available data demonstrated substantial evidence of effectiveness for tapentadol OS in pediatric patients ages 6 years and older but did not demonstrate substantial evidence of effectiveness for tapentadol OS in pediatric patients less than 6 years of age.
Risk and Risk Management	• The safety database for tapentadol OS in the pediatric population from birth to 17 years of age included 248 pediatric patients from three open-label, uncontrolled, single-dose PK studies and one double-blind, placebo-controlled multiple-dose efficacy and safety study. • The most common adverse events with tapentadol OS in pediatric patients ages 2 years and older, from the placebo-controlled, multiple-dose study, were vomiting (19.4%), nausea (12.5%), constipation (10.6%), pyrexia	Tapentadol OS has a safety profile in pediatric patients ages 2 to 17 years that is comparable to the safety profile of tapentadol OS in adults and is also similar to the safety profile of other IR opioid analgesics. No new safety signals were identified with use of tapentadol OS in pediatric patients ages 2 years and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(6.9%), somnolence (5.0%), and pruritus (4.4%). • The sample size of pediatric patients from birth to less than 2 years of age was too small to make any meaningful conclusions about the safety of tapentadol OS in this population. • Review of the safety data yielded no new safety signals with use of tapentadol OS in pediatric patients ages 2 years and older. • Tapentadol OS has a safety profile in the pediatric population 2 to 17 years of age that is similar to the safety profile in adults. • Opioid use is associated with increased risk of misuse, abuse, addiction, overdose, and death. • To ensure that the benefits of opioid analgesics outweigh the risks of misuse, abuse, and addiction, the Agency has required a REMS for all immediate-release opioid analgesics.	Use of an opioid analgesic is associated with increased risk of misuse, abuse, addiction, overdose, and death. The Agency has required a REMS for all IR opioid analgesics to ensure that the benefits of opioid analgesics outweigh the risks. The clinical team recommends the same REMS for pediatric labeling as is required for adults in the currently approved Nucynta OS and Nucynta tablets labels. Based on a complete review of the available data, the clinical team recommends an approval action for both pediatric efficacy supplements.

2. Background

2.1 Product Information

NDA 022304 Supplement 024 is a pediatric efficacy supplement for Nucynta (tapentadol) tablets (IR formulation). The Applicant, Collegium Pharmaceutical, Inc, submits this efficacy supplement to support the addition of pediatric patients (b) (4) years and older with a body weight of at least 40 kg to the indication, to support the inclusi of pediatric pharmacokinetic (PK), efficacy, and safety data in the prescribing information, to fulfill the Pediatric Research and Equity Act (PREA) post-marketing requirement (PMR) 355-5, (b) (4) for the tapentadol moiety. Nucynta tablets are available in three strengths: 50 mg, 75 mg, and 100 mg. The approved dosing regimen for Nucynta tablets in adults is to initiate treatment with 50 mg to 100 mg every 4-6 hours as needed for pain. The proposed dosing regimen for Nucynta tablets in pediatric patients (b) (4)

NDA 203794 Supplement 010 is a pediatric efficacy supplement for Nucynta oral solution (OS). The Applicant submitted this efficacy supplement to support the addition of pediatric patients (b) (4) years and older with a body weight of 16 kg to the indication, to support the inclusion of pediatric PK, efficacy, and safety data to the prescribing information, to fulfill PREA PMR 1937-3, (b) (4) for the tapentadol moiety. Nucynta oral solution is available in one concentration: 20 mg/1 mL and is co-packaged with a 5 mL syringe (b) (4). The approved dosing regimen for Nucynta oral solution in adults is to initiate treatment in a dosing range of 50 mg to 100 mg every 4 to 6 hours as needed for pain. The proposed dosing regimen for Nucynta oral solution in pediatric patients (b) (4)

The active pharmaceutical ingredient (API) in all Nucynta products is tapentadol hydrochloride (HCl). Tapentadol is a centrally acting, synthetic analgesic agent. Its exact mechanism of action is unknown. Preclinical studies have shown that tapentadol is a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. Both factors contribute to the analgesic effects of the compound. Tapentadol is a Schedule II controlled substance with a safety profile typical of an opioid. Given its structural similarity to tramadol, tapentadol has pharmacological effects similar to tramadol and, therefore, may increase the risk of seizures in patients with seizure disorders and may cause serotonin syndrome when used concomitantly with serotonergic drugs. Additionally, adverse reactions of hallucination and suicidal ideation have been reported in the post-marketing experience with tapentadol in adults.

Because tapentadol has a different mechanism of action than traditional opioids, its efficacy may not be extrapolated from adults to the pediatric population based on comparable systemic

exposure. The Applicant submitted efficacy and safety data from one adequate and well-controlled study using tapentadol OS in pediatric patients from birth to 17 years of age (Study KF5503/65) to support the addition of pediatric patients aged (b) (4) years and older to the Nucynta indication. Conclusions about the efficacy and safety of Nucynta in pediatric patients less than 2 years of age are limited because only 15 patients in this age group participated in the study. (b) (4)

The Applicant also submitted efficacy and safety data from three open-label pharmacokinetic (PK) studies (Study KF5503/59, KF5503/68, and KF5503/72) using tapentadol OS in pediatric patients from birth to 17 years of age. These studies were not adequate and well-controlled and only used single doses of tapentadol OS; therefore, the efficacy data do not meet evidentiary standards and are not adequate to support the addition of pediatric patients to the Nucynta indication. The safety data, however, can be used to support the addition of pediatric patients aged (b) (4) years and older to the Nucynta indication. (b) (4) .

The Applicant conducted studies evaluating the efficacy and safety of tapentadol OS because the liquid formulation provided significant dosing flexibility. Nucynta OS and Nucynta tablets are bioequivalent; therefore, any efficacy or safety determination for Nucynta OS in the pediatric population is also applicable to Nucynta tablets.

(b) (4) On March 30, 2023, the Applicant submitted new pharmacometrics data to both supplements. The Applicant also submitted revised Nucynta OS labeling that included a limitation of use in pediatric patients (b) (4) . This new information qualified as a major amendment to each supplement; therefore, the review clock was extended by three months with an extended user fee goal date of July 3, 2023.

During the course of the review, the clinical team identified the following concerns with these efficacy supplements:

(b) (4)

(b) (4)

b. After review of the simulation data on tapentadol exposures in pediatric patients ages 2 to less than 6 years, 6 to less than 12 years, and 12 to less than 18 years after intake of tapentadol OS 1.25 mg/kg every 4 hours as compared to tapentadol exposures in adults after intake of Nucynta tablets 50 mg, 75 mg, or 100 mg every 4 to 6 hours, we note that tapentadol exposures in the 2 years to less than 6 years age group are lower than tapentadol exposures in the 6 years to less than 12 years and 12 years to less than 18 years age groups and comparable to tapentadol exposures in adults after intake of a 50 mg Nucynta tablet, the lowest strength Nucynta tablet.

c. We also note, for certain drug classes, that infants and young children may need higher mg/kg doses than the older pediatric population and adults due to differences in pediatric physiology and drug pharmacokinetics.

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

The Chemistry, Manufacturing, and Controls (CMC) team sent an information request on March 9, 2023, asking the Applicant to provide data to ensure that accurate dosing can be administered using the proposed commercially available syringes.

(b) (4)

The above-described changes constituted major amendments to both supplements and resulted in a PDUFA clock extension of three months for both supplements.

On April 26, 2023, the Division had a teleconference with the Applicant to discuss the limitation of use for Nucynta OS and clarify how Nucynta OS will be administered to adults versus pediatric patients. The Applicant clarified that adult dosing will not change and the co-packaged (b) (4) syringe for self-administration in adults will be retained. The Applicant stated they are proposing (b) (4) . The Division was not in favor of (b) (4) The Applicant was advised to appropriately revise the Nucynta OS labeling and submit dosing accuracy data to support the use of commercially available syringes for pediatric patients being administered Nucynta OS.

On May 19, 2023, the Applicant submitted revised labeling for Nucynta OS and a dosing accuracy report to support the use of commercially available syringes for pediatric patients being administered Nucynta OS. The revised labeling (b) (4) The revised labeling stated that the co-packaged (b) (4) syringe is for Nucynta OS self-administration in adults. The revised labeling also stated that commercially available syringes are to be used for Nucynta OS administration in pediatric patients.

2.2 Analysis of Condition

Acute pain is defined as mild, moderate, or severe pain of sudden onset that is usually the result of a disease, injury, or inflammation. Pain is considered acute when it lasts for less than three months in duration. An individual in acute pain may experience sharp, throbbing, burning, or stabbing sensations or may experience weakness, numbness, and tingling. Acute pain gradually resolves with healing of the underlying cause. Examples of acute pain include

muscular or ligamentous sprains and strains, burns, bone fractures, abscesses, and the post-surgical experience. Untreated acute pain is problematic as it can lead to anxiety, depression, delayed healing, and longer hospitalization. Untreated or inappropriately managed acute pain can also alter neural pathways making future pain worse and leading to the development of chronic pain[1,2].

Pain is the most common reason people seek medical care[3]. Pain impairs sleep, impairs activities of daily living, and lowers work productivity. Untreated pain has a significant impact on quality of life with physical, psychological, social, and economic ramifications.

Pain has been misunderstood, underdiagnosed, and undertreated in children. Barriers to treatment in children have included misperceptions that children do not experience pain and do not remember painful experiences, lack of adequate pain assessment, children's limited ability or inability to communicate pain, and fear of adverse effects from analgesic medications[4,5,6]. It is now understood that pediatric patients of all ages, from neonate to adolescent, experience pain. It is also understood that pain in pediatric patients must be managed to minimize the development of hyperalgesia, to decrease morbidity and mortality, and to prevent long-term negative consequences [2,7].

Pain has sensory, emotional, cognitive, and behavioral components; therefore, a multimodal approach to pain management, using a combination of non-pharmacologic and pharmacologic strategies, is most appropriate for both adults and children. Rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, biofeedback, hypnosis, and relaxation techniques are examples of non-pharmacologic approaches. Pharmacologic options are escalated as pain intensity increases. Mild to moderate pain is managed primarily with non-opioid analgesics, such as acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs). Alternative treatment options for mild to moderate pain include topical anesthetics, antidepressants, and anticonvulsants. Moderate to severe pain is managed with lower potency opioid analgesics alone or in combination with non-opioid analgesics. If pain is poorly

[1] McGrath, Patrick J., Finley, G. Allen, Ritchie, Judith, Dowden, Stephanie J. *Pain, Pain, Go Away: Helping Children with Pain*. Second Edition. 2003.
[2] Stephens, J., Laskin, B., Pashos, C., Peña, B., Wong, J. *The Burden of Acute Postoperative Pain and the Potential Role of the COX-2-specific Inhibitors*. Rheumatology. 2003; 42(Suppl. 3); iii40-iii52.
[3] Fishman, Scott M. Recognizing Pain Management as a Human Right: A First Step. International Anesthesia Research Society. July 2007; 105 (1): 8-9.
[4] American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and the American Pain Society Task Force on Pain in Infants, Children, and Adolescents. *The Assessment and Management of Acute Pain in Infants, Children, and Adolescents*. Pediatrics. September 2001; 108 (3): 793-797.
[5] Fein, Joel A., Zempsky, William T., Cravero, Joseph P and the Committee on Pediatric Emergency Medicine and Section of Anesthesiology and Pain Medicine. *American Academy of Pediatrics Clinical Report: Relief of Pain and Anxiety in Pediatric Patients in Emergency Medical Systems*. Pediatrics. November 2012; 130 (5): e1391-1405.
[6] Kahsay, Halefom. *Assessment and Treatment of Pain in Pediatric Patients*. Curr Pediatr Res. 2017; 21(1): 148-157.
[7] King, Nicholas B, Fraser, Veronique. *Untreated Pain, Narcotics Regulation, and Global Health Ideologies*. PLoS Medicine. April 2013; 10(4): e1001411.

controlled with lower potency opioid analgesics, then higher potency opioid analgesics are used. Regional anesthesia may also be used to manage moderate to severe pain [7,8,9,10].

APAP is FDA-approved for management of pain in adults and children 2 years and older. APAP is available in suppository, suspension, tablet, and solution dosage forms for rectal, oral, and intravenous (IV) administration. It may be purchased over-the-counter (OTC) or prescribed by a healthcare provider when used in combination with opioid analgesics or administered by the IV route. Hepatotoxicity in the setting of overdose is the main safety concern with APAP.

Ibuprofen, naproxen, diclofenac, ketorolac, and aspirin (ASA) are examples of NSAIDs used to treat pain. NSAIDs are available in suspension, tablet, solution, and patch dosage forms for oral, IV, and topical administration. NSAIDs may be purchased OTC or prescribed by a healthcare provider. The associated risks with use of NSAIDs include cardiovascular, gastrointestinal, and renal toxicity. There is also an increased risk of bleeding. ASA use should be avoided in pediatric patients with viral infections because of the increased risk of Reye's syndrome in this setting.

Morphine, oxycodone, hydromorphone, and fentanyl are examples of opioid analgesics used to treat pain. Opioid analgesics are available in suspension, tablet, solution, and patch dosage forms for oral, IV, and topical administration. Opioid analgesics are also available in IR and extended-release (ER) formulations. Opioid analgesics must be prescribed by a healthcare provider. Most of the opioid analgesics available in the United States are not approved for use in children. Opioid analgesics with and without pediatric labeling are summarized in the table below.

[8] Lee, Grace Y., Yamada, Janet, O'Brien, Kyololo, Shorkey, Allyson, Stevens, Bonnie. *Pediatric Clinical Practice Guidelines for Acute Procedural Pain: A Systematic Review*. Pediatrics. March 2014; 133 (3): 500-515.
[9] Verghese, Susan T., Hannallah, Raafat S. Acute Pain Management in Children. Journal of Pain Research. July 2010; 3: 105-123.
[10] WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Geneva: World Health Organization; 2012.

Table 2 Opioid Analgesics with and without Pediatric Labeling

Opioid Analgesics and Opioid-Containing Combination Products with Pediatric Labeling or Indications	Opioid Analgesics without Pediatric Labeling
Single-Entity Opioid Analgesics • Fentanyl transdermal (chronic pain) • Buprenorphine injection • Fentanyl citrate injection • Meperidine • OxyContin (chronic pain) • Morphine sulfate OS • Morphine tablets **Combination Products** • Codeine/APAP • Hydrocodone/APAP • Pentazocine/APAP • Dihydrocodeine/ASA/Caffeine • Codeine/ASA/Butalbital/Caffeine • Oxycodone/Ibuprofen • Pentazocine/Naloxone • Carisoprodol/ASA/Codeine • Butalbital/APAP • Butalbital/APAP/Caffeine	**Single-Entity Opioid Analgesics** • Fentanyl Oral Transmucosal • Hydrocodone ER • Hydromorphone IV/IR/ER • Methadone • Morphine sulfate IV/ER • Morphine/Naltrexone ER • Oxycodone IR/ER • Oxycodone/Naloxone ER • Oxymorphone IV/IR/ER • Tramadol IR/ER • Tapentadol IR/ER • Buprenorphine transdermal • Butorphanol • Levorphanol • Nalbuphine • Pentazocine • Oliceridine

Source: Agency NDA reviews as of March 3, 2023

Common adverse reactions associated with opioid analgesics include nausea, vomiting, constipation, drowsiness, dizziness, respiratory depression, and physical dependence. Opioid analgesics also carry the risk of misuse, abuse, addiction, overdose, and death.

Healthcare providers have historically used opioid analgesics off-label in the pediatric population for management of both acute and chronic pain. Pediatric dosing recommendations for opioid analgesics can be found in a number of clinical resources, such as The Harriet Lane Handbook and the website, UpToDate. Nevertheless, it remains vitally important to assess the safety and effectiveness of these opioid analgesics in the pediatric population. It is also crucial to provide healthcare providers with correct dosing instructions for each pediatric age group for which an opioid analgesic has been determined to be safe and effective.

3. Regulatory Background

3.1 Summary of Regulatory History

The tapentadol pediatric clinical development program has been ongoing for the last 15 years with the goal of using data from this one program to fulfill the following:

- Pediatric investigation plan requirements for tapentadol as established by the Pediatric Committee of the European Medicines Agency (EU PDCO).
- PREA PMRs for three different new drug applications (NDAs) (Nucynta tablets [NDA 022304], Nucynta OS [NDA 203794], and Nucynta ER [NDA 200533]) as issued by the Food and Drug Administration (FDA).

- A pediatric WR to obtain needed pediatric information on the tapentadol moiety as issued by the FDA.

A considerable amount of correspondence has transpired between the Division and the various NDA holders for Nucynta IR tablets, Nucynta OS, and Nucynta ER tablets. Key aspects of the regulatory history are summarized below. A more detailed review of the regulatory history is provided in Appendix 1.

2008
Nucynta tablets (NDA 022304) were approved on November 20, 2008, for use in adults with the indication for the relief of moderate to severe acute pain. At the time of the approval of Nucynta tablets, submission of pediatric studies in ages birth to less than 17 years of age was deferred until June 30, 2016, to allow for accumulation of additional safety information from both the nonclinical juvenile program and the adult post-marketing database before initiating investigations in pediatric patients. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 355-1: Treatment of moderate to severe acute pain in pediatric patients ages ≥6 years to ≤17 years.
- PMR 355-2: Treatment of moderate to severe acute pain in pediatric patients ages birth to <5 years*.

*There is a typographical error in the approval letter. The correct age group for PMR 355-2 is birth to ≤6 years.

2011
Nucynta ER tablets (NDA 200533) were approved on August 25, 2011, with the indication for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The pediatric study requirement for pediatric patients less than 7 years of age was waived because the product did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and was not likely to be used in a substantial number of pediatric patients in this age group. Pediatric studies for ages 7 to less than 17 years were deferred because the product was ready for approval for use in adults and the pediatric study had not been completed. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 1815-1: A PK, efficacy, and safety study of Nucynta ER for the management of chronic pain in pediatric patients ages 7 to <17 years.

2012
Nucynta OS (NDA 203794) was approved on October 15, 2012. At the time of the approval of Nucynta OS, pediatric studies in ages birth to less than 17 years were deferred because the product was ready for approval for use in adults and the pediatric studies had not been completed. The Agency acknowledged that a pediatric program for PREA requirements under NDA 022304 (Nucynta tablets) was ongoing and those studies were intended to also fulfill the PREA requirements for Nucynta OS because the two products are bioequivalent. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 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 <17 years.
- PMR 1937-2: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe pain in pediatric patients birth to 5 years.

On December 20, 2012, Janssen Pharmaceuticals, Inc. submitted a Proposed Pediatric Study Request (PPSR) for Nucynta IR tablets, Nucynta OS, and Nucynta ER tablets.

2013
On July 8, 2013, the Agency issued a formal WR to obtain needed pediatric information on tapentadol. The study requirements for the original WR are provided in Appendix 1.

(b) (4) the Division released the original PMRs for NDA 022304 (PMRs 355-1 and 355-2) and issued the following PMRs:

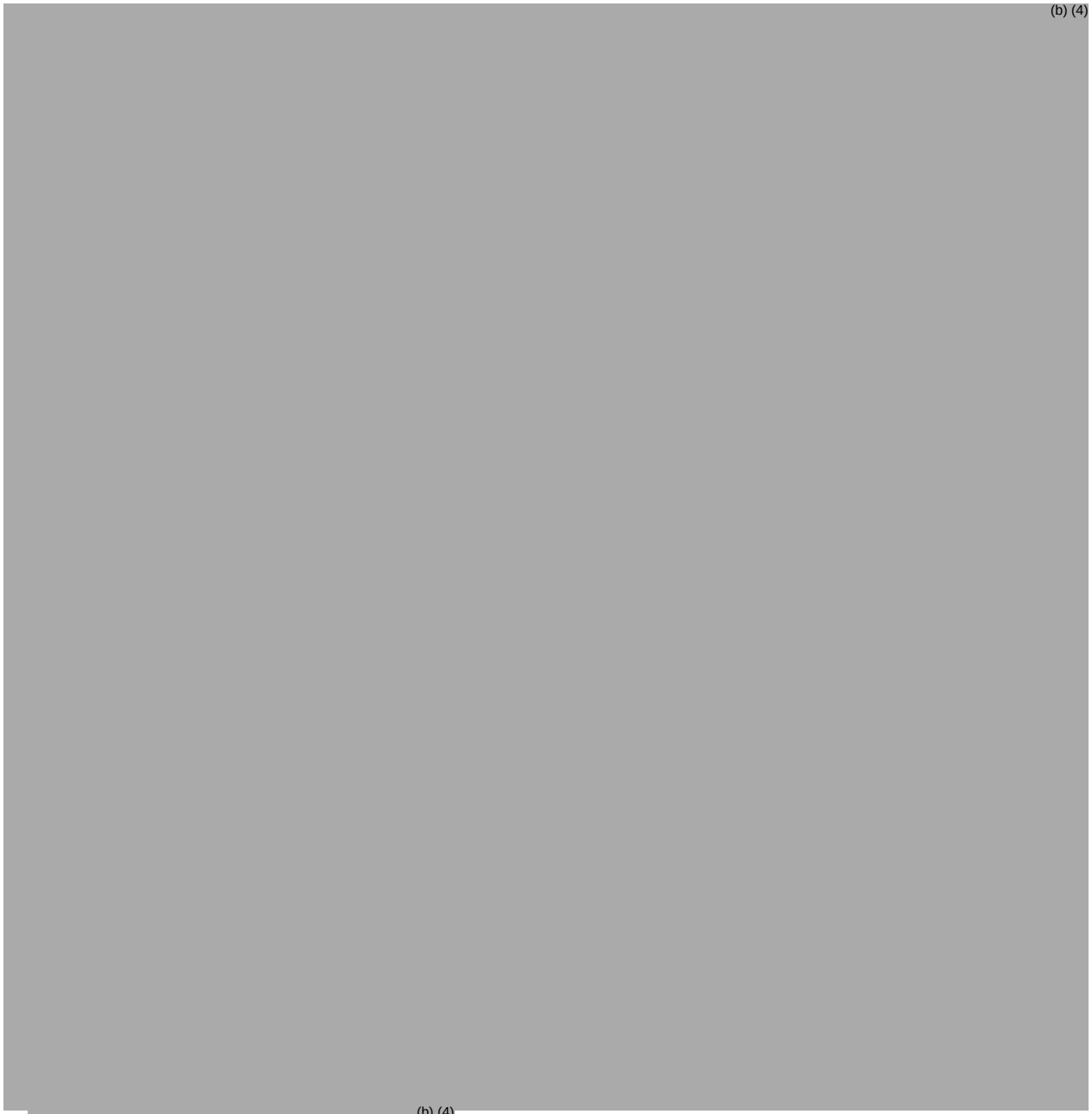
- PMR 355-3: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to <17 years.
- PMR 355-4: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to 5 years.

2015
In June 2015, based on the NDA holder's revised pediatric study plans for NDAs 022304 and 203794 (b) (4), the Division released PMRs 355-3 and 355-4 for NDA 022304 and PMRs 1937-1 and 1937-2 for NDA 203794 and issued new PMRs for both NDAs that combine the safety, PK, and efficacy studies of all age cohorts into a single trial. The reissued PMRs were as follows:

- NDA 022304 (Nucynta tablets) -
  - PMR 355-5: PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.
- NDA 203794 (Nucynta OS) -
  - PMR 1937-3: PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.

2021
On December 2, 2021, the Agency issued WR (b) (4)

(b) (4)



Upon review of the supplements for filing, the Division determined that the supplements were not sufficiently complete to permit a substantive review.

2022

On February 18, 2022, a refuse to file letter was issued to the Applicant for both supplements. The clinical and statistical deficiencies identified in the supplements and the information needed to resolve the deficiencies are listed in the table below.

Table 3 Summary of Clinical and Statistical Deficiencies and Information Needed to Resolve the Deficiencies in Supplements S-010 and S-024

Clinical/Statistical Deficiency	Information Needed to Resolve the Deficiency
You have not submitted any electronic datasets for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.	Submit all the electronic analysis datasets and SAS program codes used to produce the efficacy and safety results presented in the study reports for all four studies. Also provide corresponding define documents for the data sets and SAS codes. The datasets should include, at a minimum, subject level data on demographics, drug exposure, adverse events, protocol deviations, efficacy parameters, laboratory values, physical examination findings, ECG findings, and vital signs.
You have not submitted any of the raw data needed to derive the primary and secondary efficacy endpoints for Study KF5503/65 in Module 5.	Submit all of the raw data needed to derive the primary and secondary efficacy endpoints for Study KF5503/65.
You have not submitted Case Report Forms for serious adverse events and discontinuations due to treatment-emergent adverse events for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.	Submit an individual Case Report Form for each serious adverse event and each discontinuation due to a treatment-emergent adverse event reported in all four studies.
You have not submitted financial disclosure information for any of the investigators in studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 1.	Submit Financial Disclosure information for all of the investigators.
You have not submitted a rationale for assuming the applicability of foreign data to the U.S. population for studies KF5503/59, KF5503/65, and KF5503/72.	Submit a rationale for assuming the applicability of foreign data in studies KF5503/59, KF5503/65, and KF5503/72 to the U.S. population.

Source: Clinical Reviewer

On October 3, 2022, the Applicant resubmitted the two supplements, S-010 to NDA 203794 and S-024 to NDA 022304, and adequately addressed the clinical deficiencies enumerated above. As previously stated, the Applicant submitted pediatric data from studies XF5503/59, XF5503/68, XF5503/72, and XF5503/65 to support the addition of pediatric patients (b) (4) years and older to the indication for Nucynta tablets and Nucynta OS, to fulfill PREA PMRs 355-5 and 1937-3, (b) (4)

4. Product Quality

The Chemistry, Manufacturing, and Controls (CMC) team identified no concerns with the CMC data submitted with these pediatric efficacy supplements. For NDA 022304 S-024 (Nucynta tablets), please see the review of Afsana Akhter, PhD, with concurrence from Gurpreet Gill-Singha, PhD, dated March 6, 2023, for additional information. For NDA 203794 S-010 (Nucynta OS), the Applicant initially proposed (b) (4)

(b) (4)

The Applicant responded by (b) (4) proposing use of commercially available syringes for administration of Nucynta OS in pediatric patients. The Applicant submitted a new dosing accuracy report on May 19, 2023, to support their proposal to use commercially available syringes for administration of Nucynta OS in pediatric patients. The CMC team reviewed the dosing accuracy report and found the data acceptable. The CMC team also reviewed the updated Nucynta OS label and proposed no changes to the CMC related sections of the label. Please see the review of Afsana Akhter, PhD, with concurrence from Gurpreet Gill-Sangha, PhD, dated May 25, 2023, for a full discussion of the CMC data included in NDA 203794 S-024.

5. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology team identified no concerns with the nonclinical data submitted with these pediatric efficacy supplements. The Applicant performed a literature search in accordance with the Pregnancy and Lactation Labeling Rule (PLLR), reviewed 101 articles obtained from the PubMed database, and concluded that none of the articles provided nonclinical information on the effects of tapentadol on reproduction, development, or male and female fertility. Dr. Armaghan Emami conducted an independent search of the published literature and agreed with the Applicant's conclusion. Therefore, no updates to the prescribing information for Nucynta OS and Nucynta tablets are warranted at this time based on available published nonclinical literature. The pharmacology/toxicology team did not propose any changes to the relevant nonclinical sections of the prescribing information for Nucynta OS and Nucynta tablets. See the review of Armaghan Emami, PhD, with concurrence from Jaime D'Agostino, PhD and Jay Chang, PhD, dated March 29, 2023, for a full discussion of the nonclinical data included in these submissions.

6. Clinical Pharmacology

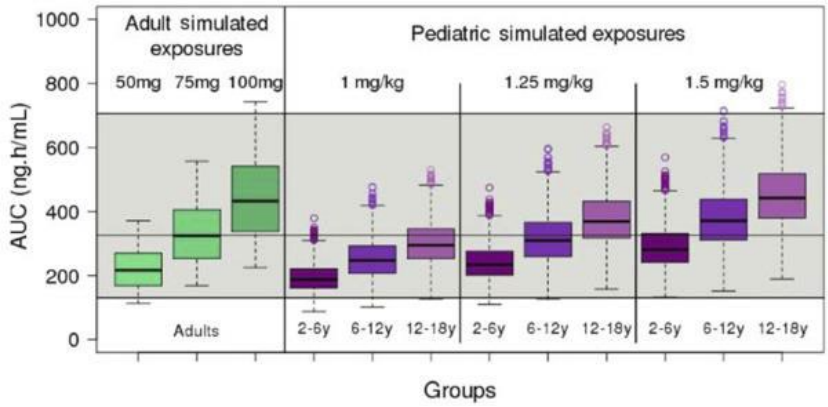
Tapentadol's exact mechanism of action is unknown; therefore, the efficacy of tapentadol may not be extrapolated from adults to pediatric patients based on comparable systemic drug exposure. The Applicant submitted results from Study KF5503/65, a multiple-dose, placebo-controlled, efficacy and safety study, to support the addition of pediatric patients ages (b) (4) years and older to the indication for the immediate-release formulation of tapentadol. As stated earlier, (b) (4) .

The Applicant utilized population PK (PPK) modeling and simulation to determine the pediatric dosing regimen that would be evaluated in Study KF5503/65. The population PK modeling and simulations were based on tapentadol exposure data from two open-label, single-dose PK studies, KF5503/59 and KF5503/68, in which tapentadol OS 1.0 mg/kg (maximum dose 75 mg) was administered to pediatric patients aged 2 to 17 years. Pediatric modeling and simulation predicted that a tapentadol OS dose of 1.25 mg/kg every 4 hours

would yield a tapentadol exposure in pediatric patients similar to that in adults who were administered 50 to 100 mg doses of tapentadol. In Study KF5503/65, pediatric patients from 6 months to 17 years of age were administered tapentadol OS at a dose of 1.25 mg/kg of body weight.

The clinical pharmacology and pharmacometrics teams identified no concerns with the clinical pharmacology, pharmacokinetic modeling, and pharmacokinetic simulation data submitted with these pediatric efficacy supplements. As stated in the clinical pharmacology review,

> "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…"

See the review of David Lee, PhD and Michael Bewernitz, PhD, with concurrence from Yun Xu, PhD and Atul Bhattaram, PhD, dated June 9, 2023, for a full discussion of the clinical pharmacology, PK modeling, and PK simulation data included with these pediatric efficacy supplements.

7. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for these pediatric efficacy supplements.

8. Clinical/Statistical- Efficacy

8.1 Table of Clinical Studies

At the time these PMRs and the WR were issued, the Agency concluded that the efficacy of tapentadol in pediatric patients could not be extrapolated from adult data because tapentadol's mechanism of action was not adequately characterized and not well understood. Additionally, given that tapentadol was a new molecular entity with a different mechanism of action than traditional opioid analgesics, the potential for adverse reactions similar to tramadol, and limited post-marketing experience in adults, the Agency required completion of PK and safety studies of IR tapentadol in pediatric patients ages 2 to less than 17 years before proceeding

with PK and safety studies in pediatric patients ages birth to less than 2 years. The Agency also required completion of PK and safety studies before initiating efficacy trials in corresponding age cohorts to inform dosing.

The tapentadol pediatric clinical development program consisted of three Phase 2, open-label, PK and safety studies (KF5503/59, KF5503/68, and KF5503/72) and one Phase 3, randomized, placebo-controlled, efficacy and safety study (KF5503/65). The PK studies followed a staggered recruitment by age to assess the safety of tapentadol OS in the older pediatric population before proceeding with studies in the younger pediatric population. Study KF5503/59 started in October 2011, ended in March 2013, and enrolled pediatric patients 6 to <18 years of age. Study KF5503/68 started in November 2012, ended in February 2014, and enrolled pediatric patients 2 to less than 18 years of age. Study KF5503/72, started in November 2014, terminated early in December 2016, and enrolled the youngest age group, patients from birth to less than 2 years of age. The primary objectives of all three PK studies were to evaluate the PK and safety of a single dose of tapentadol OS in pediatric patients with acute post-surgical pain. Efficacy was evaluated as an exploratory objective using age-appropriate, observational and subject-reported pain assessments.

In February 2015, after completion of studies KF5503/59 and KF5503/68, the Applicant initiated study KF5503/65, the confirmatory efficacy and safety study, in pediatric patients (b) (4) to less than 18 years of age. Pediatric patients ages birth to less than 2 years were later enrolled in study KF5503/65 after completion of study KF5503/72. Study KF5503/65 ended in March 2019. The primary objectives of study KF5503/65 were to evaluate the efficacy and safety of multiple doses of tapentadol OS in pediatric patients with acute post-surgical pain. Additional details on studies KF5503/59, KF5503/68, KF5503/72, and KF5503/65 are provided in the table below.

Table 4 Listing of Clinical Trials Relevant to NDA 022304 Supplement 024 and NDA 203794 Supplement 010

Trial No./ NCT No.	Trial Design	Test Product/ Route/ Dosage or Dosing Regimen	Trial Endpoints	No of Subjects Entered/ Completed	Trial Population	No. of Centers and Countries
Supportive Trials						
KF5503/59/ NCT01134536	PK and safety/ Nonrandomized, OL, multicenter, single-dose study	Tapentadol OS/ oral/ 6 to 18 years - 1 mg/kg x 1 dose (maximum dose 75 mg)	PK – serum concentrations of tapentadol and tapentadol-O-glucuronide Safety – AEs, clinical laboratory tests, labs, vital signs, PEs, ECGs Pain Assessments – McGrath Color Analog Scale and Faces Pain Scale-Revised	44/ 38	Postop pain in subjects ages 6 to <18 years	34 sites – 2 in Canada 5 in Spain 24 in U.S.
KF5503/68/ NCT01729728	PK, safety, and efficacy/ Nonrandomized, OL, single-site, single-arm, single-dose study	Tapentadol OS/ oral/ 2 to 18 years - 1 mg/kg x 1 dose (maximum dose 75 mg)	Primary – descriptive PK parameters for tapentadol and tapentadol-O-glucuronide Secondary – Pain intensity assessments using VAS, McGrath CAS, FLACC; Safety (AEs, clinical labs, ECGs, vital signs, C-SSRS, PEs)	66/ 58	Postop pain in subjects ages 2 to <18 years	1 site in U.S.
KF5503/72/ NCT02221674	PK, safety, tolerability, and efficacy/ Nonrandomized, OL, multi-site, single-dose study	Tapentadol OS/ oral/ Birth to <1 mo - 0.50 mg/kg x 1 dose 1 month to <6 mos - 0.60 mg/kg x 1 dose 6 mos to <2 years - 0.75 mg/kg x 1 dose	Primary – serum concentrations of tapentadol and tapentadol-O-glucuronide Exploratory – Change from baseline in pain intensity using FLACC, AEs, vital signs, oxygen saturation, clinical labs, ECGs, PEs, trial discontinuation due to TEAEs and drug-related AEs	19/ 18	Postop pain in subjects ages birth to <2 years	14 sites – 2 in U.K. 8 in U.S. 4 in Poland
Controlled Trials						
KF5503/65/ NCT02081391	Efficacy and safety/ R, multi-site, DB, PC, Multiple-dose study	Tapentadol OS/ oral/ Dose q4H for first 24h/ Dose q4H after first 24h Birth to <30 days - 0.1 mg/kg/ 0.1 or 0.075 mg/kg 30 days to <6 months - 0.5 mg/kg/ 0.5 or 0.3 mg/kg	Primary – US FDA Total amount of supplemental opioid analgesic medication used within the first 12 hours after first IMP intake EU PDCO Total amount of supplemental opioid analgesic medication used within the first 24 hours after first IMP intake Secondary –	219/ 150	Postop pain requiring opioid use in patients from birth to <18 years	44 sites – 3 in Bulgaria 2 in Croatia 3 in Czech Republic 3 in France 1 in Germany 3 in Hungary

Trial No./ NCT No.	Trial Design	Test Product/ Route/ Dosage or Dosing Regimen	Trial Endpoints	No of Subjects Entered/ Completed	Trial Population	No. of Centers and Countries
		6 months to <18 years - 1.25 mg/kg/ 1.25 or 1.0 mg/kg	US FDA Total amount of supplemental opioid analgesic medication used within the first 24 hours after first IMP intake EU PDCO Total amount of supplemental opioid analgesic medication used within the first 12 hours after first IMP intake			8 in Poland 5 in Spain 2 in U.K. 14 in U.S.

Source: Tabular Listing of all Clinical Studies, NDA 022304 S-024, Module 5.2

8.2 Review Strategy

The Applicant submitted PK data from studies KF5503/59, KF5503/68, and KF5503/72 along with modeling and simulation data to establish the PK profile of tapentadol in pediatric patients and support the tapentadol OS doses selected for evaluation in the three PK studies and the confirmatory efficacy study, KF5503/65. As discussed in Section 6 of this review, the clinical pharmacology and pharmacometrics teams reviewed the PK studies and the associated PK data, the Applicant's modeling and simulation approaches, and the tapentadol OS doses selected for evaluation in the PK studies and the confirmatory efficacy study, and deemed all of the above acceptable from the clinical pharmacology and pharmacometrics perspectives.

The Applicant submitted efficacy data from study KF5503/65 to support the efficacy of tapentadol OS in the pediatric population (b) (4) to less than 17 years of age. The design and conduct of this study meet the evidentiary standards for an adequate and well-controlled study. The study used a placebo-controlled design and randomization. Subjects and investigators were blinded with respect to whether subjects were administered tapentadol OS or placebo. The primary objective was to evaluate the efficacy of tapentadol OS based on the total amount of supplemental opioid analgesic used. The study was powered to evaluate efficacy as the primary endpoint. (b) (4)

(b) (4)

(b) (4)

(b) (4)

8.3 Review of Individual Trial Used to Support Efficacy

Study KF5503/65

Title: An evaluation of the efficacy and safety of tapentadol oral solution in the treatment of post-operative acute pain requiring opioid treatment in pediatric subjects aged from birth to less than 18 years old.

Study Design

Study KF5503/65 was a Phase 3, multi-site, randomized, double-blind, placebo-controlled, parallel group, multiple oral dose study designed to evaluate the efficacy and safety of tapentadol OS in pediatric patients from birth to less than 18 years of age who had moderate to severe pain after surgery requiring treatment with an opioid analgesic medication. The study was conducted as part of the tapentadol pediatric development program to fulfill different requirements as agreed with the US FDA and the Pediatric Committee of the European Medicines Agency (EU PDCO). A total of 44 clinical sites participated in the study with 14 sites in the US and 30 sites outside the US. The study was conducted over a 4-year period from February 2015 to March 2019.

The study consisted of an enrollment period that started up to 28 days before allocation to the investigational medicinal product (IMP) and lasted up until the time of allocation to IMP, a treatment and evaluation period of up to 96 hours, and a follow-up period of 10 to 14 days after the first dose of IMP. Subjects could be enrolled in the study either pre- or post-operatively.

Subjects underwent their scheduled surgery and were started on nurse-controlled analgesia (NCA) or patient-controlled analgesia (PCA) with morphine or hydromorphone, with or without a low dose background infusion of the same opioid, according to the standard of care. When subjects met all of the inclusion criteria, none of the exclusion criteria, and were able to tolerate liquids, they were allocated to tapentadol OS or placebo (randomized 2:1), given by mouth every 4 hours for a maximum duration of 72 hours.

Subjects were administered the first dose of IMP when the investigator deemed it medically appropriate for the subject to receive IMP. The background opioid infusion, if any, was discontinued at the time of administration of the first dose of IMP. NCA or PCA was continued with the same opioid as was used prior to IMP, according to investigator judgment and standard of care, after administration of the first dose of IMP.

The tapentadol OS dosing regimen was:

- Ages 6 months to less than 18 years - 1.25 mg/kg every 4 hours for the first 24 hours.
- Ages 30 days to less than 6 months - 0.5 mg/kg every 4 hours for the first 24 hours.

- Ages birth to less than 30 days old - 0.1 mg/kg every 4 hours for the first 24 hours.

After the first 24 hours of treatment, the tapentadol OS dose could be decreased if there was reduced need for analgesia, according to the investigator's judgment, to the following tapentadol OS dosing regimen:

- Ages 6 months to less than 18 years - 1.0 mg/kg every 4 hours.
- Ages 30 days to less than 6 months - 0.3 mg/kg every 4 hours.
- Ages birth to less than 30 days old - 0.075 mg/kg every 4 hours.

Subjects were closely observed, especially during the first hour after initiation of IMP. Vital signs (RR, SBP/DBP, HR), sedation scores, oxygen saturation monitoring, and pain scores were measured before each dose of IMP was administered.

Dosing with IMP was to have stopped for any of the following:

- 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.

Study Objectives

Primary Objectives

One primary objective was to evaluate the efficacy of tapentadol OS, based on the total amount of supplemental opioid analgesic medication used over 12 hours (US FDA) and 24 hours (EU PDCO) following initiation of IMP, in pediatric patients from birth to less than 17 years of age (US FDA) and from 2 to less than 18 years of age (EU PDCO) who had undergone surgery that would reliably produce moderate to severe pain requiring opioid treatment.

Another primary objective was to evaluate the safety of tapentadol OS in pediatric patients from birth to less than 17 years of age (US FDA) and from 2 to less than 18 years of age (EU PDCO) who had undergone surgery that would reliably produce moderate to severe pain requiring opioid treatment.

The primary efficacy objective for one region (either 12 hours [US FDA] or 24 hours [EU PDCO]) was considered the secondary efficacy objective for the other region.

Secondary Objectives

The secondary objectives were to evaluate the efficacy of tapentadol OS using multiple objective and subjective measures of the patient's response to treatment.

Dose Selection

The tapentadol OS dose selected for each age group was determined based on population PK modeling and simulation using the serum concentration data from the single-dose PK studies. The clinical pharmacology and pharmacometrics teams found the modeling and simulation data acceptable for use in determining the dose selection for this study.

The clinical team identified no concerns with the tapentadol doses selected for use in this study. However, upon reviewing the predicted tapentadol exposure in pediatric patients administered a tapentadol OS dose of 1.25 mg/kg every 4 hours (from the PK simulation data submitted by the Applicant), we note that tapentadol exposure is lowest in the youngest age group (2 years to less than 6 years of age) as compared to tapentadol exposures in the 6 years to less than 12 years age group and the 12 years to less than 18 years age group. Tapentadol exposure in the 2 years to less than 6 years age group is comparable to the tapentadol exposure observed in adults after administration of the lowest effective dose of tapentadol tablets (50 mg).

Study Population

The study population consisted of male and female subjects from birth (≥37 weeks gestational age) to less than 18 years of age who had undergone surgery 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 were to have received post-operative morphine or hydromorphone by NCA or PCA, with or without a background infusion of the same opioid, according to standard of care prior to allocation to IMP and were expected to require morphine or hydromorphone by NCA or PCA after starting IMP. Subjects had to be able to tolerate liquids at the time of allocation/randomization to IMP. Subjects were to remain hospitalized until the end of treatment visit. Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject-controlled epidural analgesia had to be terminated more than six hours before allocation to IMP.

The key exclusion criteria were as follows:

1. Subject has a history or current condition of any one of the following:
   a. Non-febrile seizure disorder.
   b. Epilepsy.
   c. Serotonin syndrome.
   d. Traumatic or hypoxic brain injury, brain contusion, stroke, transient ischemic attack, intracranial hematoma, post-traumatic amnesia, brain neoplasm, or episode(s) of unconsciousness of more than 24 hours.
2. Subject has a history or current condition of any one of the following:
   a. Moderate to severe renal or hepatic impairment.
   b. Abnormal pulmonary function or clinically relevant respiratory disease (e.g., acute or severe bronchial asthma, hypercapnia).
3. Subject has a concomitant disease or disorder (e.g., endocrine, metabolic, neurological, psychiatric, infection, febrile seizure, paralytic ileus) that in the opinion of the investigator may affect or compromise subject safety during the trial participation.

4. Subject has received a long-acting opioid for the treatment of pain following surgery within six hours of allocation/randomization to IMP.
5. Subject has post-operative clinically unstable systolic and diastolic blood pressure, heart rate, respiratory depression, or clinically unstable upper or lower airway conditions (in the investigator's judgment), or a peripheral oxygen saturation (SpO2) <92% at the time of allocation/randomization to IMP.
6. Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP.

Study Endpoints

Primary Endpoint

The primary efficacy endpoint was the total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg body weight) used within 12 hours (US FDA) and 24 hours (EU PDCO) following initiation of study drug.

Secondary Endpoints

The secondary efficacy endpoints were:

- The total amount of supplemental opioid analgesic medication (morphine equivalents in mg/kg study drug) used within 24 hours (US FDA) and 12 hours (EU PDCO) following initiation of study drug.
- 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 ages 2 years to less than18 years old (EU PDCO).
- Changes from baseline in pain intensity over the treatment period using age-appropriate pain scales (Face, Legs, Activity, Cry, Consolability (FLACC) Pain 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 less than 12 years, and Visual Analog Scale (VAS) for ages 12 to less than 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.

The secondary safety endpoints were:

- Percentage of subjects with TEAEs.
- Percentages of subjects who develop abnormal:
  - Vital signs.
  - Laboratory parameters.
  - 12-lead ECG parameters.
- Changes from baseline in vital signs parameters.
- Sedation scores using the University of Michigan Sedation Scale.

- Changes from baseline in safety laboratory parameters.
- Changes from baseline in 12-lead ECG parameters.
- Percentage of subjects discontinuing the study due to TEAEs and drug-related adverse events.
- Suicidal ideation/behavior in subjects aged 6 years or older using the C-SSRS scores before IMP and at the end of the study.

Statistical Analysis Plan

The US FDA required inclusion of subjects from birth to less than 17 years of age in the study population, whereas the EU PDCO required inclusion of subjects from 2 years to less than 18 years of age in the study population. Originally, the planned statistical analyses were to be reported using the US FDA study population for the US FDA endpoints and the EU PDCO study population for the EU PDCO endpoints. For safety reasons, pediatric patients less than 2 years of age were the last population enrolled in the study and also the last population to complete the study. The Applicant put forth a rationale for including adolescents aged 17 years old in the evaluation of US FDA endpoints and separately analyzing the pediatric population less than 2 years of age. After review of the Applicant's rationale, the FDA agreed to include adolescents aged 17 years old in the evaluation of US FDA primary and secondary endpoints and separately analyze the pediatric population less than 2 years of age. Hence, the Applicant reported all analyses using the EU PDCO study population complemented by descriptive analyses for the respective population of subjects less than 2 years of age.

Analysis Sets

The analysis sets were defined as follows:

The **Enrolled Set** (Enrolled-All) included all enrolled subjects (as defined in the protocol) of the study. For the EU PDCO, Enrolled-EU included all enrolled subjects (as defined in the protocol) from 2 to less than 18 years of age. For the US FDA, Enrolled-US included all enrolled subjects (as defined in the protocol) from birth to less than 17 years of age and Enrolled-US<2 included those subjects less than 2 years of age and is identical to Enrolled-All<2.

The **Allocated Set** (Allocated-All) included all enrolled subjects that are allocated (randomized) to IMP. For the EU PDCO, Allocated-EU included allocated subjects 2 years to less than 18 years of age. For the US FDA, Allocated-US included allocated subjects from birth to less than 17 years of age and Allocated-US<2 included those allocated subjects less than 2 years of age and is identical to Allocated-All<2.

The **Safety Set** (SAF) comprised all treated subjects who were administered any amount of IMP in the required age ranges for the EU PDCO and US FDA. The overall SAF (denoted by SAF-All) included all treated subjects of the study. For the EU PDCO, SAF-EU included subjects 2 to less than 18 years of age. For the US FDA, SAF-US included subjects from birth to less than 17 years of age and SAF-US<2 included those subjects less than 2 years and is identical to SAF-All<2.

The **Full Analysis Set** (FAS-All) included all subjects that were allocated and treated. For the EU PDCO, FAS-EU included allocated and treated subjects ages 2 to less than 18 years of age. For the US FDA, FAS-US included allocated and treated subjects from birth to less than 2 years of age and FAS-US<2 included those subjects less than 2 years old and is identical to FAS-All<2.

The **Per Protocol Set** (PPS) for the EU PDCO or US FDA defined subsets of subjects in the FASs without any major protocol deviations affecting the primary efficacy endpoint. The major protocol deviations that 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 less than 2 years of age.

The primary analysis set was the FAS-EU set which included all allocated (randomized) and treated subjects 2 to less than 18 years of age. A summary of the analysis populations is provided in the table below.

Table 5 Summary of the Analysis Populations

Parameter	Placebo n (%)	Tapentadol OS n (%)	Overall n (%)
EU analysis			
Allocated subjects	55 (100)	110 (100)	165 (100)
Safety Set (SAF)	52 (94.5)	108 (98.2)	160 (97.0)
Full Analysis Set (FAS)	52 (94.5)	108 (98.2)	160 (97.0)
Per Protocol Set (PPS)	46 (83.6)	94 (85.5)	140 (84.8)
US analysis <2 years			
Allocated subjects	4 (100)	11 (100)	15 (100)
Safety Set (SAF)	4 (100)	11 (100)	15 (100)
Full Analysis Set (FAS)	4 (100)	11 (100)	15 (100)
Per Protocol Set (PPS)	3 (75.0)	11 (100)	14 (93.3)
Overall			
Allocated subjects	59 (100)	121 (100)	180 (100)
Safety Set (SAF)	56 (94.9)	119 (98.3)	175 (97.2)
Full Analysis Set (FAS)	56 (94.9)	119 (98.3)	175 (97.2)
Per Protocol Set (PPS)	49 (83.1)	105 (86.8)	154 (85.6)

n = number of subjects in the respective population; OS = oral solution.
Source: CSR for KF5503/65, Table 10 on page 80/2254.

Statistical Analyses

Primary Endpoint

The primary endpoint for the US FDA (and the EU PDCO) was the amount of supplemental opioid analgesic medication used within the first 12 hours (and 24 hours) after first IMP intake. Supplemental opioid analgesia was expressed in mg/kg of morphine-equivalents. Hydromorphone doses were multiplied by five to obtain the morphine equivalent.

Supplemental opioid analgesic medications included in the analysis were opioids given via NCA or PCA, clinician bolus, and other intravenously administered opioids.

Primary Analyses

The primary null hypothesis was tested using an analysis of variance (ANOVA) which included treatment, baseline age group (2 to less than 6 years, 6 to less than 12 years, and 12 to less than 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.

Sensitivity Analyses

The analyses of the primary endpoints were repeated for the PPS:

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

See the statistical review of Yunfan Deng, PhD, dated June 9, 2023, with concurrence from Sue Jane Wang, PhD, for a discussion of the statistical handling of missing data, such as subjects who discontinue from treatment prior to 24 hours after first IMP intake and subjects who discontinue due to either "opioid analgesic medication is no longer needed" or "switch to exclusively oral opioid analgesic medication."

Secondary Endpoints

All non-descriptive statistical analyses of secondary endpoints were conducted at a significance level of $\alpha = 0.05$ and considered exploratory. There were no multiplicity adjustments for any of these analyses.

Supplemental Opioid Analgesic Medication (SOAM)

The primary endpoint for the US FDA (amount of SOAM used within the first 12 hours) evaluated using the FAS-EU set was used as a secondary endpoint for the EU PDCO. The same ANOVA model as defined above for the primary efficacy endpoint was used to assess treatment differences. The primary endpoint for the EU PDCO (amount of SOAM used within the first 24 hours) evaluated using the FAS-EU set was used as a secondary endpoint for the US FDA.

The primary efficacy endpoint for the EU PDCO and the US FDA was descriptively summarized for the FAS-US<2 and the respective age groups.

In addition, the total amount of SOAM received, evaluated in 12-hour intervals from 24 hours to 96 hours, was summarized descriptively for the FAS-EU and FAS-US<2 sets.

Pain Intensity Related to the Administration of IMP and End of Treatment Visit

Pain assessments occurred at the following times during the study:

- Before first dose of IMP (baseline)
- Between 30 minutes and 60 minutes after first dose of IMP
- Before each succeeding dose of IMP (every 4 hours)
- End of Treatment visit

Pain intensity scores and change from baseline were summarized descriptively for each time point by age-defined pain scale (i.e., FLACC/FPS-R/VAS). For the FAS-US<2, only the FLACC summary was used.

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

Also, the area under the pain curve (AUPC) up to 12 hours and 24 hours was calculated.

Clinical Global Impression of Change (CGIC)

At the End of Treatment visit, the response of the CGIC questionnaire was measured on an ordinal, seven-category scale and results were summarized descriptively. Additionally, the categories "very much improved" and "much improved", as well as the remaining five categories were pooled (CGIC responder versus CGIC non-responder) and the resulting binary variable was summarized descriptively.

Patient Global Impression of Change (PGIC)

At the End of Treatment visit, the PGIC questionnaire was completed by the subject, parent, or legal guardian. The response was measured on an ordinal, seven-category scale and results were summarized descriptively. Additionally, the categories "very much improved" and "much improved", as well as the remaining five categories were pooled (PGIC responder versus PCIG non-responder) and the resulting binary variable was summarized descriptively.

Analysis of Covariance (ANCOVA) Including Pain Intensity at Baseline as a Covariate

An ANCOVA based on each age-defined pain scale, including treatment and supplemental opioid analgesic used as factors and age at baseline and pain intensity at baseline as covariates, was conducted using the FAS-EU set. Different pain scales were used for different age groups; therefore, the analysis was performed on the following three subgroups:

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

3. Children between 12 years and less than 18 years old, including the VAS score at baseline as covariate.

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

Subgroup Analyses

Summary statistics for the primary endpoint were provided for each of the following factors using the FAS-EU set:

- Relevant age groups (2 to less than 6 years, 6 to less than 12 years, 12 to less than 18 years [12-hour and 24-hour endpoints])
- Sex (24-hour endpoint)
- Race (24-hour endpoint)
- Geographical region (24-hour endpoint)
- Type of administration of supplemental opioid analgesia (NCA vs. PCA [12-hour and 24-hour endpoints])
- Supplemental opioid analgesia used (hydromorphone vs. morphine [24-hour endpoint])

Protocol Amendments

The protocol for Study KF5503/65 was amended seven times. The first two protocol amendments occurred before the initiation of the study. The third protocol amendment was a change in sponsorship that did not impact study conduct. The fourth protocol amendment occurred four months after the study started and involved changes to the exclusion criteria, changes to the prohibited medications, a discussion of unusual circumstances when dosing with rescue medication was allowed, and clarification of the definition for stopping IMP. This protocol amendment may have impacted the study conduct. The fifth, sixth, and seventh protocol amendments defined IMP dosing for subjects less than two years old and enabled the analysis of the EU PDCO data set prior to completion of data collection in the US FDA data set. These protocol amendments did not impact study conduct overall. The protocol amendments and a high-level summary of the associated major changes to the protocol are summarized in Appendix 4.

Clinical and Statistical Conclusions on the Design and Conduct of Study KF5503/65

Study KF5503/65 meets evidentiary standards for an adequate and well-controlled study. The clinical and statistical teams identified no major concerns with the design and conduct of the study. The statistical reviewer stated,

> "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."

Refer to the statistical review of Yunfan Deng, PhD, dated June 9, 2023, with concurrence from Sue Jang Wang, PhD, for a full discussion of the statistical data included in these submissions.

Study Results

Compliance with Good Clinical Practices
The study was conducted according to Good Clinical Practice guidelines, all applicable local laws and regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Financial Disclosure
The Applicant submitted Form FDA 3454 certifying that all investigators listed did not participate in any financial arrangement with the sponsor of study KF5503/65. The Applicant also certified that they have made diligent efforts to communicate with (b) (6), a sub-investigator at site (b) (6) but were unsuccessful. (b) (6)
.

Office of Scientific Investigation Audits

Study KF5503/65 was audited for good clinical practice (GCP) inspections of two clinical investigator study sites based on large subject enrollment and no recent inspection history within the last two years. The clinical investigator study sites selected were Site US-006 (Dr. Allison K. Ross) and US-004 (Dr. Gregory B. Hammer). No significant GCP violations were observed. The audited study appears to have been conducted in compliance with GCP principles and regulations. The audited data for the two clinical investigator sites appear acceptable in support of the proposed indication. Refer to the Clinical Inspection Summary of John Lee, MD, with concurrence from Phillip Kronstein, MD and Jenn Sellers, MD, PhD, dated March 20, 2023.

Patient Disposition

Two hundred sixteen subjects (birth to less than 18 years of age) were enrolled in the study. One hundred eighty subjects were allocated to IMP (121 subjects allocated to tapentadol OS and 59 subjects allocated to placebo) and 175 subjects received IMP (119 subjects received tapentadol OS and 56 subjects received placebo). Of the 175 subjects receiving IMP, 150 subjects completed 12 hours of treatment (100 subjects (84%) in the tapentadol OS arm and 50 subjects (89%) in the placebo arm). Of the 150 subjects who completed 12 hours of treatment, 148 of these subjects (99 subjects in the tapentadol arm and 49 subjects in the placebo arm) attended the follow-up visit thereby completing the study. Overall, 104 subjects completed 24 hours of treatment (72 subjects (61%) in the tapentadol OS arm and 32 subjects (57%) in the placebo arm). Of the 104 subjects who completed 24 hours of treatment, all of the subjects attended the follow-up visit and completed the study. As per the study 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 of treatment with IMP.

Study completion rates were higher in subjects less than 2 years old (93% completing 12 hours and 87% completing 24 hours of treatment) as compared to subjects 2 years to less than 18 years old (85% completing 12 hours and 57% completing 24 hours of treatment).

Thirty-six subjects were enrolled but not allocated to IMP. Twenty-eight subjects either met an exclusion criterion or did not meet an inclusion criterion and one subject experienced an adverse event (AE). For the other seven subjects, four subjects had "withdrawal by subject" and three subjects had "other" as the reasons for discontinuation. "Withdrawal by subject" was defined as withdrawal of consent by the parent(s)/legal guardian or withdrawal of assent by the subject. "Other" was not further defined by the Applicant in the Clinical Study Report.

Five subjects were allocated to IMP but never treated with IMP. In the tapentadol OS arm, one subject either met an exclusion criterion or did not meet an inclusion criterion and one subject had "withdrawal by subject" as the reason for discontinuation. In the placebo arm one subject either met an exclusion criterion or did not meet an inclusion criterion, one subject had "withdrawal by subject", and one subject had "other" as the reasons for discontinuation.

Twenty-five subjects were treated with IMP but discontinued before completing 12 hours of treatment. Nineteen subjects in the tapentadol OS arm discontinued before completing 12 hours of treatment for the following reasons:

- AEs, four subjects
- "physician decision", four subjects
- Lack of efficacy, three subjects
- "recovery", three subjects
- "withdrawal by subject", three subjects
- "other", two subjects

Six subjects in the placebo arm discontinued before completing 12 hours of treatment for the following reasons:

- AEs, two subjects
- "withdrawal by subject", two subjects
- "other", one subject
- "physician decision", one subject

Forty-six subjects were treated with IMP but discontinued after 12 hours but before completing 24 hours of treatment. Twenty-eight subjects in the tapentadol OS arm discontinued after 12 hours but before 24 hours of treatment for the following reasons:

- "recovery", 12 subjects
- "physician decision", 10 subjects
- "other", three subjects
- Lack of efficacy, one subject
- AE, one subject

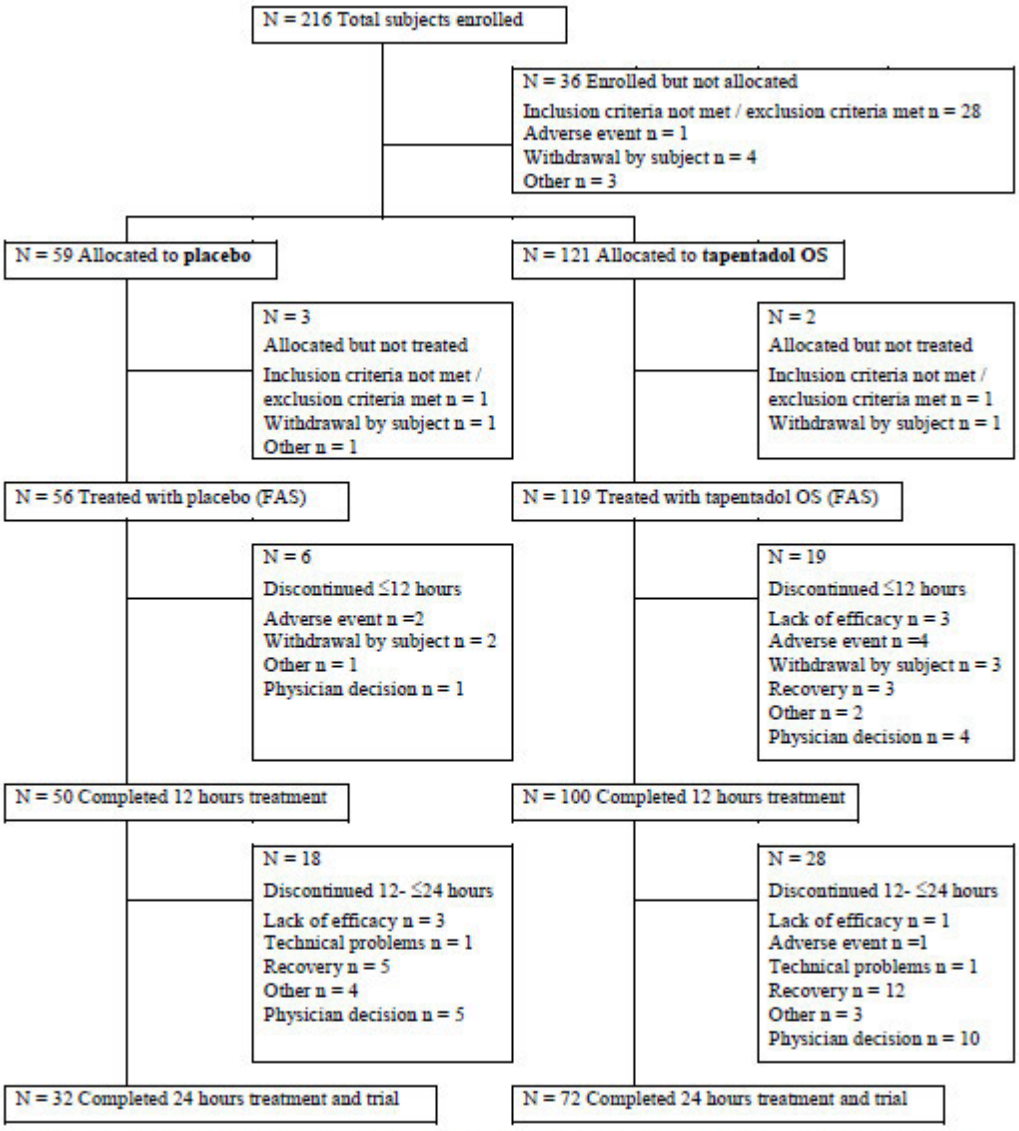
- Technical problems, one subject

Eighteen subjects in the placebo arm discontinued after 12 hours but before 24 hours of treatment for the following reasons:

- "recovery", five subjects
- "physician decision", five subjects
- "other", four subjects
- Lack of efficacy, three subjects
- Technical problems, one subject

The figure below graphically displays subject disposition in Study KF5503/65.

Figure 2 Subject 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: CSR for KF5503/65, Figure 2 on page 73/2254.

Protocol Deviations

In subjects ages 2 to less than 18 years old (N=160), 113 subjects (71%) had a protocol violation in the category of "missing essential data" where vital signs and oxygen saturation data were not captured according to the protocol, or ECGs, laboratory data, physical examination, relevant medical history, or NCA/PCA data as required by the protocol were missing. The next most frequent protocol deviations in this age group were violations of inclusion/exclusion criteria in 33 subjects (21%) and time schedule deviations in 30 subjects (19%) (see table below). The Applicant concluded that these protocol deviations did not affect the overall objectives of the study. The clinical team agrees with the Applicant's conclusion.

Table 6 Protocol Deviations – FAS-EU

Category	Placebo N = 52 n (%)	Tapentadol OS N = 108 n (%)	Overall N = 160 n (%)
Violation of Inclusion/Exclusion Criteria	12 (23.1)	21 (19.4)	33 (20.6)
Time schedule deviations	8 (15.4)	22 (20.4)	30 (18.8)
Non-compliance regarding intake of IMP	8 (15.4)	14 (13.0)	22 (13.8)
Inappropriate intake of concomitant medication	9 (17.3)	11 (10.2)	20 (12.5)
Missing essential data [a]	43 (82.7)	70 (64.8)	113 (70.6)
Other non-compliance	5 (9.6)	22 (20.4)	27 (16.9)

Subjects are counted only once per deviation category. A subject may be counted in more than one deviation category.

a) The category "missing essential data" includes protocol deviations where vital signs and oxygen saturation have not been captured according to protocol, ECGs, laboratory data, physical examination, relevant medical history, or NCA/PCA data as required by protocol are missing.

N = number of subjects in analysis set; n = number of subjects with major protocol deviation of the category; OS = oral solution; IMP = investigational medicinal product.

Source: CSR for KF5503/65, Table 7 on page 78/2254.

Demographics

One hundred sixty subjects were aged 2 to less than 18 years with 35 subjects (22%) in the 2 to less than 6 years age group, 47 subjects (29%) in the 6 to less than 12 years age group, and 78 subjects (49%) in the 12 to less than 18 years age group. There was an almost equal distribution of males (53%) and females (48%). One hundred thirty-one subjects (82%) were White, 14 subjects (9%) were Black or African-American, 8 subjects (5%) did not report race, and 5 subjects (3%) were Asian. One hundred eighteen subjects (74%) were not Hispanic or Latino, 30 subjects (19%) were Hispanic or Latino, and 12 subjects (8%) did not report ethnicity. The overall mean height was 144.4 cm, mean weight was 42.8 kg, and mean BMI was 18.92 kg/m^2 (see table below). The study population had good representation of females and adequate representation of Hispanics or Latinos, but limited representation of subjects of other races besides White. These demographic findings are fairly typical for clinical studies conducted in the United States; nevertheless, the limited racial diversity of the study population potentially hinders the generalizability of the study results.

Table 7 Demographic Data - 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)
Race			
American Indian of 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)
More than one race	0	2 (1.9)	2 (1.3)
Not Reported	3 (5.8)	5 (4.6)	8 (5.0)
Ethnicity			
Hispanic or Latino	9 (17.3)	21 (19.4)	30 (18.8)
Not Hispanic or Latino	38 (73.1)	32 (29.6)	47 (29.4)
Not Reported	25 (48.1)	53 (49.1)	78 (48.8)
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 (cm)			
Mean (SD)	143.3 (29.5)	145.0 (27.7)	144.4 (28.2)
Median (Q1,Q3)	153.0 (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 (27.7)	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

Source: CSR for KF5503/65, Table 11 on page 82/2254.

Fifteen subjects were less than 2 years of age with three subjects (20%) in the birth to less than 30 days age group, three subjects (20%) in the 30 days to less than 6 months age group, and nine subjects (60%) in the 6 months to less than 2 years age group. There was an almost equal distribution of males (53%) and females (47%). Fourteen subjects (93%) were White and one subject (7%) was Asian. Thirteen subjects (87%) were not Hispanic or Latino and two subjects (13%) did not report ethnicity (see table below). The very small sample size and the inclusion of only one non-White subject prevents one from drawing any conclusions about the efficacy (and safety) of tapentadol OS in subjects less than two years of age.

Table 8 Demographic Data - 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)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	1 (9.1)	1 (6.7)
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	4 (100)	10 (90.9)	14 (93.3)
Other	0	0	0
Not Reported	0	0	0
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)
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)

Source: CSR for KF5503/65, Table 12 on page 83/2254.

Other Baseline Characteristics

Of the subjects ages 2 to less than 18 years old who were allocated to treatment, 109 subjects (75 subjects on tapentadol and 34 subjects on placebo) received morphine and 51 subjects (33 subjects on tapentadol and 18 subjects on placebo) received hydromorphone as the supplemental opioid analgesic medication. There were no significant differences in the amount of morphine or hydromorphone taken within 24 hours prior to first IMP administration or in the duration of surgery between the tapentadol OS and placebo groups. There was a difference in the maximum time between the end of surgery and the first intake of IMP between the two treatment arms. This finding was due to one subject in the tapentadol arm who underwent a laparoscopic ileocecectomy for fistulizing Crohn's disease that required a prolonged recovery period before meeting the eligibility criteria of the study protocol (see table below).

Table 9 General Baseline Characteristics – FAS-EU

	Placebo N=52	Tapentadol OS N=108	Overall N=160
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 [minutes]			
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	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

[a] Documented only within 24 hours prior to first IMP administration; data is presented in morphine equivalents in mg/kg.
Source: CSR for KF5503/65, Table 13 on page 84/2254.

Medical History

Prior and Concomitant Diseases

A wide range of prior diseases were reported by subjects ages birth to less than 18 years old. None of reported prior diseases was predominantly present in the study population. There were no significant differences in the frequency of prior diseases between the tapentadol OS and placebo arms in subjects ages 2 to less than 18 years old. In subjects less than 2 years old, the study population is too small to draw any conclusions.

In subjects ages 2 to less than 18 years old, the most frequently reported concomitant diseases were in the following System Organ Class (SOC): congenital, familial and genetic disorders (37.5%), musculoskeletal and connective tissue disorders (23.8%), and gastrointestinal disorders (12.5%). The most frequently reported Preferred Term (PT) was scoliosis (15%). There were no significant differences in the frequency of concomitant diseases between the tapentadol OS and placebo arms.

Prior and Concomitant Medications

The most commonly used prior medications in subjects ages 2 to less than 18 years old were analgesics (99.4%), blood substitutes and perfusion solutions (38.8%), psycholeptics (35.6%), and antibacterials for systemic use (31.3%). These medications are regularly used in the post-operative setting. There were differences in prior medication use between the tapentadol and placebo arm; however, these differences did not appear to impact the study outcomes.

The most commonly used concomitant medications in subjects ages 2 to less than 18 years old were analgesics (95.6%), antibacterials for systemic use (71.9%), blood substitutes and perfusion solutions (69.4%), anti-inflammatory and anti-rheumatic products (41.9%), drugs for constipation (38.1%), and drugs for acid-related disorders (31.9%). These medications are

regularly used in the post-operative setting. As mentioned for the prior medications, there were differences in concomitant medication use between the tapentadol and placebo arms; however, these differences did not appear to impact the study outcomes.

Supplemental Opioid Analgesic Medication and Administration

In subjects ages 2 to less than 18 years old, the most common type of opioid analgesia used was morphine (70.6% of subjects). PCA (60.6%) was used more often than NCA (36.9%). The frequency of PCA and NCA use corresponded with the age distribution of the subjects. The type of opioid used for PCA was morphine in 59.8% of subjects and hydromorphone in 40.2% of subjects. The type of opioid used for NCA was morphine in 88.1% of subjects and hydromorphone in 11.9% of subjects. A background infusion of opioid was used in 33.8% of subjects. The use of morphine or hydromorphone, the use of PCA or NCA, and the use of a background infusion was similar between the tapentadol OS and placebo treatment groups (see table below).

Table 10 Type of Supplemental Opioid and Administration Used – FAS-EU

Parameter	Category	Placebo N = 52 n (%)	Tapentadol OS N = 108 n (%)	Overall N = 160 n (%)
Type of opioid analgesia used (eCRF)	Hydromorphone	18 (34.6)	28 (25.9)	46 (28.8)
	Morphine	34 (65.4)	79 (73.1)	113 (70.6)
	Missing	0	1 (0.9)	1 (0.6)
Type of administration	NCA	19 (36.5)	40 (37.0)	59 (36.9)
	PCA	33 (63.5)	64 (59.3)	97 (60.6)
	Missing	0	4 (3.7)	4 (2.5)
Type of opioid analgesia used for NCA	NCA	19 (100)	40 (100)	59 (100)
	-Hydromorphone [a]	4 (21.1)	3 (7.5)	7 (11.9)
	-Morphine [a]	15 (78.9)	37 (92.5)	52 (88.1)
Type of opioid analgesia used for PCA	PCA	33 (100)	64 (100)	97 (100)
	-Hydromorphone [b]	14 (42.4)	25 (39.1)	39 (40.2)
	-Morphine [b]	19 (57.6)	39 (60.9)	58 (59.8)
Background infusion	Yes	15 (28.8)	39 (36.1)	54 (33.8)
	No	37 (71.2)	69 (63.9)	106 (66.3)
Type of opioid analgesia used for background infusion	Background infusion	15 (100)	39(100)	54 (100)
	-Hydromorphone [c]	1 (6.7)	3 (7.7)	4 (7.4)
	-Morphine [c]	13 (86.7)	33 (84.6)	46 (85.2)
	-Other [c]	1 (6.7)	3 (7.7)	4 (7.4)

a) The denominator for the calculation of the percentage was the total number of subjects on NCA in the respective treatment groups.

b) The denominator for the calculation of the percentage was the total number of subjects on PCA in the respective treatment groups.

c) The denominator for the calculation of the percentage was the total number of subjects on background infusion in the respective treatment groups.

N = number of subjects in analysis set; n = number of subjects; OS = oral solution; NCA = Nurse controlled analgesia; PCA = Patient controlled analgesia; eCRF = electronic case report form.

Source: CSR for KF5503/65, Table 23 on page 97/2254.

Surgery

Subjects ages 2 to less than 18 years old underwent many different types of surgery. The most common surgeries in this age group were spinal fusion surgery (22 subjects [13.8%]), urethral

repair (14 subjects [8.8%]), maxillofacial operation (12 subjects [7.5%]), and thoracic operation (10 subjects [6.3%]).

Baseline Pain Intensity

In subjects ages 2 to less than 18 years old, there were no significant differences in baseline pain intensity between the tapentadol arm and the placebo arm for any of the three pain scales; however, there were differences in baseline pain intensity between age groups. Baseline pain intensity was lowest in the youngest age group (2 to less than 6 years) using the FLACC [mean (SD) pain intensity 2.5 (2.60) in the placebo group and 2.7 (2.40) in the tapentadol OS group]. Baseline pain intensity in subjects ages 6 to less than 12 years old using the FPS-R [mean (SD) pain intensity 3.9 (3.28) in the placebo group and 4.3 (2.69) in the tapentadol OS group] was higher than baseline pain intensity in the youngest age group. Baseline pain intensity in subjects ages 12 to less than 18 years old using the VAS [mean (SD) pain intensity 42.2 (31.42) in the placebo arm and 38.4 (24.34) in the tapentadol OS arm] was higher than baseline pain intensity in the youngest age group and comparable to baseline pain intensity in subjects ages 6 to less than 12 years old. Subjects ages 2 to less than 6 years old started with lower pain scores at baseline than subjects ages 6 to less 12 years old and 12 to less than 18 years old. It appears that patients ages 2 to less than 6 years old had a mean baseline pain score that was mild in intensity while patients ages 6 years and older had a mean baseline pain score that was mild to moderate in intensity. This difference in baseline pain intensity between age groups could be attributed to the pain scales used to evaluate pain intensity. Pain intensity in subjects ages 2 to less than 6 years old (and those subjects unable to self-report using the FPS-R or VAS) was evaluated using an observational scale (the FLACC), whereas pain intensity in subjects ages 6 years and older was evaluated using self-reporting scales (FPS-R and VAS). This difference in baseline pain intensity between age groups likely confounds the interpretability of the study results.

Treatment Compliance

The exact IMP administration times were to have been recorded in the electronic CRF and the source documents. The IMP was to have been administered in the controlled environment of a clinical research site with direct observation of the administration of IMP by trial staff to ensure compliance with trial requirements. The bottles of oral solution (tapentadol or placebo) were to have been weighed to determine the amount of drug product used and the information was to have been documented in the drug accountability log. For subjects ages 2 to less than 18 years old, 102 out of 108 subjects (94.4%) in the tapentadol arm and 51 out of 52 subjects (98.1%) in the placebo arm were within range of expected cumulative doses.

Efficacy Results

Primary and Key Secondary Endpoints

Table 11 presents the efficacy results for the primary endpoint for the US FDA (and the secondary endpoint for the EU PDCO) 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 first administration of IMP

(p=0.0404). The estimated [least square] mean (standard error [SE]) difference between tapentadol OS and placebo was -0.05 (0.02) mg/kg body weight of morphine equivalents (95% CI [-0.09, -0.00]).

Table 11 Analysis of the Amount of Supplemental Opioid Analgesic Medication Used Within 12 Hours After First IMP Intake – FAS-EU

Statistic	Placebo N = 52	Tapentadol OS N = 108
Missing	0	0
N	52	108
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
LSmean (SE)	0.13 (0.02)	0.08 (0.01)
95% CI of LSmean	(0.09, 0.17)	(0.05, 0.11)
Difference tapentadol-placebo (SE)		-0.05 (0.02)
95% CI of difference		(-0.09, -0.00)
p-value [a]		0.0404

p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance.

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: CSR for KF5503/65, Table 28 on page 103/2254.

Table 12 presents the efficacy results for the primary endpoint for the EU PDCO (and the secondary endpoint for the US FDA) 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 24 hours after first IMP intake in the FAS-EU population (p=0.0154). The estimated (least square) mean (SE) difference between tapentadol OS and placebo was -0.1 (0.04) mg/kg body weight of morphine equivalents (95% CI [-0.18, -0.02]).

Table 12 Analysis of the Amount of Supplemental Opioid Analgesic Medication Used Within 24 Hours After First IMP Intake – FAS-EU

Statistic	Placebo N = 52	Tapentadol OS N = 108
Missing	0	0
N	52	108
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
LSmean (SE)	0.24 (0.03)	0.14 (0.03)
95% CI of LSmean	(0.17, 0.30)	(0.09, 0.19)
Difference tapentadol-placebo (SE)		-0.10 (0.04)
95% CI of difference		(-0.18, -0.02)
p-value [a]		0.0154

p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance.

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: CSR for KF5503/65, Table 27 on page 102/2254.

Sensitivity Analyses

Table 13 presents the results of sensitivity analyses using the per protocol analysis set, the placebo mean imputation, and the treatment mean imputation to impute missing values for the FAS-EU population for the US FDA primary endpoint. The results generally support the primary analysis results.

Table 13 Sensitivity Analyses of the Amount of Supplemental Opioid Analgesic Medication Used Within 12 Hours of First IMP Intake - FAS-EU

Sensitivity analysis	Statistic	Placebo	Tapentadol OS
Per Protocol Set	N	46	94
	LSmean (SE)	0.13 (0.02)	0.08 (0.02)
	95% CI of LSmean	(0.09, 0.17)	(0.05, 0.11)
	Difference tapentadol - placebo (SE)		- 0.05 (0.02)
	95% CI of difference		(-0.09, 0.00)
	p-value [a]		0.0492
Placebo Mean	N	52	108
	LSmean (SE)	0.12 (0.02)	0.08 (0.01)
	95% CI of LSmean	(0.09, 0.16)	(0.06, 0.11)
	Difference tapentadol - placebo (SE)		-0.04 (0.02)
	95% CI of difference		(-0.08, 0.00)
	p-value [a]		0.0613
Treatment Mean	N	52	108
	LSmean (SE)	0.12 (0.02)	0.08 (0.01)
	95% CI of LSmean	(0.09, 0.16)	(0.05, 0.10)
	Difference tapentadol - placebo (SE)		-0.04 (0.02)
	95% CI of difference		(-0.08, -0.00)
	p-value [a]		0.0424

a) p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance

The ANOVA (analysis of variance) 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; SE = standard error; CI = confidence interval; LS = least square.

Source: CSR for KF5503/65, Table 29 on page 104/2254.

Table 14 presents the results of sensitivity analyses using the per protocol analysis set, the placebo mean imputation, and the treatment mean imputation to impute missing values for the FAS-EU population for the EU PDCO primary endpoint. The results generally support the primary analysis results.

Table 14 Sensitivity Analyses of the Amount of Supplemental Opioid Analgesic Medication Used Within 24 Hours of First IMP Intake - FAS-EU

Sensitivity Analysis	Statistic	Placebo	Tapentadol OS
Per Protocol Set	N LSmean (SE) 95% CI of LSmean Difference tapentadol – placebo (SE) 95% CI of difference p-value[a]	46 0.23 (0.03) (0.16, 0.30)	94 0.13 (0.03) (0.08, 0.19) -0.10 (0.04) (-0.18, -0.01) 0.0209
Placebo Mean	N LSmean (SE) 95% CI of LSmean Difference tapentadol – placebo 95% CI of difference p-value[a]	52 0.21 (0.03) (0.16, 0.27)	108 0.14 (0.02) (0.09, 0.18) -0.08 (0.04) (-0.15, -0.01) 0.0253
Treatment Mean	N LSmean (SE) 95% CI of LSmean Difference tapentadol – placebo 95% CI of difference p-value[a]	52 0.21 (0.03) (0.15, 0.27)	108 0.12 (0.02) (0.08, 0.17) -0.09 (0.03) (-0.16, -0.02) 0.0108

[a] p-value for testing superiority of tapentadol compared to placebo based on analysis of variance.
Note: The ANOVA (analysis of variance) 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.
CI = confidence interval; LS = least square; N = number of subjects; SE = standard error
Source: CSR for KF5503/65, Tables 15.2.2.1.1, 15.2.2.1.2, and 15.2.2.1.3 on pages 441 – 443.

Table 15 presents the results of additional sensitivity analyses performed for the US FDA primary endpoint, as agreed with the US FDA, for the FAS-EU population using a different approach to determine imputation for subjects based on the reason why they stopped treatment. The results did not demonstrate statistically significant differences between the two treatments except for the analysis using treatment mean imputation. However, the estimated least square means (SE) for each treatment arm were similar to the least square means (SE) provided in Table 11 and generally support the primary analysis results.

Table 15 Additional Sensitivity Analyses as Agreed with the US FDA – FAS EU

Sensitivity analysis	Statistic	Placebo	Tapentadol OS
Primary Analysis	N	52	108
	LSmean (SE)	0.13 (0.02)	0.09 (0.02)
	95% CI of LSmean	(0.09, 0.18)	(0.06, 0.13)
	Difference tapentadol - placebo (SE)		-0.04 (0.03)
	95% CI of difference		(-0.09, 0.01)
	p-value [a]		0.1215
Per Protocol Set	N	46	94
	LSmean (SE)	0.13 (0.02)	0.08 (0.02)
	95% CI of LSmean	(0.09, 0.17)	(0.05, 0.11)
	Difference tapentadol - placebo (SE)		-0.05 (0.02)
	95% CI of difference		(-0.10, 0.00)
	p-value [a]		0.0508
Placebo Mean	N	52	108
	LSmean (SE)	0.12 (0.02)	0.09 (0.01)
	95% CI of LSmean	(0.09, 0.16)	(0.06, 0.11)
	Difference tapentadol - placebo (SE)		-0.04 (0.02)
	95% CI of difference		(-0.08, 0.00)
	p-value [a]		0.0743
Treatment Mean	N	52	108
	LSmean (SE)	0.12 (0.02)	0.08 (0.01)
	95% CI of LSmean	(0.09, 0.16)	(0.05, 0.11)
	Difference tapentadol - placebo (SE)		-0.04 (0.02)
	95% CI of difference		(-0.08, 0.00)
	p-value [a]		0.0458

The ANOVA (analysis of variance) 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..

a) p-value for testing superiority of Tapentadol compared to Placebo based on analysis of variance. Imputation rule: For subjects who discontinued from treatment prior to 12 hours after first IMP intake for reasons other than "Opioid analgesic medication is no longer needed" the amount of supplemental opioid analgesic medication was extrapolated linearly. Else the amount of supplemental opioid analgesic medication was used as intake until time of discontinuation.

Source: CSR for KF5503/65, Table 30 on page 106/2254.

Other Secondary Endpoints

Supplemental Opioid Analgesic Medication Use Analyzed by Age Subgroup

The table below presents an analysis of the amount of supplemental opioid analgesic medication (SOAM) used within the first 12 and 24 hours by age subgroup. There was no difference in the amount of SOAM used within the first 12 hours between the placebo and tapentadol OS groups in the 2 to less than 6 years age group. Comparatively, there was more SOAM used in the placebo group than in the tapentadol OS group in the 6 to less than 12 years and the 12 to less than 18 years age groups. There was more SOAM used within the first 24 hours in the tapentadol OS group than in the placebo group in the 2 to less than 6 years age group. Comparatively, there was more SOAM used within the first 24 hours in the placebo group than in the tapenadol OS group in the 6 to less than 12 years and the 12 to less than 18 years age groups. These findings demonstrate that tapentadol was no better than placebo for

acute pain management in pediatric patients ages 2 to less than 6 years, whereas tapentadol was better than placebo for acute pain management in pediatric patients ages 6 to less than 18 years.

Table 16 Amount of Supplemental Opioid Analgesic Medication Used Within the First 12 and 24 Hours by Age Subgroup – FAS-EU

	Placebo		Tapentadol OS	
Age group	**n**	**Mean (SD) mg/kg**	**n**	**Mean (SD) mg/kg**
12 hours				
2 years to <6 years	12	0.04 (0.04)	23	0.04 (0.06)
6 years to <12 years	15	0.10 (0.12)	32	0.05 (0.09)
12 years to <18 years	25	0.21 (0.25)	53	0.14 (0.13)
24 hours				
2 years to <6 years	12	0.05 (0.06)	23	0.06 (0.10)
6 years to <12 years	15	0.17 (0.23)	32	0.10 (0.16)
12 years to <18 years	25	0.40 (0.42)	53	0.23 (0.22)

Supplemental opioid analgesia was expressed in mg/kg of morphine IV-equivalents.

FAS = Full Analysis Set; n = number of subjects; SD = standard deviation; OS = oral solution.

Source: CSR for KF5503/65, Table 32 on page 108/2254.

Supplemental Opioid Analgesic Medication Use Analyzed by Other Subgroups

The Applicant performed an analysis of SOAM used within the first 24 hours after IMP intake by gender, race, geographical region, administration type (NCA versus PCA), and SOAM type (morphine versus hydromorphone). The statistical reviewer performed an analysis of SOAM used within the first 12 hours after IMP intake by age, gender, race, geographical region, and administration type (NCA or PCA). The table below presents the results of these analyses. More SOAM was used by the older age groups (6 years to less than 12 years old and 12 years to less than 18 years old) than the younger age group (2 years to less than 6 years old). More SOAM was used by females than males. More SOAM was used in the US than in Europe. More SOAM was used by PCA than NCA. No meaningful conclusions can be made for the analysis by race given the predominance of White subjects and the very small number of subjects of other races. For almost all of these analyses, SOAM use at 12 and 24 hours was numerically higher in the placebo group than in the tapentadol group and supportive of the results of the primary analysis. However, for the analyses of SOAM use by age group, the results for the 2 years to less than 6 years age group demonstrated either comparable SOAM use between the treatment groups or more SOAM use in the tapentadol group and were not consistent with the results of the primary analysis.

Table 17 Supplemental Opioid Analgesic Medication Use by Subgroups – Age, Gender, Race, Geographical Region, and Administration Type (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.

Source: Statistical Review, Table 13 on page 23/26.

Supplemental Opioid Analgesic Medication Use Analyzed for Each Age-Defined Pain Scale

The use of SOAM was analyzed by pain scale used to assess pain intensity for subjects 2 to less than18 years of age. The table below presents the results of this analysis. Subjects assessed using the FLACC generally used the lowest amounts of SOAM. There was slightly higher SOAM use reported in the tapentadol OS group than in the placebo group. In subjects

assessed with the FPS-R pain scale, there was higher SOAM use reported in the placebo group than in the tapentadol OS group. In subjects assessed with the VAS pain scale, there was statistically significantly higher SOAM use reported in the placebo group than in the tapentadol OS group. It appears that subjects whose pain was assessed using the FLACC used less SOAM than subjects whose pain was assessed using the FPS-R or VAS pain scales. It also appears that there was more use of SOAM in the tapentadol OS group than in the placebo group for subjects whose pain was assessed using the FLACC. Comparatively, there was more use of SOAM in the placebo group than in the tapentadol OS group for subjects whose pain was assessed using the FPS-R or VAS pain scales. These differences in SOAM use by age-defined pain scale could be attributed to the pain scales used to evaluate pain intensity. As mentioned earlier in the review, an observational scale (the FLACC) was used to evaluate pain in subjects ages 2 to less than 6 years old and those subjects unable to self-report, whereas self-reporting scales (the FPS-R and the VAS) were used to evaluate pain in subjects ages 6 years and older.

Table 18 Amount of Supplemental Opioid Analgesic Medication Used Within 24 Hours after IMP Intake Analyzed by Pain Scale – FAS-EU

Pain scale	Statistic	Placebo	Tapentadol OS
Face, Legs, Activity, Cry, Consolability scale	N	13	23
	LSmean (SE)	0.06 (0.02)	0.08 (0.02)
	95% CI of LSmean	(0.01, 0.11)	(0.04, 0.12)
	Difference tapentadol - placebo (SE)		0.02 (0.03)
	95% CI of difference		(-0.04, 0.08)
	p-value [a]		0.4822
Faces Pain Scale–Revised	N	14	32
	LSmean (SE)	0.22 (0.05)	0.12 (0.03)
	95% CI of LSmean	(0.12, 0.31)	(0.05, 0.18)
	Difference tapentadol - placebo (SE)		-0.10 (0.05)
	95% CI of difference		(-0.21, 0.01)
	p-value [a]		0.0665
Visual analog scale	N	25	53
	LSmean (SE)	0.40 (0.06)	0.24 (0.04)
	95% CI of LSmean	(0.28, 0.52)	(0.16, 0.32)
	Difference tapentadol - placebo (SE)		-0.16 (0.07)
	95% CI of difference		(-0.31, -0.02)
	p-value [a]		0.0292

a) p-value for testing superiority of tapentadol compared to placebo based on analysis of covariance.

N = number of subjects; SE = standard error; CI = confidence interval; LS = least square; IMP = investigational medicinal product; OS = oral solution; FAS = Full Analysis Set.

Source: CSR for KF5503/65, Table 31 on page 107/2254.

Supplemental Opioid Analgesic Medication Use from 24 Hours to 96 Hours after First Dose of IMP

The use of SOAM was analyzed in 12-hour intervals from 24 hours to 96 hours after the first dose of IMP for subjects 2 to less than 18 years of age. The mean (SD) amount of SOAM used from 24 hours to 36 hours in the FAS-EU group was numerically higher in the placebo group (0.14 [0.21] mg/kg) than in the tapentadol OS group (0.08 [0.09] mg/kg). For each 12-hour interval between 36 hours and 60 hours after the first dose of IMP, there was no numerical difference in the mean amount of SOAM used between the placebo group and the tapentadol OS group. The mean amount of SOAM used from 60 hours to 72 hours was numerically slightly higher in the tapentadol OS group (0.06 [0.08] mg/kg) than in the placebo group (0.03 [0.07] mg/kg). There was no SOAM used in either treatment group after 72 hours. The decreased use of SOAM over time and the more equal use of SOAM between treatment groups over time can be explained based on the natural healing process with reduced need for analgesia as more time passes after surgery.

Area Under the Pain Curve (AUPC) up to 12 Hours and 24 Hours

The AUPC was calculated using the pain intensity difference between baseline and subsequent pain assessments with a larger AUPC reflecting a higher improvement in pain values. The table below presents the AUPC up to 12 hours and up to 24 hours after first IMP intake in the FAS-EU analysis set using age-appropriate pain scales (FLACC for subjects ages birth to less than 6 years or in older subjects who are not able to report their pain using the other scales, FPS-R for subjects ages 6 years to less than 12 years, and VAS for subjects ages 12 years to less than 18 years). For the FLACC scale, there was no significant difference in the mean AUPC up to 12 hours and up to 24 hours between the placebo group and the tapentadol OS group. For the FPS-R and the VAS, there was a significant difference in the mean AUPC up to 12 hours and up to 24 hours between the placebo group and the tapentadol OS group. For the FPS-R, the mean (SD) AUPC up to 12 hours and the mean (SD) AUPC up to 24 hours were larger in the tapentadol OS group (12.69 [20.87] and 26.20 [141.26]) than in the placebo group (1.51 [23.43] and 4.60 [43.37]). For the VAS, the mean (SD) AUPC up to 12 hours and the mean (SD) AUPC up to 24 hours were larger in the tapenadol OS group (100.36 [222.39] and 217.01 [446.49]) than in the placebo group (64.77 [182.42] and 118.84 [381.75]). These findings indicate no notable difference in pain relief between tapentadol OS and placebo for subjects assessed using the FLACC (primarily subjects less than six years of age), but greater pain relief with tapentadol OS than with placebo for subjects assessed using the FPS-R and the VAS (primarily subjects six years of age and older). These differences in pain relief between treatment groups in subjects assessed using the FLACC versus subjects assessed using the FPS-R and the VAS could be attributed to the pain scales used to evaluate pain intensity. Again, the FLACC is an observational pain scale that was used to evaluate pain in subjects ages 2 to less than 6 years old (and those subjects unable to self-report), whereas the FPS-R and the VAS are self-reporting pain scales that were used to evaluate pain in subjects ages 6 years and older.

Table 19 Area Under the Pain Curve Based on 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 (Q1, Q3)	16.83 (1.88, 23.50)	29.49 (3.72, 47.10)	11.75 (0.00, 33.10)	35.98 (0.00, 71.61)
	Min - Max	-1.6 - 70.8	-4.8 - 142.8	-19.4 - 54.3	-31.4 - 97.0
	95 % CI	(5.60, 29.60)	(11.41, 63.09)	(7.75, 24.88)	(17.74, 52.15)
FPS-R	n	14	14	31	31
	Missing	0	0	1	1
	Mean (SD)	1.51 (23.43)	4.60 (43.37)	12.69 (20.87)	26.20 (41.26)
	Median (Q1, Q3)	0.00 (-12.91, 15.52)	3.73 (-21.00, 39.52)	11.15 (-0.51, 23.67)	24.54 (-4.00, 55.95)
	Min - Max	-36.9 - 47.0	-83.4 - 72.2	-19.3 - 61.8	-39.7 - 114.0
	95 % CI	(-12.02, 15.04)	(-20.44, 29.64)	(5.03, 20.34)	(11.07, 41.34)
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 (Q1, Q3)	40.83 (-33.71, 152.84)	62.74 (-82.38, 297.65)	60.29 (-49.10, 235.36)	152.38 (-89.81, 473.79)
	Min - Max	-406.5 - 449.0	-617.1 - 918.9	-365.2 - 819.7	-574.3 - 1601.1
	95 % CI	(-10.53, 140.07)	(-38.73, 276.42)	(39.06, 161.66)	(93.94, 340.07)

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; Qx = quartile; min = minimum; max = maximum; CI = confidence interval; OS = oral solution; VAS = visual analog scale; IMP = investigational medicinal product.

Source: CSR for KF5503/65, Table 37 on page 116/2254.

Clinical Global Impression of Change (CGIC)

The CGIC was completed by the investigator/clinician after completion of the double-blind IMP treatment period. The table below presents the descriptive statistics for CGIC at the end of treatment in the FAS-EU analysis set. When looking at the percentage of CGIC responders versus non-responders in each treatment group, there was no significant numerical difference in the percentage of subjects classified as CGIC responders and CGIC non-responders between the placebo group and the tapentadol OS group. This finding demonstrates that pain was well-controlled in both treatment groups with the availability of rescue opioid via NCA or PCA for all subjects.

Table 20 Clinical Global Impression of Change at End of Treatment – FAS-EU

Category	Placebo N = 52 n (%)	Tapentadol OS N = 108 n (%)
Very much improved	12 (23.1)	15 (13.9)
Much improved	22 (42.3)	58 (53.7)
Minimally improved	8 (15.4)	18 (16.7)
No change	4 (7.7)	11 (10.2)
Minimally worse	2 (3.8)	3 (2.8)
Much worse	1 (1.9)	1 (0.9)
Very much worse	0 (0.0)	0 (0.0)
Missing	3 (5.8)	2 (1.9)
Clinical Global Impression of Change responder [a]	34 (65.4)	73 (67.6)
Clinical Global Impression of Change non-responder [b]	15 (28.8)	33 (30.6)

a) Clinical Global Impression of Change responder category included categories "Very much improved" and "Much improved".

b) Clinical Global Impression of Change non-responder category included "Minimally improved", "No change", "Minimally worse", "Much worse", and "Very much worse".

N = number of subjects in analysis set; n = number of subjects; OS = oral solution; FAS = Full Analysis Set.

Source: CSR for KF5503/65, Table 34 on page 111/2254.

Patient Global Impression of Change (PGIC)

The PGIC was completed by subjects/parents/legal guardians after the completion of the double-blind IMP treatment period. The table below presents the descriptive statistics for PGIC at the end of treatment in the FAS-EU analysis set. Similar to the results for the CGIC, there was no significant numerical difference in percentage of subjects classified as GCIG responders and CGIC non-responders between the placebo group and the tapentadol OS group. As stated previously, this finding demonstrates that pain was well-controlled in both treatment groups with the availability of rescue opioid via NCA or PCA for all subjects.

Table 21 Patient Global Impression of Change at End of Treatment – FAS-EU

Category	Placebo N = 52 n (%)	Tapentadol OS N = 108 n (%)
Very much improved	11 (21.2)	16 (14.8)
Much improved	23 (44.2)	53 (49.1)
Minimally improved	12 (23.1)	21 (19.4)
No change	3 (5.8)	13 (12.0)
Minimally worse	0 (0.0)	1 (0.9)
Much worse	0 (0.0)	1 (0.9)
Very much worse	0 (0.0)	0 (0.0)
Missing	3 (5.8)	3 (2.8)
Patient global impression of change responder [a]	34 (65.4)	69 (63.9)
Patient global impression of change non-responder [b]	15 (28.8)	36 (33.3)

a) Patient Global Impression of Change responder category included categories "Very much improved" and "Much improved".

b) Patient Global Impression of Change non-responder category included "Minimally improved", "No change", "Minimally worse", "Much worse", and "Very much worse".

FAS = Full Analysis Set; N = number of subjects in analysis set; n = number of subjects; OS = oral solution.

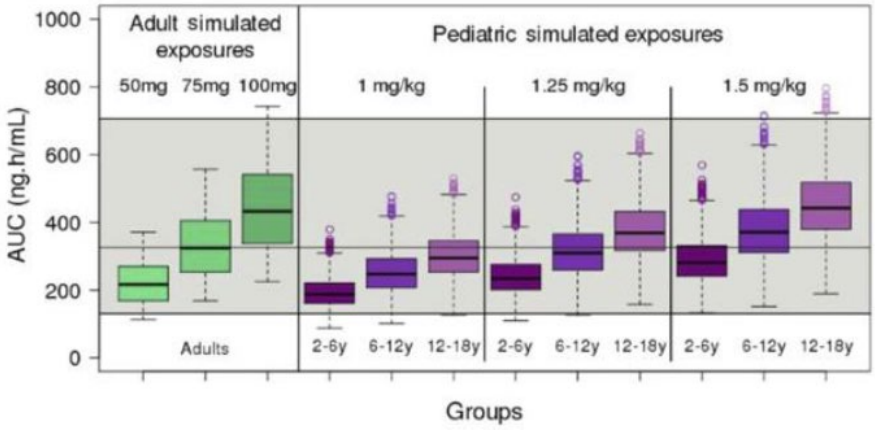
Source: CSR for KF5503/65, Table 35 on page 112/2254.

Efficacy Conclusions

The Applicant has provided substantial evidence of effectiveness for tapentadol in pediatric patients ages six years and older. The results from Study KF5503/65 demonstrate that tapentadol OS at a dose of 1.25 mg/kg every 4 hours is more effective than placebo for management of acute pain in subjects 6 years and older. However, the Applicant has not provided substantial evidence of effectiveness for tapentadol in pediatric patients less than 6 years old. The results of a subgroup analysis of SOAM use by age group from Study KF5503/65 demonstrate that tapentadol OS at a dose of 1.25 mg/kg every 4 hours is not more effective than placebo at 12 hours and is less effective than placebo at 24 hours for management of acute pain in pediatric patients 2 years to less than 6 years old.

Tapentadol's lack of efficacy in pediatric patients 2 years to less than 6 years old can be explained based on the PK simulation data. As seen in the figure below, a tapentadol OS dose of 1.25 mg/kg every 4 hours in pediatric patients ages 2 to less than 6 years yields a PK exposure that is lower than the PK exposure in pediatric patients ages 6 years to less than 18 years and comparable to the PK exposure in adults administered the lowest efficacious dose of tapentadol (50 mg).

Figure 3 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, 1.5 mg/kg q4h of tapentadol (from Figure 4 of Watson, et al., J Pain Res 2019:12;2835-2850)



Source: Sponsor's email response to an information request, dated February 16, 2023.

Additionally, we already know that, for certain drug classes, infants and young children may need higher mg/kg doses than the older pediatric population or adults due to differences in pediatric physiology and drug pharmacokinetics. The clinical team hypothesizes that pediatric patients ages two to less than six years may need a higher mg/kg dose of tapentadol OS than 1.25 mg/kg to have adequate analgesic effect. The clinical team concludes that the benefits of treating pediatric patients 2 years to less than 6 years of age with a potentially subtherapeutic dose of tapentadol OS do not outweigh the known risks associated with use of opioid analgesics. Therefore, the clinical team recommends approval of tapentadol OS for acute pain management in pediatric patients ages 6 years and older.

9.Safety

9.1 Safety Review Approach

Safety data for these submissions consisted of individual safety data from the open-label, single-dose, PK studies (KF5503/59, KF5503/68, and KF5503/72) and the double-blind, placebo-controlled, efficacy and safety study (KF5503/65). The Applicant presented the safety data from each study separately and, for Study KF5503/65, presented the safety data in pediatric patients 2 to less than 18 years old separately from the safety data in pediatric patients from birth to less than 2 years old. The clinical team evaluated the safety information presented in the CSRs, datasets, and CRFs. Given the similarities in study design and patient population, the clinical team pooled the safety data from the open-label, single-dose, PK studies. However, because of differences in study design, the clinical team evaluated the safety data from the controlled, multiple-dose, efficacy study (KF5503/65) separately. The clinical team focused the safety review on Study KF5503/65 because the study evaluated tapentadol OS at a dose of 1.25 mg/kg every 4 hours for up to 72 hours in post-surgical pediatric patients anticipated to have moderate to severe acute post-operative pain which is the recommended dose being considered for inclusion in the tapentadol label.

9.2 Review of Safety Database

Studies KF5503/59, KF5503/68, KF5503/72

The safety analysis set consisted of all subjects who received any amount of tapentadol OS. The safety analysis set was used for safety data summaries.

Study KF5503/65

The safety set consisted of all treated subjects in the required age ranges for the EU PDCO (2 to less than 18 years) and the US FDA (birth to less than 17 years). A patient was considered treated if administered any amount of IMP. The safety set was used for safety data summaries and was analyzed as treated.

Exposure

All Conducted Studies (Studies KF5503/59, KF5503/68, KF5503/72, and KF5503/65)

The table below summarizes the number and age range of subjects exposed to either single or multiple doses of tapentadol OS and whether comparator was used in all studies conducted in support of the pediatric program for immediate-release tapentadol.

Table 22 Number of Subjects, Age Ranges, and Tapentadol OS Exposure in All Conducted Studies

Study	Number of Subjects Exposed	Age Range	Tapentadol OS Dose	Comparator
KF5503/59	44	6 to < 18 years	1 mg/kg (max 75 mg) single dose	None
KF5503/68	66	2 to < 18 years	1 mg/kg (max 75 mg) single dose	None
KF5503/72	8	6 months to < 2 years	0.75 mg/kg single dose	None
	6	1 month to < 6 months	0.60 mg/kg single dose	None
	5	Birth to < 1 month	0.50 mg/kg single dose	None
KF5503/65	108	2 to < 18 years	1.25 mg/kg every 4 hours for first 24 hours, then 1.25 mg/kg or 1.0 mg/kg every 4 hours	Placebo
	7	6 months to < 2 years	1.25 mg/kg every 4 hours for first 24 hours, then 1.25 mg/kg or 1.0 mg/kg every 4 hours	Placebo
	2	30 days to < 6 months	0.5 mg/kg every 4 hours for the first 24 hours, then 0.5 mg/kg or 0.3 mg/kg every 4 hours	Placebo
	2	Birth to < 30 days	0.1 mg/kg every 4 hour for the first 24 hours, then 0.1 mg/kg or 0.075 mg/kg every 4 hours	Placebo

Source: Summary of Clinical Safety, Table 10 on page 24/53.

The table below summarizes the number of subjects who received tapentadol OS in each pediatric age range by individual study and overall for all studies conducted in support of the pediatric program for immediate-release tapentadol.

Table 23 Number of Subjects who Received Tapentadol OS by Age Subgroup in All Conducted Studies

Age range	KF5503/65	KF5503/59	KF5503/68	KF5503/72	Overall
Total number of subjects	119	44	66	19	248
12 years to <18 years	53 [a]	30	21	-	104
6 years to <12 years	32	14	28	-	74
2 years to <6 years	23	-	17	-	40
6 months to <2 years	7	-	-	8	15
1 month to <6 months	2	-	-	6	8
Birth to <1 month [b]	2	-	-	5	7

[a] 45 subjects aged 12 <17 years and 8 subjects aged 17 years to <18 years (see Table 4).
[b] From birth (must be 32 weeks to <37 weeks gestational age) to a postmenstrual age of ≤41 weeks.
OS = oral solution.

Source: Summary of Clinical Safety, Table 12 on page 26/53.

Duration of Exposure

Studies KF5503/59, KF5503/68, KF5503/72

Subjects in these studies were all exposed to a single dose of tapentadol OS.

Study KF5503/65

For subjects from 2 to less than 18 years of age (SAF-EU), 52 subjects were exposed to placebo and 108 subjects were exposed to tapentadol OS. The mean (SD) duration of exposure was comparable between the two groups: 28.27 (17.26) hours in the placebo group and 28.88 (18.01) hours in the tapentadol OS group. Forty-four subjects in the placebo group and 90 subjects in the tapentadol OS group had at least 12 hours of exposure. Twenty-six subjects in the placebo group and 59 subjects in the tapentadol OS group had at least 24 hours of exposure. Ten subjects in the placebo group and 20 subjects in the tapentadol OS group had between 48 and 72 hours of exposure.

Table 24 Duration of Exposure to Investigational Medicinal Product in Study KF5503/65

Exposure to IMP in SAF-EU Population	Placebo N=52	Tapentadol OS N=108
Duration of exposure (hours) Mean (SD)	28.27 (17.26)	28.88 (18.01)
At least 12 hours exposure Number of subjects	44	90
At least 24 hours exposure Number of subjects	26	59
Between 48 and 72 hours exposure Number of subjects	10	20

Source: CSR for KF5503/65, Table 40 on page 124/2254.

Relevant Demographic Characteristics of the Safety Population

Studies KF5503/59, KF5503/68, KF5503/72

For Study KF5503/59, more female (54.5%) than male (45.5) subjects were enrolled in the study. Most subjects were White (84.1%) followed by Black or African-American and other (6.8% each) and Native Hawaiian or Other Pacific Islander (2.3%). The mean (SD) age was 13.0 (3.37) years. For Study KF5503/68, more female (51.5%) than male (48.5%) subjects were enrolled in the study. The vast majority of subjects were White (95.5%) and not Hispanic or Latino (93.9%). The mean (SD) age was 9.3 (4.9) years. For Study KF5503/72, more male (52.6%) than female (47.4%) subjects were enrolled in the study. Most subjects were White (73.7%) and not Hispanic or Latino (73.7%) followed by Asian, Black or African-American, and Other (10.5% each). The mean (SD) age was 210.0 (209.0) days.

Study KF5503/65

The demographic characteristics of the safety population in this study are essentially the same as those of the efficacy population. The safety population had good representation of females and adequate representation of Hispanics or Latinos, but limited representation of subjects of other races besides White.

The table below summarizes the demographic characteristics of all subjects who received tapentadol OS in the studies conducted in support of the pediatric program for immediate-release tapentadol.

Table 25 Demographic Characteristics of Subjects in All Conducted Studies

Parameter	Category	KF5503/65 n (%)	KF5503/59 n (%)	KF5503/68 n (%)	KF5502/72 n (%)
Total number of subjects		119	44	66	19
Sex	Male	61 (51.3)	20 (45.5)	32 (48.5)	10 (52.6)
	Female	58 (48.7)	24 (54.5)	34 (51.5)	9 (47.4)
Race	White	101 (84.9)	37 (84.1)	63 (95.5)	14 (73.7)
	Asian	4 (3.4)	0	0	2 (10.5)
	Black or African American	7 (5.9)	3 (6.8)	1 (1.5)	2 (10.5)
	Native Hawaiian or other Pacific Islander	0	1 (2.3)	0	0
	Other/more than 1 race	2 (1.7)	3 (6.8)	2 (3.0)	2 (10.5)
	Not reported	5 (4.2)			
Ethnicity	Hispanic or Latino	21 (17.6)		4 (6.1)	5 (26.3)
	Not Hispanic or Latino	90 (75.6)		62 (93.9)	14 (73.7)
	Not Reported	8 (6.7)	44 (100)	0	0
Age (years [a])	Mean (SD)	9.88 (5.38)	13.0 (3.37)	9.3 (4.9)	210.0 (209.0)
	Median	11.0	14.0	8.0	120.0
	Range	0.1 – 17.0	(6 – 17)	(2 – 17)	8 – 690
BMI (kg/m^2)	Mean (SD)	18.47 (4.14)	20.3 (3.99)	17.61 (2.85)	15.55 (2.24)
	Median	17.80	20.0	16.75	15.90
	Min - Max	9.5 - 29.7	(14 – 33)	(13.7 – 25.6)	(9.8 – 18.8)

[a] Mean age for Study KF5502/72 reported in days.
BMI = body mass index; Max = maximum; Min = minimum; N/n = number of subjects; OS = oral solution; SD = standard deviation.

Source: Summary of Clinical Safety, Table 11 on page 25/53.

Adequacy of the Safety Database

There is relatively equal representation of males and females across the safety population. There is some, though limited, representation of races and ethnicities other than White. (b) (4) The clinical team concludes that the safety database for these submissions is adequate to allow for generalizability of the safety findings to the pediatric patient population for which tapentadol OS is indicated.

9.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

These supplements were submitted in Electronic Common Technical Document (eCTD) format. The datasets were submitted in SAS format. The submissions appeared to be of good quality, were well organized, and easily navigated. Several information requests were sent to the Applicant over the course of the review cycle. These information requests were appropriately addressed by the Applicant. No issues concerning the quality or integrity of these submissions were identified. There were no outstanding clinical information requests at the time of completion of this review.

Categorization of AEs

Study KF5503/59

The Applicant summarized all treatment-emergent adverse events (TEAEs) reported during Study KF5503/59. TEAEs were coded by system organ class (SOC) and dictionary-derived term (DDT) using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

Study KF5503/68

The Applicant summarized all TEAEs reported during Study KF5503/68. TEAEs were coded by SOC and preferred term (PT) using MedDRA version 16.1.

Study KF5503/72

The Applicant summarized all non-TEAEs and TEAEs reported during Study KF5503/72. Non-TEAEs and TEAEs were coded by SOC and PT using MedDRA version 19.1.

Study KF5503/65

The Applicant summarized all TEAEs reported during Study KF5503/65. TEAEs were coded by SOC and PT using MedDRA version 19.1.

The Applicant's approach to categorization of AEs was acceptable in all three, single dose uncontrolled studies and also in the one, multiple-dose, controlled study.

Routine Clinical Tests

Study KF5503/59

Clinical laboratory assessments in Study KF5503/59 consisted of blood and urine samples for hematology, chemistry, and urinalysis in all subjects and pregnancy testing in all females who were postmenarchal or at least 12 years old at screening and at end of treatment. Vital signs (HR, RR, SBP/DBP, oxygen saturation) were measured at screening, at baseline on Day 1, at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 11 hours, and 15 hours after dosing on Day 1, and at end of treatment or early withdrawal. 12-lead ECG was recorded at screening and end of treatment. The safety monitoring in Study KF5503/59 was acceptable.

Study KF5503/68

Clinical laboratory assessments in Study KF5503/68 consisted of blood and urine samples for hematology, chemistry, and urinalysis in all subjects, urine drug screening in subjects who were 12 years old or older, and pregnancy testing in all females who were postmenarchal or at least 12 years old at the enrollment visit, pre-dose, and at end of treatment. Vital signs (HR, RR, BP) were measured at the enrollment visit, pre-dose on Day 1, at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 11 hours, and 15 hours after dosing on Day 1, and at end of treatment or early withdrawal. Oxygen saturation was monitored continuously during the first hour after dosing on Day 1 with documentation at 15 minutes, 30 minutes, and 1 hour. Oxygen saturation was also documented at 2 hours, 4 hours, 6 hours, 11 hours, and 15 hours after dosing on Day 1 and at end of treatment or early withdrawal. 12-lead ECG was recorded at the enrollment visit and end of treatment. The Columbia Suicide Severity Rating Scale (C-SSRS) was recorded in subjects who were 12 years of age or older with parental consent at the enrollment visit and end of treatment. The safety monitoring in Study KF5503/68 was acceptable.

Study KF5503/72

Clinical laboratory assessments in Study KF5503/72 consisted of blood samples for hematology and chemistry in all subjects at the enrollment visit and at end of treatment. Vital signs (HR, RR, BP) were measured at the enrollment visit, at pre-dose on Day 1, at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 12 hours after dosing on Day 1, and at end of treatment or early withdrawal. Heart rate, respiratory rate, and oxygen saturation were monitored continuously during the first 4 hours after dosing on Day 1. Oxygen saturation was documented at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, and 11 hours after dosing on Day 1 and at end of treatment or early withdrawal. 12-lead ECG was recorded at the enrollment visit and end of treatment. The safety monitoring in Study KF5503/72 was acceptable.

Study KF5503/65

Clinical laboratory assessments in Study KF5503/65 consisted of blood samples for hematology and chemistry in all subjects at the enrollment visit and at end of treatment and pregnancy testing within 48 hours prior to allocation to IMP in females who were 12 years or older, or postmenarchal, or sexually active. Heart rate, respiratory rate, and oxygen saturation

were monitored continuously for 24 hours after the first dose of IMP. Heart rate, respiratory rate, BP, and oxygen saturation were recorded at the enrollment visit, at baseline before first dose of IMP, and every 4 hours thereafter immediately prior to the next dose of IMP. Oxygen desaturation events defined as a pulse oximetry measurement below 92% for at least 60 seconds were recorded as well. A 12-lead ECG was recorded at the enrollment visit and at the end of treatment. The C-SSRS was administered, and the results recorded at the enrollment visit and end of treatment in subjects six years of age and older. Sedation scores were recorded using the University of Michigan Sedation Scale Score immediately before each dose of IMP in all subjects. The safety monitoring in Study KF5503/65 was acceptable.

9.4 Safety Results

Deaths

No deaths occurred in any of the studies conducted in support of the pediatric program for immediate-release tapentadol.

Serious Adverse Events

Studies KF5503/59 and KF5503/72

There were no serious adverse events (SAEs) in either study.

Study KF5503/68

One subject in Study KF5503/68 experienced one SAE of post-operative bleeding. Subject (b) (6) underwent a tonsillectomy, was administered a single dose of tapentadol OS for post-operative pain, and experienced post-operative bleeding six days after tapentadol OS administration that resulted in hospitalization. A summary of the SAE is provided below.

Subject Number: (b) (6)
PT: Post procedural haemorrhage

Subject (b) (6) is a 7-year-old, White male, not Hispanic in ethnicity, with a past medical history of chronic tonsillitis and chronic otitis media status post bilateral myringotomy and pressure equalization tube placement. On (b) (6), he had a tonsillectomy. At (b) (6) he had one episode of emesis that was considered not related to study drug. At (b) (6) he received one dose of tapentadol OS 30 mg for post-operative pain. After receiving treatment with tapentadol OS, he had another episode of emesis that was considered possibly related to study drug. At (b) (6) he was discontinued from the study because he met the protocol-defined discontinuation criteria of "vomiting within first 3 hours of tapentadol administration." On (b) (6) six days after receiving treatment with tapentadol OS, he experienced hematemesis that resulted in hospitalization and return to the operating room for cauterization due to post-operative bleeding. The post-operative bleeding resolved after cauterization. The investigator considered the SAE of post-procedural hemorrhage severe in intensity and not related to study drug. The clinical team agrees with the investigator's determination that the SAE of hematemesis/post-procedural hemorrhage was not related to study drug. Post-operative bleeding is a known complication of tonsillectomy.

Study KF5503/65

Two subjects in Study KF5503/65 experienced SAEs of abdominal abscess and seizure. Subject [redacted] had an ileectomy, received four days of treatment with tapentadol OS for procedural pain, and experienced an intra-abdominal abscess three days after the first dose of study drug. Subject [redacted] has coarctation of the aorta repair, received three doses of tapentadol OS, and experienced a seizure less than one day after the last dose of study drug. Summaries of the SAEs are provided below.

Subject Number: [redacted]
PT: Abdominal abscess

Subject [redacted] is a 16-year-old male with a past medical history of Crohn's disease who underwent an ileectomy on [redacted]. He was treated with tapentadol OS 92 mg every 4 hours for four days. Concomitant medications were pantoprazole, diphenhydramine, and fat emulsions. On [redacted], two days after the first dose of tapentadol OS, he experienced pyrexia and was treated with paracetamol 650 mg. On [redacted], three days after the first dose of tapentadol OS, he experienced vomiting and diarrhea. An x-ray and an abdominal ultrasound were performed to rule out pneumonia or an abdominal source of infection. A 1.5 cm x 6.2 cm x 5.8 cm intra-abdominal collection was found in the left lower quadrant. The subject was started on intravenous antibiotics, Zosyn 3.375 grams IV every 8 hours. On [redacted], his nausea and vomiting resumed. A CT scan of the abdomen identified a fluid collection in the anterior part of the intra-abdominal cavity. On [redacted], the subject went to interventional radiology for ultrasound-guided drain placement and percutaneous drainage of the abscess. Approximately 150 cc's of dark yellow and brown fluid was removed. The subject continued to have sporadic fevers until [redacted], after which time he remained afebrile and his condition continued to improve. On [redacted] 19 days after the first dose of tapentadol OS, the subject was doing well and was discharged home on intravenous antibiotics and total parenteral nutrition. The abdominal abscess was considered resolved on [redacted] The investigator considered the SAE of abdominal abscess moderate in severity and not related to the administration of IMP. The clinical team agrees with the investigator's determination. Abdominal abscess is a known potential complication of abdominal surgery.

Subject Number: [redacted]
PT: Seizure

Subject [redacted] is a 9-year-old male with a past medical history of coarctation of the aorta, bicuspid aortic valve, hypertension, and asthma who had coarctation of the aorta repair on [redacted] He was treated with three doses of tapentadol OS 42 mg for post-procedural pain on the day of surgery. On [redacted], about 10.5 hours after the last dose of tapentadol OS, he experienced a generalized tonic-clonic seizure that resolved within five minutes without medication. He was given supplemental oxygen and one dose of magnesium sulfate. An arterial blood gas analysis identified an elevated lactate level and hyponatremia (sodium level 125). His glucose level was normal in the 110s. Concomitant medications given prior to the seizure were furosemide and nitroprusside sodium. The subject was reportedly afebrile with no marked blood pressure elevation – systolic blood pressure in the 110s and 120s with increase to 130s during the seizure. He remained post-ictal with a neurologic examination that was remarkable for dilated pupils that were equal and responsive,

intact extraocular muscles, symmetric facies, normal tone in the upper extremities and the right lower extremity, and increased tone in the left lower extremity. He was nonverbal and nonresponsive to commands, but eventually started making some purposeful movement with rubbing of his eye with the left hand. The subject was given 3 ml/kg of 3% saline for hyponatremia. A head CT showed no intracranial abnormality. An EEG showed diffuse waveforms consistent with encephalopathy. On (b) (6), the subject was started on levetiracetam 670 mg two times per day. He was also started on fludrocortisone for management of hyponatremia. He had an MRI which showed nonspecific changes in the basal ganglia possibly caused by a previous seizure or metabolic encephalopathy. On (b) (6) a lumbar puncture was performed. The cerebrospinal fluid (CSF) results showed no red blood cells or white blood cells, a negative gram stain, and normal glucose and protein. The CSF culture and Herpes Simplex Virus 1 and 2 polymerase chain reaction test were negative. On (b) (6), the results of a genetic evaluation for underlying metabolic disorder were considered "not clinically significant." The subject had no further episodes of seizure recorded. The investigator considered the SAE of seizure moderate in severity and not related to the administration of IMP. The investigator suspected hyponatremia secondary to cerebral salt wasting as the cause of the subject's seizure. The clinical team agrees with the investigator's determination that the seizure was caused by hyponatremia and not related to tapentadol OS. Whether or not the subject had cerebral salt wasting remains unclear as additional laboratory results would be needed to confirm the underlying reason for the subject's hyponatremia. Nevertheless, hyponatremia is a common occurrence after all types of surgical procedures and could be provoked by surgical stress.

TEAEs leading to Discontinuation

Studies KF5503/59, KF5503/68, and KF5503/72

Five subjects in Study KF5503/59 and six subjects in Study KF5503/68 discontinued from the trial due to a TEAE of vomiting within three hours of tapentadol administration which was a protocol-defined discontinuation criterion in both studies. No subjects in Study KF5503/72 discontinued from the study due to a TEAE.

Study KF5503/65

For subjects ages 2 to less than 18 years old, 10 subjects in the tapentadol OS group and two subjects in the placebo group discontinued from treatment (but not from the study) due to a TEAE. The TEAEs leading to discontinuation in the tapentadol OS group were known adverse reactions for tapentadol or the opioid class (see table below).

Table 26 Treatment-Emergent Adverse Events Leading to Discontinuation from Treatment in Study KF5503/65 – SAF-EU

	Placebo		Tapentadol OS		Overall	
Primary System Organ Class / Preferred Term	Subjects n (%)	Events e (%)	Subjects n (%)	Events e (%)	Subjects n (%)	Events e (%)
Total	52	3	108	10	160	13
All SOCs	2 (3.8)	3 (100)	10 (9.3)	10 (100)	12 (7.5)	13 (100)
Gastrointestinal disorders	1 (1.9)	1 (33.3)	6 (5.6)	6 (60.0)	7 (4.4)	7 (53.8)
Abdominal distension	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)
Dysphagia	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)
Nausea	1 (1.9)	1 (33.3)	2 (1.9)	2 (20.0)	3 (1.9)	3 (23.1)
Vomiting	0	0	2 (1.9)	2 (20.0)	2 (1.3)	2 (15.4)
Nervous system disorders	2 (3.8)	2 (66.7)	3 (2.8)	3 (30.0)	5 (3.1)	5 (38.5)
Headache	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)
Sedation	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)
Somnolence	2 (3.8)	2 (66.7)	1 (0.9)	1 (10.0)	3 (1.9)	3 (23.1)
Skin and subcutaneous tissue disorders	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)
Pruritus	0	0	1 (0.9)	1 (10.0)	1 (0.6)	1 (7.7)

Adverse events were coded according to MedDRA version 19.1.
N = number of subjects in analysis set; n = number of subjects with TEAE; E = total number of TEAEs; e = number ofTEAEs; TEAE = treatment emergent adverse event; OS = oral solution; SOC = System Organ Class; PT = preferred term; MedDRA = Medical Dictionary for Regulatory Activities; SAF = Safety Set.

Source: Summary of Clinical Safety, Table 22 on page 37/53.

Treatment Emergent Adverse Events and Adverse Reactions

Studies KF5503/59, KF5503/68, and KF5503/72

The most commonly reported TEAEs across the single dose studies were vomiting, nausea, and dizziness.

Study KF5503/65

For subjects ages 2 to less than 18 years old, 62 out of 108 subjects (57.4%) in the tapentadol OS group and 26 out of 52 subjects in the placebo group had at least one TEAE. The most common TEAEs, occurring in at least 5% of subjects in at least one treatment group, were vomiting (19.4%), nausea (12.5%), constipation (10.6%), pyrexia (6.9%), somnolence (5.0%), and pruritus (4.4%) (see table below).

Table 27 Treatment Emergent Adverse Events Occurring in at Least 5% of Subjects in at Least One Treatment Group – SAF-EU

	Placebo		Tapentadol OS		Overall	
Preferred Term	Subjects n (%)	Events e (%)	Subjects n (%)	Events e (%)	Subjects n (%)	Events e (%)
Total	52	46	108	161	160	207
All PTs	26 (50.0)	46 (100)	62 (57.4)	161 (100)	88 (55.0)	207 (100)
Vomiting	6 (11.5)	8 (17.4)	25 (23.1)	36 (22.4)	31 (19.4)	44 (21.3)
Nausea	4 (7.7)	5 (10.9)	16 (14.8)	22 (13.7)	20 (12.5)	27 (13.0)
Pyrexia	1 (1.9)	1 (2.2)	10 (9.3)	19 (11.8)	11 (6.9)	20 (9.7)
Constipation	6 (11.5)	6 (13.0)	11 (10.2)	11 (6.8)	17 (10.6)	17 (8.2)
Somnolence	2 (3.8)	2 (4.3)	6 (5.6)	6 (3.7)	8 (5.0)	8 (3.9)
Pruritus	3 (5.8)	3 (6.5)	4 (3.7)	4 (2.5)	7 (4.4)	7 (3.4)

Adverse events were coded according to MedDRA version 19.1.

n = number of subjects with TEAE; e = number of TEAEs; TEAE = treatment emergent adverse event; OS = oral solution; MedDRA = Medical Dictionary for RegulatoryActivities; PT = Preferred Term.

Source: Summary of Clinical Safety, Table 18 on page 32/53.

Study KF5503/65 - Incidence of TEAEs by Intensity

For subjects ages 2 to less than 18 years old, 72.9% of the TEAEs were labeled mild intensity, 26.1% of the TEAEs were labeled moderate intensity, and 1.0% of the TEAEs were labeled severe intensity. TEAEs of mild intensity occurred more frequently in subjects in the placebo group (73.1%) than in subjects in the tapentadol OS group (54.8%). TEAEs of moderate intensity occurred more frequently in subjects in the tapentadol OS group (41.9%) than in subjects in the placebo group (26.9%). The two TEAEs of severe intensity occurred in two subjects in the tapentadol OS group. These TEAEs were abdominal distension and headache. Both TEAEs led to discontinuation of tapentadol OS (see table below).

Table 28 Treatment Emergent Adverse Events by Intensity – SAF-EU

	Placebo		Tapentadol OS		Overall	
Intensity	N = 52 n (%)	E = 46 e (%)	N = 108 n (%)	E = 161 e (%)	N = 160 n (%)	E = 207 e (%)
TEAEs	26 (100)	46 (100)	62 (100)	161 (100)	88 (100)	207 (100)
Mild	19 (73.1)	35 (76.1)	34 (54.8)	116 (72.0)	53 (60.2)	151 (72.9)
Moderate	7 (26.9)	11 (23.9)	26 (41.9)	43 (26.7)	33 (37.5)	54 (26.1)
Severe	0	0	2 (3.2)	2 (1.2)	2 (2.3)	2 (1.0)

For multiple occurrences of a TEAE in a subject only the worst intensity is used for the summary table.

N = number of subjects in analysis set; n = number of subjects with TEAE; E = total number of TEAEs; e = number of TEAEs; TEAE = treatment emergent adverse event; OS = oral solution.

Source: CSR for KF5503/65, Table 47 on page 132/2254.

Study KF5503/65 - Incidence of TEAEs by Age Subgroup

For subjects ages 2 to less than 6 years, nine out of 23 subjects (39.1%) reported 24 TEAEs in the tapentadol group and five out of 12 subjects (41.7%) reported 5 TEAEs in the placebo

group. The most common TEAEs by PT in the tapentadol OS group were vomiting (17.4%) and constipation, nausea, and pyrexia (8.7% each).

Table 29 Treatment Emergent Adverse Events by Preferred Term in the Two Years to less than Six Years Age Subgroup

Age Group = 2 years to less than 6 years

	Placebo		Tapentadol		Overall	
	N=12	E=5	N=23	E=24	N=35	E=29
PT	n(%)	e(%)	n(%)	e(%)	n(%)	e(%)
All PT	5 (41.7)	5 (100)	9 (39.1)	24 (100)	14 (40.0)	29 (100)
Vomiting	0	0	4 (17.4)	4 (16.7)	4 (11.4)	4 (13.8)
Constipation	0	0	2 (8.7)	2 (8.3)	2 (5.7)	2 (6.9)
Nausea	0	0	2 (8.7)	2 (8.3)	2 (5.7)	2 (6.9)
Pruritus	1 (8.3)	1 (20.0)	1 (4.3)	1 (4.2)	2 (5.7)	2 (6.9)
Pyrexia	0	0	2 (8.7)	6 (25.0)	2 (5.7)	6 (20.7)
Somnolence	0	0	1 (4.3)	1 (4.2)	1 (2.9)	1 (3.4)

N=total number of subjects; n=number of subjects with TEAE; E=total number of TEAEs; e=number of TEAEs. Adverse events are coded using MedDRA version 19.1.
Source: CSR for KF5503/65, Table 15.3.1.1.11 on page 573/2254.

For subjects ages 6 to less than 12 years old, 15 out of 32 subjects (46.9%) reported 34 TEAEs in the tapentadol OS group and six out of 15 subjects (40.0%) reported seven TEAEs in the placebo group. The most common TEAEs in the tapentadol group were vomiting (25.0%) and constipation and nausea (6.3% each).

Table 30 Treatment Emergent Adverse Events by Preferred Term in the Six Years to less than Twelve Years Age Subgroup

Age Group = 6 years to less than 12 years

	Placebo		Tapentadol		Overall	
	N=15	E=7	N=32	E=34	N=47	E=41
PT	n(%)	e(%)	n(%)	e(%)	n(%)	e(%)
All PT	6 (40.0)	7 (100)	15 (46.9)	34 (100)	21 (44.7)	41 (100)
Vomiting	1 (6.7)	1 (14.3)	8 (25.0)	14 (41.2)	9 (19.1)	15 (36.6)
Constipation	0	0	2 (6.3)	2 (5.9)	2 (4.3)	2 (4.9)
Nausea	0	0	2 (6.3)	4 (11.8)	2 (4.3)	4 (9.8)
Pruritus	1 (6.7)	1 (14.3)	1 (3.1)	1 (2.9)	2 (4.3)	2 (4.9)
Pyrexia	1 (6.7)	1 (14.3)	1 (3.1)	1 (2.9)	2 (4.3)	2 (4.9)
Somnolence	0	0	1 (3.1)	1 (2.9)	1 (2.1)	1 (2.4)

N=total number of subjects; n=number of subjects with TEAE; E=total number of TEAEs; e=number of TEAEs. Adverse events are coded using MedDRA version 19.1.
Source: CSR for KF5503/65, Table 15.3.1.1.11 on page 574/2254.

For subjects ages 12 to less than 18 years old, 38 out of 53 subjects (71.7%) reported 103 TEAEs in the tapentadol group and 15 out of 25 subjects (60.0%) reported 34 TEAEs in the placebo group. The most common TEAEs in the tapentadol group were vomiting (24.5%), nausea (22.6%), and constipation and pyrexia (13.2% each).

Table 31 Treatment Emergent Adverse Events by Preferred Term in the Twelve Years to less than Eighteen Years Age Subgroup

Age Group = 12 years to less than 18 years

PT	Placebo N=25 n(%)	Placebo E=34 e(%)	Tapentadol N=53 n(%)	Tapentadol E=103 e(%)	Overall N=78 n(%)	Overall E=137 e(%)
All PT	15 (60.0)	34 (100)	38 (71.7)	103 (100)	53 (67.9)	137 (100)
Vomiting	5 (20.0)	7 (20.6)	13 (24.5)	18 (17.5)	18 (23.1)	25 (18.2)
Nausea	4 (16.0)	5 (14.7)	12 (22.6)	16 (15.5)	16 (20.5)	21 (15.3)
Constipation	6 (24.0)	6 (17.6)	7 (13.2)	7 (6.8)	13 (16.7)	13 (9.5)
Pyrexia	0	0	7 (13.2)	12 (11.7)	7 (9.0)	12 (8.8)
Somnolence	2 (8.0)	2 (5.9)	4 (7.5)	4 (3.9)	6 (7.7)	6 (4.4)
Pruritus	1 (4.0)	1 (2.9)	2 (3.8)	2 (1.9)	3 (3.8)	3 (2.2)

N=total number of subjects; n=number of subjects with TEAE; E=total number of TEAEs; e=number of TEAEs. Adverse events are coded using MedDRA version 19.1.
Source: CSR for KF5503/65, Table 15.3.1.1.11 on page 575/2254.

Study KF5503/65 - Onset of Treatment Emergent Adverse Events

For subjects ages 2 to less than 18 years old, 138 out of 207 TEAEs (66.7%) started within 24 hours of the first dose of IMP, 53 out of 207 TEAEs (25.6%) started between 24 and 48 hours after the first dose of IMP, and 16 out of 207 TEAEs (7.8%) started more than 48 hours after the first dose of IMP (see table below).

Table 32 Treatment Emergent Adverse Events by Time to Onset After First Dose of Investigational Medicinal Product – SAF-EU

	Placebo		Tapentadol OS		Overall	
Time to onset (hours)	**N = 52 n (%)**	**E = 46 e (%)**	**N = 108 n (%)**	**E = 161 e (%)**	**N = 160 n (%)**	**E = 207 e (%)**
Total number of TEAEs	26 (100)	46 (100)	62 (100)	161 (100)	88 (100)	207 (100)
≤1 hour	4 (15.4)	4 (8.7)	19 (30.6)	22 (13.7)	23 (26.1)	26 (12.6)
>1 - ≤4 hours	7 (26.9)	10 (21.7)	19 (30.6)	23 (14.3)	26 (29.5)	33 (15.9)
>4 - ≤12 hours	4 (15.4)	5 (10.9)	18 (29.0)	29 (18.0)	22 (25.0)	34 (16.4)
>12 - ≤24 hours	10 (38.5)	10 (21.7)	25 (40.3)	35 (21.7)	35 (39.8)	45 (21.7)
>24 - ≤48 hours	7 (26.9)	11 (23.9)	25 (40.3)	42 (26.1)	32 (36.4)	53 (25.6)
>48 - ≤72 hours	4 (15.4)	5 (10.9)	7 (11.3)	9 (5.6)	11 (12.5)	14 (6.8)
>72 hours	1 (3.8)	1 (2.2)	1 (1.6)	1 (0.6)	2 (2.3)	2 (1.0)

For the subject-based analysis, a subject may be counted more than once.
N = number of subjects in analysis set; n = number of subjects with TEAE; E = total number of TEAEs; e = number of TEAEs; TEAE = treatment emergent adverse event; OS = oral solution.
Source: CSR for KF5503/65, Table 54 on page 137/2254.

KF5503/65 - Vital Signs

Respiratory rate, systolic and diastolic blood pressure, and pulse rate were measured at enrollment after surgery, before first administration of study drug, before each subsequent dose of study drug, and at end of treatment. Oxygen saturation was measured continuously from before first dose of study drug until four hours after the last dose of study drug. Oxygen saturation was recorded at enrollment after surgery, before first dose of study drug, before each subsequent dose of study drug, and at end of treatment.

Body Temperature

AEs of Pyrexia

Nineteen subjects (five in the placebo group and 14 in the tapentadol OS group) had abnormalities in body temperature that were reported as AEs. The dictionary-derived term for the AEs was pyrexia. Eighteen subjects had AEs that were considered mild in intensity. One subject had an AE that was considered moderate in intensity. For nine out of nineteen subjects, the AEs started before initiation of study drug. For the remaining ten subjects, the AEs started after initiation of study drug. The investigators considered all of the AEs of pyrexia not related to study drug. The clinical team reviewed the applicable datasets and agrees with the investigators' conclusions that AEs of pyrexia are unrelated to tapentadol. A search on the internet site, UpToDate, identified fever in the first few days after surgery as a common finding following most major surgeries. Possible causes of post-operative fever include inflammation as a direct consequence of surgery, trauma- or burn-induced inflammation, immune-mediated reactions to blood products or medications, and infection. Pyrexia is not a known adverse drug reaction in adults administered tapentadol and is also not a typical adverse reaction for the opioid drug class. Given that post-operative fever is common and potentially explained by a number of etiologies other than relatedness to tapentadol, the clinical team concludes that AEs of pyrexia were likely related to subjects' post-operative status and not likely related to tapentadol administration.

Respiratory Rate

AEs Related to Respiratory Rate Abnormalities

Four subjects (two in the placebo group and two who were not treated with study drug) had respiratory rate abnormalities that were reported as AEs. One subject who was treated with placebo had an AE of bradypnea that was moderate in severity and started about three minutes after study drug administration. The investigator considered this AE possibly related to study drug. The other subject who was treated with placebo had an AE of hypopnea that was mild in severity and started before study drug administration. The subject was given supplemental oxygen. The investigator considered this AE not related to study drug. For the two subjects who were not treated with study drug, one subject had an AE of hypoventilation that was mild in severity and the other subject had an AE of respiratory failure that was moderate in severity. The subject who experienced hypoventilation was managed with continuous positive airway pressure (CPAP), whereas the subject who had respiratory failure was managed with mechanical ventilation. Since neither subject was treated with study drug, the investigators considered both AEs not related to study drug. The clinical team reviewed the applicable datasets and concludes that the above-described AEs of bradypnea, hypopnea, hypoventilation, and respiratory failure are unrelated to tapentadol administration.

Respiratory Rate Values over Time

The clinical team reviewed the descriptive statistics for respiratory rate values. The mean respiratory rates at baseline were generally similar to the mean respiratory rates at end of treatment. There was a slightly higher incidence of low respiratory rates in the tapentadol OS

group as compared to the placebo group. Overall, there were no clinically meaningful differences in respiratory rate trends between treatment groups.

Oxygen Saturation

Eight subjects (one subject in the placebo group and seven subjects in the tapentadol group) had ten episodes of oxygen desaturation that were reported as AEs. The dictionary-derived terms for the AEs were oxygen saturation decreased, pO2 decreased, and hypoxia.

One subject who was treated with placebo had one documented AE that started 10 minutes after the fifth dose of placebo and lasted for three minutes. The lowest measured oxygen saturation was 78%. The subject had a normal respiratory rate at the time of the AE. The AE was considered mild in severity and not related to study drug.

Seven subjects who were treated with tapentadol had nine documented AEs that ranged in start time from 45 minutes to 63 hours after first dose of study drug. Six of the nine AEs were considered mild in severity and three of the nine AEs were considered moderate in severity. Two subjects had chest wall surgery (thoracic operation for pectus carinatum and pectus excavatum), two subjects had cardiac surgery (mitral valve replacement and atrial septal defect repair), one subject had a pulmonary resection, one subject had a maxillofacial operation, and one subject had a nephrectomy. Actions taken to manage these AEs were as follows: four subjects were given supplemental oxygen, one subject's PCA dose was decreased from 0.1 mg to 0.08 mg and supplemental oxygen was increased from 1L/minute to 2L/minute, and one subject was given incentive spirometry.

The subject who underwent an atrial septal defect repair had two documented AEs of oxygen desaturation. The first started two hours after the fourth dose of tapentadol OS and lasted for 15 minutes. The second started almost five hours after the last dose of tapentadol OS and lasted for five and one-half hours with fluctuating oxygen saturation values. This subject was also diagnosed with left lower lobe atelectasis and pulmonary edema. The lowest measured oxygen saturation level was 65%. The subject was given supplemental oxygen. The AEs were considered unlikely related and not related to study drug.

The subject who underwent a nephrectomy had one documented AE of oxygen desaturation. The AE started three hours and 42 minutes after the first dose of tapentadol OS and lasted for 38 hours with intermittent periods of normal oxygen saturation and variable respiratory rate. This subject was also diagnosed with mycoplasma pneumonia post-operatively. The lowest oxygen saturation recorded was 78%.

All but one of the documented AEs in subjects in the tapentadol group were considered not related to study drug. The clinical team reviewed the applicable datasets and concludes that all of the subjects in the tapentadol group had confounding factors that could contribute to or cause oxygen desaturation, such as underlying cardiac or maxillofacial conditions, surgical manipulation of the airway, heart, lungs or chest wall, and post-surgical pneumonia.

Oxygen Saturation Values over Time

The clinical team reviewed the descriptive statistics for oxygen saturation values. Mean oxygen saturation values at baseline were similar to mean oxygen saturation values at end of

treatment for both treatment groups. There were small, not clinically meaningful changes in oxygen saturation over time in both treatment groups with no consistent trend observed with tapentadol OS.

Heart Rate

AEs Related to Heart Rate Abnormalities

See the electrocardiograms section below for a discussion of AEs related to heart rate abnormalities.

Heart Rate Values over Time

The clinical team reviewed the descriptive statistics for heart rate values. Mean heart rate values were slightly lower at the end of treatment as compared to mean heart rate values at baseline in both treatment groups. The slight decrease in mean heart rate values over time is not clinically meaningful.

Blood Pressure

AEs related to Blood Pressure Abnormalities

Six subjects had episodes of blood pressure elevation that were reported as AEs of hypertension. Three subjects were in the tapentadol group, two subjects were in the placebo group, and one subject was not treated with study drug. All but one subject was enrolled at site US004 which specialized in cardiac surgery. Four of the six subjects had AEs that were considered mild in severity and two of the six subjects had AEs that were considered moderate in severity. All of the AEs started before initiation of study drug and were considered not related to study drug.

Two subjects had episodes of decreased blood pressure that were reported as AEs of hypotension. Both subjects were in the tapentadol group and had AEs that started before initiation of study drug. Both AEs were considered mild in severity and not related to study drug.

The clinical team reviewed the applicable datasets and concludes that the above-described AEs of hypertension and hypotension were not related to study drug given the timing of the AEs as well as other confounding factors, such as underlying cardiac conditions, surgical procedures performed, post-surgical fluid status, and post-surgical pain, that may have contributed to or caused changes in blood pressure.

Blood Pressure Values over Time

The clinical team reviewed the descriptive statistics for systolic and diastolic blood pressure values. Mean blood pressure values at baseline were similar to mean blood pressure values at end of treatment. There were small, not clinically meaningful changes in blood pressure values over time in both treatment groups with no consistent trend observed with tapentadol OS.

KF5503/65 - Laboratory Findings

Blood for clinical laboratory parameters (chemistry and hematology) was collected at the enrollment visit (after surgery) and at the end of treatment visit. For subjects ages 2 to <18 years old, blood samples were analyzed for chemistry and hematology using a central laboratory; therefore, a full set of statistical analyses were performed in the SAF-EU population.

Hematology

AEs Related to Abnormalities in Laboratory Hematology Values

Eight subjects (three in the placebo group and five in the tapentadol OS group) had abnormalities in hematology values that were reported as AEs. The dictionary-derived terms for the AEs were as follows: haemoglobin decreased, haematocrit decreased, haemorrhagic anaemia, anaemia postoperative, and anaemia. Five subjects had AEs that were considered mild in severity. Two subjects had AEs that were considered moderate in severity. One subject had an AE that was considered severe in severity. For six out of eight subjects (two in the placebo group and four in the tapentadol OS group), the AEs started after initiation of study drug; however, no action was taken with study drug for any of these subjects. For two out of eight subjects (one in the placebo group and one in the tapentadol OS group), the AEs started before initiation of study drug. Four out of eight subjects received a blood transfusion and one subject was started on iron administration in response to the AEs. All of the AEs were considered unrelated to IMP by the investigators. The reasons given for the AEs were perioperative or postoperative blood loss. The clinical team reviewed the laboratory abnormalities and agrees with the investigators' conclusions that hematology abnormalities related to anemia were secondary to blood loss from surgery and not related to study drug. Anemia is a known potential consequence of surgery.

Laboratory Hematology Values over Time

The values for hematology parameters were generally similar at the baseline visit and the end of treatment visit in subjects ages two to less than 18 years old (SAF-EU analysis set) in both the placebo group and the tapentadol OS group. The mean eosinophil count was numerically higher at the end of treatment visit in both treatment groups. The investigators considered this finding to be secondary to stress from surgery, consistent with the postoperative status of all subjects, and not clinically significant. The clinical team agrees with the investigators' conclusions that increases in the eosinophil count are unrelated to study drug and not clinically meaningful.

Chemistry

AEs Related to Abnormalities in Laboratory Chemistry Values

Four subjects (one in the placebo group and three in the tapentadol OS group) had abnormalities in chemistry values that were reported as AEs. The dictionary-derived terms for the AEs were as follows: blood creatine increased, total protein decreased, hyperbilirubinemia, gamma-glutamyltransferase (GGT) decreased, hyperglycaemia, blood urea nitrogen (BUN) decreased, hepatic enzyme increased, aspartate aminotransferase (AST) increased, alanine

aminotransferase (ALT) increased. The AEs were considered mild or moderate in severity. For two out of four subjects (both in the tapentadol OS group), the AEs of hepatic enzyme increased, AST increased, and ALT increased started after initiation of study drug and were considered possibly or likely related to study drug by the investigators. For the other two subjects (one in the placebo group and one in the tapentadol OS group), the AEs of blood creatine increased, total protein decreased, hyperbilirubinemia, GGT decreased, hyperglycaemia, and BUN decreased started before initiation of study drug and were considered unrelated to study drug by the investigators. The clinical team reviewed the laboratory abnormalities listed above and agrees with the investigators' conclusions that increased AST and ALT are possibly related to study drug while the other AEs related to chemistry value abnormalities are not related to study drug.

AEs of hypokalemia (reported in eight subjects), hypomagnesemia (reported in six subjects), lactic acidosis (reported in four subjects), and metabolic acidosis (reported in six subjects) were reported in both treatment groups at only one specific study site - US004. All of the subjects at this site had underlying cardiac disease or congenital anomalies and underwent cardiac surgery. All of the AEs were considered mild or moderate in severity. All but two of the AEs started before initiation of study drug. The investigators considered all of the AEs unrelated to study drug. The clinical team reviewed these laboratory abnormalities and agrees with the investigators' conclusions that hypokalemia, hypomagnesemia, lactic acidosis, and metabolic acidosis are unrelated to study drug but rather an outcome of cardiac surgery and perioperative intravenous fluid replacement.

In addition, AEs of hyperglycemia were reported in six subjects from three different study sites (HR001, US004, and US008). All six subjects were in the tapentadol OS group. Four out of six subjects were enrolled at study site US004, had underlying cardiac congenital anomalies, and underwent cardiac surgery. All but one of the AEs were considered mild in severity. All but one of the AEs started before initiation of study drug. The investigators considered all of the AEs unrelated to study drug. The clinical team reviewed these laboratory abnormalities and agrees with the investigators' conclusions that hyperglycemia is unrelated to study drug. Hyperglycemia is more likely a consequence of stress from surgery and perioperative intravenous fluid replacement.

Laboratory Chemistry Values over Time

The values for chemistry parameters were generally similar at the baseline visit and the end of treatment visit in the SAF-EU analysis set in both the placebo group and the tapentadol OS group. There were some numerical increases in mean ALT, mean creatine kinase, and mean lactate dehydrogenase values at the end of treatment visit in both treatment groups. The investigators considered these findings to be secondary to muscle tissue injury from surgery with subsequent changes in clinical chemistry. The clinical team agrees with the investigators' conclusions that increases in ALT, creatine kinase, and lactate dehydrogenase may be a result of muscle tissue injury during surgery. However, increases in ALT may also be a result of tapentadol OS exposure. As noted in the Nucynta label, less than 1% of adults treated with Nucynta in pooled safety data from nine Phase 2/3 clinical studies experienced increased GGT, increased ALT, and increased AST. And, as noted above, two pediatric subjects who were administered tapentadol OS also experienced increased ALT and increased AST that was considered possibly and likely related to study drug.

KF5503/65 – Electrocardiograms

Twelve-lead electrocardiograms (ECGs) were recorded at the enrollment visit after surgery and at the end of treatment visit.

AEs Related to ECG Abnormalities

Ten subjects (three in the placebo group and seven in the tapentadol OS group) had AEs of tachycardia or sinus tachycardia reported during the study. Six out of ten subjects had underlying cardiac disease or cardiac congenital anomalies and underwent cardiac surgery. The other four subjects had a variety of different surgeries including maxillofacial operations, "cancer surgery", and a ureteropyelostomy. All but one of the AEs were considered mild in severity. All but two of the AEs started before initiation of study drug. The investigators considered all of the AEs not related or unlikely related to study drug. The clinical team reviewed these AEs and agrees with the investigators' conclusions that these AEs of tachycardia are unrelated to study drug. Tachycardia is more likely related to post-surgical hypovolemia, or a consequence of the surgery performed, particularly for those subjects who underwent cardiac surgery.

One subject in the tapentadol group had an AE of ventricular tachycardia. Subject (b) (6) is a 16-year-old male with a past medical history of Ebstein's anomaly with severe tricuspid regurgitation who underwent a cardiac operation and had an episode of ventricular tachycardia post-operatively while on telemetry in the cardiovascular intensive care unit. The AE started before initiation of study drug and was considered mild in intensity. The subject was monitored on telemetry with no further episodes of ventricular tachycardia. The investigator considered the AE not related to study drug. The clinical team reviewed this AE and agrees with the investigator's conclusion that this AE of ventricular tachycardia is unrelated to tapentadol.

One subject in the tapentadol group had an AE of supraventricular tachycardia. Subject (b) (6) is a 10-year-old male with a past medical history of Ebstein's anomaly with moderate to severe tricuspid regurgitation who underwent a heart valve operation and had an episode of supraventricular tachycardia post-operatively that necessitated synchronized electrical cardioversion. The AE started before initiation of study drug and was considered moderate in intensity. The subject had no further episodes of supraventricular tachycardia. The investigator considered the AE not related to study drug. The clinical team reviewed the AE and agrees with the investigator's conclusion that this AE of supraventricular tachycardia is unrelated to tapentadol.

ECG Parameters over Time

The mean 12-lead ECG values were generally similar at the baseline visit and the end of treatment visit in the SAF-EU analysis set in both the placebo group and the tapentadol OS group. There were small differences between treatment groups for PR interval, QRS interval, QT interval, and RR interval; however, these differences were not clinically meaningful. Of note, there were zero subjects in the placebo group and five subjects in the tapentadol OS group with QT values corrected according to Fridericia (QTcF) that fell into the Applicant's alert range. These cases will be discussed below.

QT Prolongation

The shift table below presents the subjects in the SAF-EU analysis set with QT prolongation using QTcF values >450 ms. There were two subjects in the placebo group and nine subjects in the tapentadol OS group with 12-lead ECGs that had prolonged QTcF values at baseline. The 12-lead ECGs for the two subjects in the placebo group had normal QTcF values at the end of treatment visit. The 12-lead ECGs for six out of the nine subjects in the tapentadol OS group had normal QTcF values at the end of treatment visit.

Table 33 Twelve-lead ECG Shift Table for QTcF – SAF-EU

			Value at baseline		
Treatment	Value at End of Treatment Visit	Total n (%)	Normal n (%)	Prolonged [a] n (%)	Missing n (%)
Placebo	Total	52 (100)	48 (100)	2 (100)	2 (100)
	Normal	47 (90.4)	44 (91.7)	2 (100)	1 (50.0)
	Prolonged [a]	0	0	0	0
	Missing	5 (9.6)	4 (8.3)	0	1 (50.0)
Tapentadol OS	Total	108 (100)	96 (100)	9 (100)	3 (100)
	Normal	96 (88.9)	89 (92.7)	6 (66.7)	1 (33.3)
	Prolonged [a]	5 (4.6)	1 (1.0)	3 (33.3)	1 (33.3)
	Missing	7 (6.5)	6 (6.3)	0	1 (33.3)

Baseline was defined as last non-missing assessment before first IMP intake.

a) Values of QTcF >450 ms (prolonged is "high" in the source table). All 5 subjects were at 1 site, which specialized in cardiac surgery. This site calculated the baseline QTcF values for these subjects and reported all to be in the normal range.

OS = oral solution.

Source: CSR for KF5503/65, Table 65 on page 154/2254.

For the five subjects in the tapentadol OS group with prolonged QTcF values at the end of treatment visit, all of the subjects were enrolled at one site that specialized in cardiac surgery. Three of the five subjects had prolonged QTcF at the baseline visit that persisted at the end of treatment visit. These same three subjects underwent cardiac surgery and had signs of right bundle branch block, intraventricular conduction delay, or a pacemaker placed on their 12-lead ECGs. The investigator evaluated all three 12-lead ECGs at the end of treatment visit as abnormal but not clinically significant.

One subject had a missing QTcF value at baseline and a prolonged QTcF value at end of treatment. This subject underwent cardiac surgery and had right bundle branch block recorded on the 12-lead ECG at the start of tapentadol OS administration that continued throughout treatment. A QTcF value could not be calculated at baseline by the central ECG reader. The investigator calculated the QTcF as 460 ms at baseline and 468 ms at end of treatment. The central ECG reader calculated the QTcF as 486 ms at end of treatment. The investigator considered the 12-lead ECG abnormal but not clinically significant.

One subject had a normal QTcF at baseline and a prolonged QTcF value at end of treatment. This subject underwent cardiac surgery for a ventricular septal defect. The QTcF was calculated as 400 ms at baseline and 455 ms at end of treatment. The investigator calculated a QTcF value of 458 ms at baseline. The 12-lead ECG showed sinus tachycardia (heart rate of 142) and right bundle branch block at baseline. The 12-lead ECG showed a heart rate of 99 and continued right bundle branch block at end of treatment. The investigator considered both 12-lead ECGs abnormal but not clinically significant.

The clinical team reviewed the electronic datasets for instances of QT prolongation and agrees with the investigators' conclusions that the finding of QT prolongation in these five subjects is unrelated to tapentadol and not clinically significant. QT prolongation in the subjects described above is more likely related to underlying cardiac disease or a consequence of cardiac surgery. An online search yielded an explanation for QT prolongation in the setting of right bundle branch block. Repolarization abnormalities, such as arrhythmias or bundle branch blocks, widen the QRS complex and lead to QT interval prolongation without significant alterations to the repolarization duration, making estimation of the true repolarization time difficult. Therefore, more recent recommendations from the American Heart Association suggest focusing on the JT interval rather than the QT interval when interpreting an ECG in the presence of left or right bundle branch block.[11]

KF5503/65 – Physical Examination Findings

A physical examination was performed at the enrollment visit and at the end of treatment visit. For the vast majority of subjects, physical examination findings at the end of treatment visit were mostly unchanged from the findings at enrollment. In those subjects where physical examination findings had changed since enrollment, the new findings at the end of treatment visit were mostly surgery-related, such as pain, weakness, or swelling secondary to surgery or a dressing, bandage, or wound at the surgical site. There were no clinically meaningful changes in physical examination findings at the end of treatment.

KF5503/65 - Adverse Events of Special Interest

Suicidal Ideation Using the Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and suicidal behavior were assessed at baseline and at end of treatment in subjects ages six years and older using the C-SSRS, in countries where this assessment was not rejected by the ethics committee. Subjects and parents had the choice to participate or not participate in the C-SSRS assessment. One hundred twenty-five subjects were ages six years and older. Of these 125 subjects, 69 subjects (approximately 55%) participated in the C-SSRS assessment. The main reason for not completing the C-SSRS was parental refusal or subject refusal to consent to the assessment. There were two subjects who responded with positive replies to questions asked at the baseline visit. One subject (b) (6) had a past medical history of prolonged grief syndrome after the death of her father and responded with positive replies to questions about non-active suicidal ideation and non-suicidal self-injurious behavior

[11] Bogossian, Harilaos, Liz, Dominik, Heijman, Jordi, Bimpong-Buta, Nana-Yaw, Bandorski, Dirk, Frommeyer, Gerrit, Erkapic, Damir, Seyfarth, Melchior, Zarse, Markus, Crijns, Harry J. *QTc evaluation in patients with bundle branch block*. IJC Heart & Vasculature 30 (2020) 100636.

in the past. Another subject (b) (6) experienced bullying at school and responded with a positive reply to a question about self-injurious behavior with unknown intent in the past. At the end of treatment visit, all subjects responded with negative replies to all questions asked. These findings demonstrate that short-term use (up to 72 hours) of tapentadol OS for the management of acute postoperative pain in pediatric patients was not associated with suicidal ideation or behavior.

Sedation Using the University of Michigan Sedation Scale

Sedation scores were documented before the first dose of study drug, before subsequent doses of study drug, and at end of treatment using the University of Michigan Sedation Scale. After review of the sedation scores over time for the SAF-EU analysis set, the clinical team notes the following:

- A higher percentage of subjects in the tapentadol OS group than in the placebo group was reported to be moderately sedated before the first, second, third, fourth, seventh, and ninth doses of IMP.
- A higher percentage of subjects in the placebo group than in the tapentadol OS group were reported to be moderately sedated before the sixth dose of IMP.
- There was no difference between treatment groups in the percentage of subjects who were reported to be deeply sedated before the first, second, third, fourth, eighth, and ninth doses of IMP.
- There was no difference between treatment groups in the percentage of subjects who were reported to be moderately sedated before the fifth and eighth doses of IMP.
- The numbers of subjects with sedation scores before the tenth dose of IMP and beyond were too small to make any meaningful conclusions about sedation levels between treatment groups.

Overall, most subjects ages two to less than 18 years of age were reported to be awake and alert or minimally sedated at each sedation evaluation before administration of IMP. No subjects were reported to be unarousable throughout the study. These findings demonstrate that short term use (up to 72 hours) of tapentadol OS for the management of acute postoperative pain in pediatric patients was not associated with excessive sedation.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reported overdoses in any of the conducted studies.

There was one reported case of withdrawal symptoms (agitated, restless) in Study KF5503/65. Subject (b) (6) was a four-year-old male who underwent urethral repair for hypospadias, was administered placebo, and became agitated and restless starting at about 92 hours after first intake of study drug. The investigator considered the agitation and restlessness to be consistent with withdrawal symptoms of moderate intensity and deemed the AE as probably related to study drug. The clinical team reviewed this AE and determined that the subject's agitation and restlessness were unrelated to study drug given that the subject was treated with placebo. However, it is possible that the subject's agitation and restlessness were related to the morphine he was administered during the study.

The potential for overdose, abuse, withdrawal, and rebound exists with all opioid medications. These safety concern have been appropriately addressed in the prescribing information for all opioid medications, including tapentadol.

Safety Conclusions

Review of the safety data from the controlled, multiple-dose study, KF5503/65, and the uncontrolled, single dose studies, KF5503/59, KF5503/68, and KF5503/72, yielded no new safety signals with use of tapentadol OS in pediatric patients ages 2 years and older with acute pain. There were no deaths in any of the studies. There was one SAE in Study KF5503/68 and two SAEs in Study KF5503/65 that were unrelated to administration of IMP. In Study KF5503/65, 10 subjects in the tapentadol group and two subjects in the placebo group were discontinued from IMP because of TEAEs. Most of the TEAEs leading to discontinuation were known adverse reactions associated with tapentadol or use of an opioid analgesic medication. There were no findings of suicidal ideation or suicidal behavior on the C-SSRS at end of treatment. Sedation scores were as expected for an opioid analgesic. Changes in vital signs and laboratory values were as expected for subjects being managed with opioid analgesics in the post-surgical setting. The most commonly reported TEAEs were vomiting (19.4%), nausea (12.5%), constipation (10.6%), pyrexia (6.9%), somnolence (5.0%), and pruritus (4.4%). Single and multiple doses of tapentadol OS were generally well-tolerated in pediatric patients ages 2 years and older. Tapentadol OS has a safety profile in pediatric patients ages 2 years and older that is consistent with post-operative observations and known AEs associated with opioid analgesic medication use.

10. Advisory Committee Meeting

An advisory committee meeting was not convened for these efficacy submissions because there were no issues in the submissions that required discussion at an advisory committee meeting.

11. Pediatrics

The approval of tapentadol OS in the pediatric population 6 years and older is based on efficacy and safety data from one, randomized, double-blind, placebo-controlled, efficacy and safety study of tapentadol OS in pediatric patients from birth to 17 years of age undergoing surgery anticipated to produce moderate to severe acute pain and supported by safety data from three, open-label PK and safety studies of a single dose of tapentadol OS in pediatric patients from birth to 17 years of age with acute post-operative moderate to severe pain. (b) (4)

These submissions were discussed at the Pediatric Review Committee (PeRC) on March 3, 2023. The PeRC members agreed with the Division that the data from Study KF5503/65 included in these supplements supports approval of both Nucynta OS and Nucynta tablets in pediatric patients 6 years to 17 years of age. Because the Applicant conducted a study in pediatric patients from birth to 17 years of age, agreement was reached that PMRs 1937-3 and

355-5 have been fulfilled if the Division and the Applicant reach agreement on dosing recommendations and labeling for both products.

The Division of Pediatric and Maternal Health (DPMH) was consulted to review and update the prescribing information for both Nucynta OS and Nucynta tablets. DPMH provided recommendations to the Division about language for inclusion in the following sections of the Nucynta OS and Nucynta tablets labels: Highlights, Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, and Clinical Studies.

The Applicant [redacted] (b) (4)

12. Other Relevant Regulatory Issues

Safety Labeling Change (SLC) Notification for Opioid Analgesics

The FDA issued an SLC notification for the entire class of opioid analgesics on April 14, 2023. The SLC notification stated that FDA has become aware of the risk of hyperalgesia and allodynia associated with the use of opioid analgesics and current labeling lacks information on the treatment of opioid-induced hyperalgesia. In addition, opioid-involved overdoses and deaths continue, prescription opioids continue to contribute to opioid overdose deaths, and data suggest that increasing the dosage of prescription opioids increases the risk of misuse, abuse, addiction, overdose, and death. The FDA considers the above information to be "new safety information" that warrants additional changes in the labeling of opioid analgesic products.

The Applicant submitted a rebuttal statement on May 12, 2023, asserting that the labeling changes pertaining to opioid-induced hyperalgesia (OIH) and allodynia are not warranted. In their rebuttal statement, the Applicant contends that there is limited data and information about the definition, diagnosis, and treatment of opioid-induced hyperalgesia and it is premature to add opioid-induced hyperalgesia to labeling.

The Division sent a response to the Applicant's rebuttal via email on June 9, 2023, providing additional rationale for the Agency's decision to issue an SLC notification for the class of opioid analgesics with the inclusion OIH and allodynia in labeling.

At the time of completion of this review, the Applicant had agreed to the addition of OIH and allodynia to the labels for Nucynta oral solution and Nucynta tablets.

13. Labeling

Prescribing Information

The prescribing information for both supplements required major revisions to the Indications and Usage section, the Dosage and Administration section, the Adverse Reactions section, the Use in Specific Populations section, and the Clinical Studies section. At the time of completion of this review, labeling discussions had concluded. The Applicant agreed to all of the major revisions proposed by the Division. Summaries of the major revisions proposed for the prescribing information for each supplement are provided below.

Nucynta Oral Solution

- Indications and Usage section:
  - Proposed indication: 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.
  - (b) (4)
- Dosage and Administration section:
  - In Section 2.1, Important Dosage and Administration Instructions, the Division proposed revisions to the language about the appropriate syringe for use when administering Nucynta oral solution to an adult versus a pediatric patient.
  - The language was revised to more clearly distinguish that the co-packaged syringe is for use in adults only. The pharmacist should provide a commercially available syringe of the correct size (3 mL or 5 mL) based on the dose volume being prescribed for use in pediatric patients.
  - The Division agreed with the Applicant's proposal to include language stating that Nucynta oral solution should be administered by an adult and not self-administered by a pediatric patient, including adolescents.
  - In Section 2.4, Dosage in Pediatric Patients, the Applicant proposed a (b) (4)
  - The Division did not agree with (b) (4)

- [redacted] (b) (4)
- The Division did not agree with the Applicant's new dosing [redacted] (b) (4)
- The Division proposed deleting the [redacted] (b) (4) and instructing providers to calculate the individual dose of Nucynta oral solution for each pediatric patient who weighs 16 to less than 40 kg based on the patient's weight (1.25 mg/kg body weight). Providers are instructed to convert the dose from mg to mL, round the mL dose to the nearest 0.1 mL for doses less than 3 mL and to the nearest 0.2 mL for doses larger than 3 mL, and document the dose in mg and mL. For pediatric patients who weigh greater than or equal to 40 kg, providers are instructed to start with 50 mg (2.5 mL) every 4 hours and adjust the dose as needed to a maximum of 1.25 mg/kg every 4 hours to maintain adequate analgesia with acceptable tolerability.
- Additionally, the Division proposed including language that the efficacy and safety of doses higher than 1.25 mg/kg (maximum single dose of 100 mg) have not been studied and are not recommended.

- Adverse Reactions section:
  - In Section 6.1, Clinical Trials Experience, the Division proposed revisions to the paragraph summarizing the safety data submitted in support of a pediatric indication for Nucynta oral solution. The revised language focused on adverse reactions reported in Study KF5503/65 in pediatric patients aged 6 years and older.
- Use in Specific Populations section:
  - In Section 8.4, Pediatric Use, the Division proposed revisions to the paragraph summarizing the efficacy and safety data submitted in support of a pediatric indication for Nucynta oral solution. The revised language focused on the data from Study KF5503/65 supporting the efficacy of Nucynta oral solution in pediatric patients aged 6 years and older.
  - Additionally, the Division proposed language stating that efficacy and safety have not been established in pediatric patients less than 6 years of age, pediatric patients who weigh less than 16 kg, or pediatric patients with hepatic or renal impairment.
- Clinical Studies section:
  - The Applicant proposed [redacted] (b) (4)
  - The Division proposed revised language that described the efficacy of Nucynta oral solution in pediatric patients aged 6 years and older, the lack of efficacy of Nucynta oral solution in pediatric patients less than 6 years of age [redacted] (b) (4)

(b) (4)

Nucynta tablets

- Indications and Usage section:
  - Proposed indication: 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 and older with a body weight of at least 40 kg.
  - The Division proposed revising the indication to pediatric patients ages 6 years and older who weigh at least 40 kg based on the efficacy data from Study KF5503/65.
- Dosage and Administration section:
  - In Section 2.4, Dosage in Pediatric Patients, the Applicant proposed (b) (4)
  - The Division did not agree with this (b) (4)
  - The Division did not agree with the Applicant's (b) (4)
  - The Division proposed deleting (b) (4) and instructing providers to prescribe Nucynta tablets as follows:
    - For patients weighing 40 to 59 kg, administer 50 mg every 4 hours. If adequate analgesia is not achieved with a 50 mg Nucynta tablet every 4 hours, do not increase to a 75 mg Nucynta tablet. Instead consider use of

another Nucynta product that allows for more flexible dosing, such as Nucynta oral solution.

- For patients weighing 60 to 79 kg, initiate treatment with 50 mg every 4 hours. Increase the dose if needed to 75 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. Do not exceed a maximum single dose of 75 mg. If adequate analgesia is not achieved with a 75 mg NUCYNTA tablet every 4 hours, do not increase to a 100 mg NUCYNTA tablet. Instead consider use of another NUCYNTA product that allows for more flexible dosing, such as NUCYNTA oral solution.
- For patients weighing greater than or equal to 80 kg, initiate treatment with 50 mg every 4 hours. Increase the dose if needed to 75 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. If adequate pain relief is not attained with a 75 mg NUCYNTA tablet every 4 hours, increase the dose to 100 mg every 4 hours to maintain adequate analgesia with acceptable tolerability. Do not exceed a maximum single dose of 100 mg.

  - Additionally, the Division proposed including language that the efficacy and safety of doses higher than 1.25 mg/kg (maximum single dose of 100 mg) have not been studied and are not recommended.

- Adverse Reactions section:
  - In Section 6.1, Clinical Trials Experience, the Division proposed revisions to the paragraph summarizing the safety data submitted in support of a pediatric indication for Nucynta tablets. The revised language focused on adverse reactions reported in Study KF5503/65 in pediatric patients aged 6 years and older.
- Use in Specific Populations section:
  - In Section 8.4, Pediatric Use, the Division proposed revisions to the paragraph summarizing the efficacy and safety data submitted in support of a pediatric indication for Nucynta tablets. The revised language focused on the data from Study KF5503/65 supporting the efficacy of Nucynta tablets in pediatric patients ages 6 years and older who weigh at least 40 kg.
  - Additionally, the Division proposed language stating that efficacy and safety of Nucynta tablets have not been established in pediatric patients who weigh less than 40 kg or pediatric patients with hepatic or renal impairment.
- Clinical Studies section:
  - The Applicant proposed (b) (4)
  - The Division proposed revised language that described the efficacy of Nucynta oral solution in pediatric patients aged 6 years and older, the lack of efficacy of Nucynta oral solution in pediatric patients less than 6 years of age (see Section 8.1 Clinical/Statistical – Efficacy), and emphasized that Nucynta tablets are not approved for use in pediatric patients who weigh less than 40 kg.

Other Prescription Drug Labeling

Nucynta OS

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed the Applicant's proposed Nucynta Oral Solution medication guide, instructions for use, carton label, and carton labeling. DMEPA 1 did not identify areas of vulnerability that may lead to medication errors in the proposed medication guide. However, DMEPA 1 did identify areas of vulnerability in the Nucynta oral solution prescribing information, instructions for use, container label, and carton labeling. DMEPA 1 made recommendations to the Division regarding the prescribing information and to the Applicant regarding the instructions for use, container label, and carton labeling. See the review of Damon Birkemeier, PharmD, with concurrence from Valerie S. Vaughan, PharmD, dated May 26, 2023, for a detailed discussion of the recommended revisions to the prescribing information, instructions for use, container label, and carton labeling for Nucynta OS.

14. Postmarketing Recommendations

Risk Evaluation and Mitigation Strategy (REMS)

REMS are required risk management plans that use risk minimization strategies beyond the product labeling to ensure that the product's benefits outweigh its risks in the postmarket setting. The elements of a REMS are a timetable for submission of assessments of a REMS, and one or more of the following elements: medication guide or patient package insert, communication plan, elements to assure safe use, and/or an implementation system.

All immediate-release opioids require a REMS. We will recommend the same REMS for pediatric labeling as is required for adults in the currently approved Nucynta OS and Nucynta tablets labels. The REMS language found in Section 5 Warnings and Precautions is as follows:

> **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**
>
> To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:
>
> - Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
> - Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their

caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.

- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Postmarketing requirements (PMRs) and Commitments (PMCs)

None at this time.

15.Appendix

Appendix 1 Regulatory History for supplemental NDAs 022304 and 203794

2008
Nucynta tablets (NDA 022304) were approved on November 20, 2008, for use in adults with the indication for the relief of moderate to severe acute pain. At the time of the approval of Nucynta tablets, submission of pediatric studies in ages birth to less than 17 years of age was deferred until June 30, 2016, to allow for accumulation of additional safety information from both the nonclinical juvenile program and the adult post-marketing database before initiating investigations in pediatric patients. The deferred pediatric studies issued as post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) were as follows:

- PMR 355-1: Treatment of moderate to severe acute pain in pediatric patients ages ≥6 years to ≤17 years.
- PMR 355-2: Treatment of moderate to severe acute pain in pediatric patients ages birth to <5 years*.

*There is a typographical error in the approval letter. The correct age group for PMR 355-2 is birth to ≤6 years.

2010
In May 2010, Janssen Pharmaceuticals, Inc. submitted a protocol (study KF5503/59) under IND 108134 to conduct a single-dose PK study in pediatric patients 6 to 17 years of age.

In June 2010, the Division placed study KF5503/59 on full clinical hold because of safety concerns about an unexpectedly large number of reports of CNS disorders, such as seizure, serotonin syndrome, and hallucinations, in the post-marketing experience with tapentadol IR in adults. The Division stated the proposed study in pediatric patients cannot be considered safe to proceed until a thorough post-marketing safety evaluation of Nucynta tablets has been completed (as provided for by the Food and Drug Administration Amendment Act of 2007 (FDAAA), Section 915).

In November 2010, the post-marketing safety evaluation of Nucynta tablets was completed.

2011
In March 2011, study KF5503/59 was removed from full clinical hold and allowed to proceed with the following revisions to the protocol:

- The addition of safety monitoring for seizures and suicidal ideation.
- Excluding the use of serotonergic drugs that may interact with tapentadol and potentially result in serotonin syndrome.
- The requirement for inpatient observation.
- The enrollment of adolescents first with subsequent enrollment of younger age groups once safety data from the older age group had been reviewed.

Nucynta ER tablets were approved on August 25, 2011, with the indication for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock

opioid analgesic is needed for an extended period of time. The pediatric study requirement for pediatric patients less than 7 years of age was waived because the product did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and was not likely to be used in a substantial number of pediatric patients in this age group. Pediatric studies for ages 7 to less than 17 years were deferred because the product was ready for approval for use in adults and the pediatric study had not been completed. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 1815-1: A PK, efficacy, and safety study of Nucynta ER for the management of chronic pain in pediatric patients ages 7 to <17 years.

2012

In June 2012, the Division sent an advice letter to the NDA holder agreeing with their plan to open enrollment in study KF5503/59 to all subjects 6 to less than 18 years of age and administer a single dose of tapentadol OS 1 mg/kg (maximum dose of 75 mg) given extremely slow enrollment in the study.

In August 2012, Grünenthal GmbH, the marketing holder in numerous European countries of Palexia IR and ER (the tradename of tapentadol IR and ER tablets), submitted a protocol (study KF5503/68) under IND (b) (4) to conduct a single-dose PK study in pediatric patients 6 to less than 18 years of age. The Division reviewed the protocol and allowed the study to proceed.

Nucynta OS (NDA 203794) was approved on October 15, 2012. At the time of the approval of Nucynta OS, pediatric studies in ages birth to less than 17 years were deferred because the product was ready for approval for use in adults and the pediatric studies had not been completed. The Agency acknowledged that a pediatric program for PREA requirements under NDA 022304 (Nucynta tablets) was ongoing and those studies were intended to also fulfill the PREA requirements for Nucynta OS. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 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 <17 years.
- PMR 1937-2: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe pain in pediatric patients birth to 5 years.

On October 18, 2012, the Division and Janssen Pharmaceuticals, Inc. had a Type C face-to-face meeting to discuss the ongoing pediatric clinical programs for Nucytna IR and ER tablets. The high-level conclusions regarding the design and conduct of the efficacy and safety study for acute pain in the pediatric population are as follows:

- The Division recommended that subjects be provided standard of care opioid for pain management with tapentadol and placebo treatment added on to standard of care to improve enrollment and feasibility for a randomized, double-blind, placebo-controlled acute pain trial in pediatric patients. The amount of opioid used, including standard of

care and rescue, would be the efficacy outcome measure compared for the primary endpoint.
- The primary endpoint based on the 12-hour dosing duration is acceptable.
- Using the trial design described above, the amount of opioid used, including SOC and rescue, would be the efficacy outcome measure compared for the primary endpoint.
- The Division agreed with the proposed secondary endpoints of patient/parent-reported pain intensity, time to first rescue, and functionality assessments.
- The Division stated that at least 100 patients must be exposed to Nucynta for the treatment of acute pain, with at least 25 exposed for at least 48 hours. The patients should be approximately evenly distributed across the entire pediatric age range. Data can be collected in the double-blind trials and open-label trials to fulfill the safety database requirements.
- The Division agreed with the proposal to collect a minimal number of PK samples or no PK samples during the double-blind studies in subjects with acute pain provided adequate and reliable pediatric PK data are obtained in the planned open-label studies with tapentadol.
- The Division stated that the C-SSRS is suitable for use in pediatric patients ages 6 years and older, and its use or a comparable measure is recommended in the short-term multiple-dose studies.

On December 20, 2012, Janssen Pharmaceuticals, Inc. submitted a Proposed Pediatric Study Request (PPSR) for Nucynta IR tablets, Nucynta OS, and Nucynta ER tablets.

2013

On July 8, 2013, the Agency issued a formal WR to obtain needed pediatric information on tapentadol. The WR included the following study requirements:

(b) (4)

On July 10, 2013, (b) (4) the Division released the original PMRs for NDA 022304 (PMRs 355-1 and 355-2) and issued the following PMRs:

- PMR 355-3: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to <17 years.
- PMR 355-4: 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.

In December 2013, Janssen and Grünenthal submitted a protocol (study KF5503/65) under IND 108134 (b) (4) respectively, to conduct a placebo-controlled, efficacy and safety study of tapentadol OS in pediatric patients from birth to less than 18 years of age with staggered enrollment of patients ages 6 to less than 18 years first, followed by patients ages 2 to less than 6 years, and then patients ages birth to less than 2 years after PK and safety data are obtained. The Division reviewed the protocol and allowed the study to proceed.

2014

In May 2014, Janssen and Grünenthal submitted a protocol (study KF5503/72) under IND 108134 (b) (4) respectively, to conduct an open-label, PK and safety study with pain intensity evaluated as an exploratory outcome measure in pediatric patients from birth to less than 2 years of age. The Division reviewed the protocol and allowed the study to proceed.

In August 2014, the Division sent an advice letter to Janssen regarding study KF5503/65 with the following comments:

- Although we agree with your rationale for dosing all subjects with tapentadol OS, including older pediatric subjects who could otherwise take the immediate-release tablet formulation, which would be more reflective of what is likely to occur in clinical practice, we recommend that you consider how you would apply the dosing

information from the proposed study using the oral solution to an immediate-release tablet, given the greater flexibility in dosing that can be achieved with an oral solution compared to fixed-dose strength tablets. Therefore, consider simulating potential doses for the immediate-release tablet in the proposed study (e.g., in 5 mg increments) so that dosing information can be readily applied to an immediate-release tablet formulation for use in an older pediatric population.

- You state that the Agency stipulated, (b) (4)

2015

In June 2015, based on the NDA holder's revised pediatric study plans for NDAs 022304 and 203794 (b) (4) the Division released PMRs 355-3 and 355-4 for NDA 022304 and PMRs 1937-1 and 1937-2 for NDA 203794 and issued new PMRs for both NDAs that combine the safety, PK, and efficacy studies of all age cohorts into a single trial. The reissued PMRs are as follows:

- NDA 022304 –
  PMR 355-5: PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.
- NDA 203794 –
  PMR 1937-3: PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.

2016

In 2016, FDA issued a safety labeling change for all immediate-release opioid products that included a class-wide revision of the indication. Consequently, the indication for Nucynta OS and tablets was changed from (b) (4) to "management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."

2017

In April 2017, the Division sent an advice letter regarding Study KF5503/65 with the following comments:

- You should begin to consider how the dosing information from the proposed study using the oral solution can eventually inform dosing recommendations for the IR tablet formulation, given the greater flexibility in dosing that can be achieved with an oral solution compared to fixed-dose-strength tablets.
- We do not agree with your imputation method for subjects that discontinue treatment because they switched exclusively to an oral opioid analgesic medication. This method assumes that these subjects did not take any additional opioid medication, which is

incorrect. Continue to record the amount of opioid analgesic medication being used which can then be converted to morphine equivalents. However, if you failed to record the amount of oral opioid analgesic medication used after a subject switched to oral opioid medication, you should utilize the imputation method described for subjects who discontinue for any reason other than "opioid analgesic medication is no longer needed" (i.e., estimate the cumulative use over time using uniform extrapolation, such as mg/kg per hour multiplied by 12 hours (or 24 hours)).

2018

In July 2018, the NDA holder proposed a rationale for including 17-year-olds in the pediatric population being evaluated for the US FDA primary and secondary endpoints and separately analyzing pediatric patients from birth to less than 2 years old. The NDA holder stated that the physiological response to tapentadol exposure is comparable between adolescents aged 17 years old and younger adolescents. Information on subjects who are 17 years old will add further value and reliability to the analysis. Subjects less than 2 years old will be analyzed separately. The primary endpoint analysis is unlikely to be impacted considerably as only 15 subjects are planned in this age range. This will also not affect the secondary endpoint and safety analyses as the relevant data in subjects less than 2 years old complement the already reported data in subjects 2 to less than 18 years old.

In December 2018, the Division issued an advice letter in response to the NDA holder's statistical analysis plan for Study KF5503/65 with the following comments:

- The proposed method to address the introduction of potential bias to the analysis in the birth to 2 years age group due to unblinding of the data from the 2 to 17-year-old age group appears acceptable.
- (b) (4)

2019

In July 2019, a new PMR (1815-2) for NDA 200533 (Nucynta ER) was issued based on new information provided by the NDA holder. PMR 1815-1, issued at the time of product approval, requires demonstration of efficacy. (b) (4)

1815-2 An open-label, PK and safety study or studies of an extended-release formulation of tapentadol in patients 7 to <17 years of age who are anticipated to have pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Draft Protocol Submission:	10/2019
Final Protocol Submission:	04/2020
Study Completion:	04/2022
Final Report Submission:	08/2022

The NDAs have changed ownership over the years. At times, the NDA holders for Nucynta tablets and Nucynta OS have requested extensions of the submission deadlines for the pediatric PMRs. The Agency has reviewed these extension requests and, when appropriate, granted deadline extensions. (b) (4)

(b) (4)

(b) (4)

2022

On February 18, 2022, a refuse to file letter was issued to the Applicant for both supplements. The clinical and statistical deficiencies identified in the supplements and the information needed to resolve the deficiencies are listed in the table below.

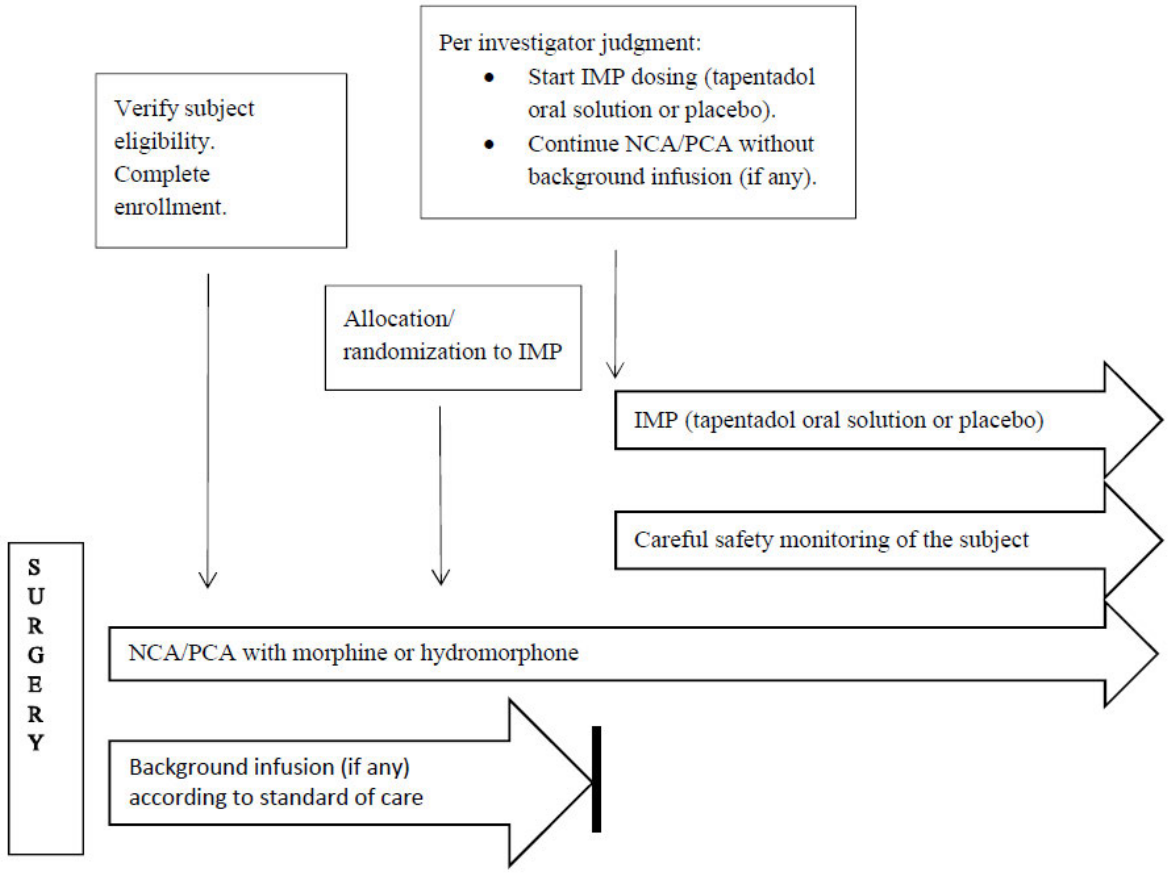
Table 34 Summary of Clinical and Statistical Deficiencies and Information Needed to Resolve the Deficiencies in Supplements S-010 and S-024

Clinical/Statistical Deficiency	Information Needed to Resolve the Deficiency
You have not submitted any electronic datasets for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.	Submit all the electronic analysis datasets and SAS program codes used to produce the efficacy and safety results presented in the study reports for all four studies. Also provide corresponding define documents for the data sets and SAS codes. The datasets should include, at a minimum, subject level data on demographics, drug exposure, adverse events, protocol deviations, efficacy parameters, laboratory values, physical examination findings, ECG findings, and vital signs.
You have not submitted any of the raw data needed to derive the primary and secondary efficacy endpoints for Study KF5503/65 in Module 5.	Submit all of the raw data needed to derive the primary and secondary efficacy endpoints for Study KF5503/65.
You have not submitted Case Report Forms for serious adverse events and discontinuations due to treatment-emergent adverse events for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.	Submit an individual Case Report Form for each serious adverse event and each discontinuation due to a treatment-emergent adverse event reported in all four studies.

You have not submitted financial disclosure information for any of the investigators in studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 1.	Submit Financial Disclosure information for all of the investigators.
You have not submitted a rationale for assuming the applicability of foreign data to the U.S. population for studies KF5503/59, KF5503/65, and KF5503/72.	Submit a rationale for assuming the applicability of foreign data in studies KF5503/59, KF5503/65, and KF5503/72 to the U.S. population.

On October 3, 2022, the Applicant resubmitted the two supplements, S-010 to NDA 203794 and S-024 to NDA 022304, and adequately addressed the clinical deficiencies enumerated above. As previously stated, the Applicant submitted pediatric data from studies XF5503/59, XF5503/68, XF5503/72, and XF5503/65 to support extending the indication for Nucynta IR tablets and Nucynta OS to pediatric patients (b) (4) years and older.

Appendix 2 Study KF5503/65 Study Flow Diagram



NCA = Nurse controlled analgesia; PCA = Patient controlled analgesia; IMP = investigational medicinal product.

Figure 1: Flow diagram of the trial

Appendix 3 Study KF5503/65 Schedule of Events

Table 2: Schedule of events

Period:	Enrollment		Treatment and evaluation					Follow-up
Visit:	1		2				3 [a]	4 [b]
Time:	≤28 days before allocation/ randomization		First dose Day 1		Subsequent doses		End of Treat-ment	Day 10 to Day 14
			Before	After	Before	After		
	Any time	After surgery						
Obtain informed consent/assent [c]	X							
Record date of signing the informed consent/assent form, sex, race/ethnicity, and height.	X [e]							
Record weight after surgery (can be measured before surgery if the surgery is not expected to notably change the weight) [d]		X						
Record age at time of allocation/randomization [z]		X						
Record clinically relevant medical/surgical history	X [e]							
Record details about the surgery		X [f]						
Perform a physical examination	X [e]						X [g]	
Record intake of prior/concomitant medication and therapies, as appropriate [h]	X		X	<----------	----------	----------	---------->	X
Detailed recording of analgesics [i]		X		X	X		X	
Record C-SSRS [j]		X					X	
Continuous heart- and respiratory-rate recording for 24 hours after first IMP [k]			<----------	----------	---------->			
Record vital signs [l]		X [m]	X [n]		X [n]		X	
Record sedation score			X [n]		X [n]			
Continuous oxygen saturation measurement until 4 hours after the last administration of IMP [o]			<----------	----------	----------	---------->		
Record oxygen saturation		X [m]	X [n]		X [n]		X	
Record 12-lead electrocardiogram		X					X	
Take blood for safety laboratory		X [p]					X	
Perform a pregnancy test	X [q]							
Check inclusion/exclusion criteria		X						
Allocate subject to IMP		X						
Stop background infusion (if any) of opioids at time of first IMP dose			X					
Detailed recording of NCA/PCA and background infusion (if any) [r]		X	<----------	----------	----------	---------->		
			no background infusion					
Administer IMP (record time and dose) [s]			X		X			

Period:	Enrollment		Treatment and evaluation					Follow -up
Visit:	1		2				3 [a]	4 [b]
Time:	≤28 days before allocation/ randomization		First dose Day 1		Subsequent doses		End of Treat- ment	Day 10 to Day 14
			Before	After	Before	After		
	Any time	After surgery						
Record pain intensity [u]			X [n]	X [v]	X [n]		X	
Record pain intensity before each NCA/PCA activation [u,t]				<----------	----------	----------	>	
Record palatability and acceptability [w]				X			X	
Global impression of change [x]							X	
Perform and document drug accountability							X	
Assess and record adverse events [y]	<----------	----------	----------	----------	----------	----------	----------	---------->
Assess discontinuation criteria			X		X		X	
Dispense subject trial card	X							

Day 1 is defined as the day of first administration of IMP. Trade names should be given in preference to generic names when recording medication in the CRF. The generic name may be used if the trade name is not available.

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

b) Can be performed by phone.

c) Subjects from whom assent is requested after surgery will be asked to give assent when they are properly stable and able to give assent according to the investigator's judgment.

d) The body mass index will be calculated automatically.

e) May be extracted from the hospital charts if already available according to the standard of care.

f) Includes the date of surgery, the indication, type of surgical procedure, start time and completion time of surgery.

g) Record that a full examination has been performed and record changes to Visit 1 only.

h) Record all medications, including opioid and non-opioid analgesics but excluding anesthetics and medication used during the surgery (Section 12.1.2). This includes the recording of prohibited medication used by breastfeeding mothers and prohibited prior medication used by mothers of a newborn subject.

i) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.2).

j) In subjects aged 6 years or older. The administration of the C-SSRS "children's baseline" must be performed after surgery. A refusal to answer the questions in the questionnaire that are appropriate for the subject must be recorded with the reason. The initials of the interviewer are to be recorded. The C-SSRS will only be used at a trial site if its use has not been rejected by the responsible ethics committee.

k) Record clinically relevant values as adverse events.

l) Respiratory rate, systolic and diastolic blood pressure, and pulse rate.

m) Directly before allocation to IMP.

n) Directly before IMP (i.e., within 10 minutes).

o) Using pulse oximetry. Record values below 92% for at least 60 seconds (excluding technical failures or artifacts).

p) When the subject is considered clinically stable after surgery. The values of the local laboratory will be used for verification of exclusion criteria.

q) For female subjects if aged 12 years or older, or post-menarchal, or sexually active. Within 48 hours prior to allocation to IMP.

r) Recording of detailed information is limited to after surgery (starting up to 24 hours before first IMP dose) up to the End of Treatment Visit (Section 12.1.2.1). NCA/PCA is with morphine or hydromorphone in accordance with the standard of care at the site. Detailed information on use will be recorded at times consistent with the memory of the NCA/PCA pump. Details will be recorded of dosing of intravenous morphine or hydromorphone used if the NCA/PCA fails, or a clinician bolus is given.

s) IMP will be administered as an oral solution. The dosing interval is 4 hours (range ±15 minutes). The reason for any delay in dosing beyond 4 hours 15 minutes needs to be documented. If the subject is sleeping at the time of the scheduled dose they must be woken to take the IMP within a maximum of 6 hours after the previous dose. The dose of IMP must be taken as soon as possible after the subject is awake. After 24 hours, the investigator may decrease the dose of IMP to 1.0 mg/kg according to the investigator's judgment of the subject's reduced need for analgesia.

t) Pain intensity scores should be obtained before each NCA/PCA activation, whenever possible. However, the NCA/PCA activation should not be unduly delayed by the pain intensity assessment. Pain intensity scores should also be obtained if intravenous morphine or hydromorphone is given if the NCA/PCA line fails, or if a clinician bolus is given.

u) The different pain scales are recorded in different age ranges: FLACC – birth to less than 6 years or in older children who are not able to report their pain using the other scales; FPS-R – 6 years to less than 12 years old; VAS – 12 years to less than 18 years old.

v) Between 30 minutes and 60 minutes after IMP. Subjects do not need to be woken for this assessment.

w) In subjects aged 2 years to less than 18 years old.

x) Clinical Global Impression of Change completed by investigator/clinician, and Patient Global (overall) Impression of Change by subject if capable of completing the questionnaire (or parent/legal guardian).

y) Adverse events are to be recorded from the time after signing the informed consent form/assent form. Adverse events are to be recorded and assessed at the time when they occur. A blood sample for analysis of serum concentrations of tapentadol needs to be drawn if there is a serious adverse event.

z) Years for subjects aged 2 years and older, months for subjects aged 2 months (i.e., 60 days) to <2 years, and days for subjects aged <2 months (i.e., <60 days).

CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; FPS-R = Faces Pain Scale–Revised; FLACC = Face, Legs, Activity, Cry, and Consolability (scale); IMP = investigational medicinal product (tapentadol oral solution or placebo); NCA = Nurse-controlled analgesia; PCA = Patient-controlled analgesia; VAS = visual analog scale.

Appendix 4 Protocol Amendments

Table 35 Protocol Amendments

Protocol Amendment Number/ Date	Major Protocol Changes
Amendment 01/ November 27, 2013	• Site of manufacture of IMP changed for logistical reasons.
Amendment 02/ October 14, 2014	• Not all endpoints will be analyzed according to the regional age ranges (2 years to less than 18 years for the EU PDCO and from birth to less than 17 years for the US FDA). This was clarified in the text and in the statistical analysis plan. In addition, the additional analysis of the primary endpoint by predefined narrow age strata was introduced. • Based on a request from US FDA, the following data were to have been collected: when possible, the investigator/delegate or subject recorded a pain intensity score prior to each administration of NCA/PCA. Pain data collected for this purpose, i.e., directly before each administration of NCA/PCA, whenever possible, was to have been used only for the purpose of exploratory analysis. • The definition of completers was amended. • Subjects who were cognitively impaired in the investigator's judgment such that they could not comply with the protocol were to have been excluded from participation in the trial. • The age range of the palatability and taste questionnaire was extended downwards from 3 years to 2 years as recruitment was open to younger subjects who were capable of performing the assessment. • It was no longer necessary that any background infusion to the NCA/PCA is at a "constant" low dose rate. • The dose of tapentadol oral solution for subjects between 2 years and less than 6 years was now defined. • The list of prohibited medication taken within 14 days of allocation/randomization to IMP was extended to include all serotonergic drugs, including selective serotonin/norepinephrine reuptake inhibitors, tricyclic antidepressants, linezolid, triptans, and St. John's Wort (hypericum perforatum) for safety reasons. The time interval during which medication for sedation was prohibited was extended to 6 hours before allocation to IMP. The use of benzodiazepines for muscle cramps and anxiety was explicitly allowed. • The use of IMP after 24 hours was modified to reflect medical practice by allowing its use every 4 hours to 6 hours, and by

Protocol Amendment Number/ Date	Major Protocol Changes
	extending use up to 72 hours to comply with a requirement to assess for at least 48 hours. • The use of the University of Michigan Sedation Scale was added for assessing sedation. • The length of time the oxygen saturation was below 92% was made consistent across descriptions in the protocol. The phrasing was also aligned in other sections. • The primary endpoint was also be evaluated using Bayesian statistics as a supportive analysis. The methodology was described in the statistical analysis plan.
Amendment 03/ April 16, 2015	• Change in sponsor from Janssen Research & Development, LLC to Grünenthal GmbH. As a consequence, the functions of the sponsor and the operational lead were merged.
Amendment 04/ June 23, 2015	• The definition for stopping IMP was clarified. • Dosing with morphine or hydromorphone was allowed for technical reasons if an NCA/PCA dose could not be given. • A clinician bolus or intravenous bolus of morphine or hydromorphone was allowed if the subject had unbearable pain in exceptional cases. This was enacted to ensure that subjects were not exposed to more pain than would normally be the case. • Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia was added to the list of prohibited medications from 6 hours prior to time of allocation/randomization to IMP until 4 hours after the last administration of IMP. • Continuous positive airway pressure or mechanical ventilation was excluded from time of allocation/randomization to IMP until 4 hours after the last administration of IMP. • Two exclusion criteria were modified to: – 8. Subject is obese in the investigator's judgment. Obesity can be determined based on appropriate BMI charts or tables; e.g., a BMI above the 97th percentile for children based on the World Health Organization growth charts (see Section 19.9). – 16. Peri- or post-operative analgesia supplied by a continuous regional technique (e.g., nerve block, wound infiltration catheter) or subject controlled epidural analgesia that was terminated less than 6 hours before allocation/randomization to IMP. • An exclusion criterion of: Subject requires continuous positive airway pressure or mechanical ventilation, at the time of allocation to IMP was added.

Protocol Amendment Number/ Date	**Major Protocol Changes**
	• Allowed the use of non-sponsor supplied dosing syringes. This was enacted for logistical reasons and did not affect the outcome parameters. • Restricted CGIC and PGIC data to a descriptive analysis in the final report.
Amendment 05/ October 27, 2015	• Defined the dosing for subjects aged 6 months to <2 years old. • Provided restrictions for the medication that could be taken by mothers of a newborn or breastfeeding mother. • Allowed the safety laboratory blood sample analysis to be performed at a local laboratory for subjects <2 years old to limit the amount of blood taken.
Amendment 06/ August 19, 2016	• Enabled the EU PDCO data set to be analyzed for regulatory requirements prior to completion of the US FDA data set. • Removed the analysis of non-opioid analgesic medication as a secondary endpoint for logistical reasons. • Clarified an inconsistency with regard to the start of continuous oxygen saturation monitoring.
Amendment 07/ March 24, 2017	• Specified the doses of tapentadol oral solution to give to subjects less than 6 months old. • Limited the safety laboratory blood sampling for subjects with a low body weight to a subset of clinical chemistry evaluations only.

Source: Clinical Reviewer

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/

LISA M WILTROUT
07/03/2023 08:55:06 AM

ALLA T BAZINI
07/03/2023 08:57:11 AM

RIGOBERTO A ROCA
07/03/2023 09:04:36 AM