Combined Clinical &
Cross-Discipline Team Leader Review

Application Type	NDA 22-195 (morphine sulfate oral solution) NDA 22-207 (morphine sulfate oral tablet) (Pediatric supplements to fulfill PREA Post Marketing Requirements)
Application Number(s)	22-195/S-010; 22-207/S-005
Priority or Standard	Standard
Date of Re-Submission	December 2, 2020
Date of Original Submission	March 23, 2015
PDUFA Goal Date	June 2, 2021
Division/Office	Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)/Office of Neuroscience/CDER
From	Elizabeth Kilgore, MD, MS, DAAP Emily Deng, MD, MPH, Clinical team leader, DAAP
Established/Proper Name	Morphine sulfate oral solution Morphine sulfate oral tablet
Trade Name	Same as above
Applicant	Hikma
Dosage Form	Oral Solution (NDA 22-195): Solution available as 10 mg per 5 ml (2 mg/mL) and 20 mg per 5 mL (4 mg/mL) Oral Tablet (NDA 22-207): Tablet available as 15 mg and 30 mg
Applicant Proposed Dosing Regimen(s)	0.15 mg/kg – 0.3 mg/kg Initial Dose
Agency Proposed Dosing Regimen(s)	0.15 mg/kg – 0.3 mg/kg Initial Dose not to exceed 20 mg (adult dose) for short term (acute) use
Applicant Proposed Indication(s)/Population(s)	Management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Agency Proposed Indication(s)/Population(s)	Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Solution: pediatric patients 2 years of age and older with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Tablets: adults and pediatric patients 12-17 years old weighing at least 50 kg with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Regulatory Action	Oral Solution: Approval for pediatric population ages 2 to 17 years for management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Oral Tablet: Approval for pediatric population ages 12-17 years for management of acute pain severe enough to require an opioid analgesic with a minimum weight of 50 kg

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

Material Reviewed/Consulted

Clinical Review	Elizabeth Kilgore, MD, MS; Emily Deng, MD, MPH
Nonclinical pharmacology	Carlic Huynh, PhD; Newton Woo, PhD; Daniel Mellon, PhD
Clinical Pharmacology	Srikanth Nallani, PhD; Michael Bewernitz, PhD; Yun Xu, PhD
DPMH	Ndidi Nworkorie, MD; Mona Khurana, MD; John Alexander, MD
DMEPA	Valerie Vaughn, PharmD

DPMH: Division of Pediatrics and Maternal Health; DMEPA: Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

NDA 22-195 (morphine sulfate oral solution) and NDA 22-207 (morphine sulfate oral tablet) were initially approved via 505(b)(2) on March 7, 2008 in adults for the indication of moderate- to- severe acute and chronic pain where an opioid analgesic is appropriate. The joint approval letter contained a post-marketing requirement (PMR) for a deferred single pediatric study in patients ages 0 to 17 years, as required under the Pediatric Research Equity Act (PREA). This single pediatric study requirement was later replaced with a requirement to conduct a PK and safety study in ages 2-17 years (PMR 204-3) and a PK, safety, and efficacy study in birth-2 years (PMR 204-4).

The Applicant submitted a pediatric efficacy supplement intended to fulfill PREA PMR 204-3 on March 23, 2015 for the NDAs and received a Complete Response on January 21, 2016, primarily because the Division found that the PK results from the original study, MORP-OS+T-(2-17)-SPK-1, did not demonstrate comparable systemic exposure to morphine between adults and pediatric patients ages 2 to <17 years and, therefore, could not solely serve as the basis for extrapolation of efficacy or allow for an adequate assessment of safety. On December 2, 2020, the Applicant submitted a Complete Response to address the January 21, 2016 CR letter in which they conducted an additional single, open-label, PK and safety study MORP-OS+ T-(2-17)-SPK-2, which is the subject of this second cycle review.

This resubmission includes data from a single, open-label, PK and safety study MORP-OS+ T-(2-17)-SPK-2. The applicant enrolled at least 10 patients per age group, as recommended in prior Agency advice. During the study, single- and multiple- dose PK were obtained from patients. The initial starting dose was based on a PK modeling and simulation conducted by the Applicant utilizing pharmacokinetic data from bioavailability studies in adults and previous study MORP-OS+T-(2-17)-SPK-1. The PK database consisted of samples from 66 subjects.

The efficacy of morphine sulfate for acute pain and chronic pain has been well established in adults. The efficacy of morphine as an analgesic can be extrapolated from adults to pediatric patients 2 year of age and older[1]. Pharmacokinetic data from pediatric studies MORP-OS+T-(2-17)-SPK-1 (reviewed in 2015) and MORP-OS+T-(2-17)-SPK-2 (reviewed in this submission), and the population PK analysis can serve as the basis for extrapolation of efficacy for morphine sulfate solution and tablets and support an initial dose of 0.15 mg/kg to 0.3 mg/kg in pediatrics, not to exceed the adult dose of 20 mg for morphine oral solution and adult dose

[1] Berde, C. B., Walco, G. A., Krane, E. J., Anand, K. J. S., Aranda, J. V., Craig, K. D., ... & Zempsky, W. T. (2012). Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics*, *129*(2), 354-364.

of 30 mg for morphine oral tablets.

The safety profile of morphine has been well established in adults. However, safety data cannot be extrapolated from adults to the pediatric population nor can we extrapolate safety from an acute pain pediatric population to a chronic pain pediatric population. The safety database (defined as subjects who received at least one dose of morphine sulfate) included 81 post-operative pediatric patients stratified by age groups 2-<4 years, 4-<6 years, 6-<12 years, 12-≤17 years for the oral solution (N=63) and 12-≤17 years for the tablet formulation (N=18). A total 43 patients received initial dosing of 0.15 mg/kg to 0.3 mg/kg, 33 patients received initial dosing of more than 0.3 mg/kg and 5 patients received dosing less than 0.15 mg/kg. The median treatment duration was 20 hours with a maximum treatment duration of 36 hours. No new safety signal has been identified for short term use of morphine oral solution or tablets in pediatric patients aged 2-17 years old. The most common treatment emergent adverse reactions appear generally consistent with known opioid-related adverse reactions (i.e., nausea, vomiting, constipation, and decreased oxygen saturation), which are dose-dependent. Based upon the data submitted, the Agency review team determined that 0.15 mg/kg to 0.3 mg/kg is a safe and tolerable initial dose for pediatric patients 2-17 years old.

The size of safety database is small, however, morphine sulfate oral solution and tablets have been used "off-label" in the pediatric population for many years. Safety data submitted in the NDA efficacy supplement, in combination with the Applicant's submitted literature, are adequate to support the safety of initial dosing of 0.15 mg/kg to 0.3 mg/kg in the 2- 17 years old for morphine oral solution and in 12 years and older with a minimum weight of 50 kg for morphine oral tablets. Safety data submitted in the NDA efficacy supplement only support the safety of short term (acute) use of morphine oral solution or tablets.

All opioids carry serious risks including death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion, and overdosage (intended or accidental). These serious risks can be mitigated through labeling. Morphine sulfate is currently approved for use in adults. The label includes a Risk Evaluation and Mitigation Strategy (REMS). Approval of morphine sulfate for use in pediatrics age 2-17 years will have the same REMS as used for adult labeling.

The Agency is acutely aware of the ongoing public health crisis related to opioids but believe that the data from this study provide important safety and efficacy information which add to the long history of morphine use in the pediatric population for acute pain management and that the benefits of approval outweigh the risks which can be mitigated through appropriate labeling and ongoing safety surveillance.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is a serious medical condition which can cause suffering and negatively affect function and quality of life in both adult and pediatric patients. • Pain can occur in a variety of medical illnesses, post-operatively, or following trauma. • Untreated pain not only can cause suffering and negatively impact quality of life but can also progress to chronic pain. • The goal of treatment is to control pain with minimal drug-related side effects. • A variety of treatments options are available for the management of pain (described below).	Pediatric patients are subject to pain associated with both malignant and nonmalignant conditions. Pain in pediatric patients needs to be managed effectively to minimize suffering and impact on day-to-day functioning, and potential long-term negative consequences. There is a public health need for medications to manage pain in pediatric patients.
Current Treatment Options	• Non-pharmacologic management of pain includes physical therapy, acupuncture, relaxation techniques, and massage. Also, a variety of treatment modalities are available including heat, cold, electrical stimulation, and ultrasound. • Pharmacologic options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids. Prescription medications are often a component of a multimodal analgesic approach. • The two major pharmacologic classes of analgesics for treating pain include opioid and non-opioid analgesics. Opioid analgesics or opioid-containing combination products are indicated for the management of severe pain when alternative treatments are inadequate.	Multiple treatment options are available for the management of pain including nonopioid analgesics and opioid analgesics for the management of severe pain. In a hospital setting, the management of pain may initially require intravenous analgesics followed by oral analgesic therapy. Although opioids, including morphine, have historically been used off-label in the pediatric population for both acute and chronic cancer and non-cancer pain and dosing recommendations are readily available from

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Availability of opioid-containing analgesics with pediatric labeling or indications is limited to certain opioid or opioid combination products (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs [oral and IV])	clinical sources, it remains vitally important to establish the safety and effectiveness (including proper dosing) of these products in the pediatric population. All opioids have potential risks that include respiratory depression and CNS depression, which may result in death, and other known opioid-related adverse effects, such as constipation, nausea, and vomiting.
Benefit	• Morphine oral solution and tablet were studied in MORP-OS+T-(2-17)-SPK-2, an open-label, multiple-dose, PK , and safety study in pediatric patients aged 2-17 years with post-operative acute pain for this review cycle. • The Study population were pediatric surgical patients who had not received opioids in the 7 days prior to surgery or used opioids chronically for >7 days in the month prior to surgery anticipated to require inpatient hospitalization postoperatively and to have moderate-to- severe postoperative pain requiring the use of oral opioids for treatment. Patients could receive intravenous (IV) analgesics postoperatively up to 48 hours until the patient was able to tolerate oral morphine. Approximately 70% of patients received concomitant opioids such as hydromorphone IV or oral as rescue analgesics. Sixty-six patients who received a wide range of initial dosing were included as the PK population. • The single- and multiple dose pharmacokinetic results from study MORP-OS+ T-(2-17)-SPK-2 in combination with population PK analysis demonstrate that the initial dosing of 0.3 mg/kg in pediatric patients aged 2-17 years old provides comparable systemic exposure to that of adult dose of 10-20 mg dose for	The effectiveness of morphine for the treatment of acute pain and chronic pain has been well established in adults. Based on an understanding of neurodevelopment, the physiology of pain, and the pharmacology of opioid analgesics, it is reasonable to extrapolate a finding of efficacy for morphine as an analgesic from adults to pediatric patients over the age of 2 years. Individual adjustment of dosage may be necessary based on response to pain relief and adverse reactions. Some pediatric patients will benefit from the initial dosing lower than 0.3 mg/kg. Pharmacokinetic data from pediatric studies MORP-OS+T-(2-17)-SPK-1 (reviewed in 2015) and MORP-OS+T-(2-17)-SPK-2 (reviewed in this

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	morphine oral solution in adults. For morphine oral tablets, initial dosing 0.3 mg/kg (15 mg or 30 mg) in pediatric patients 2 to ≤17 years of age with a minimum weight of (b) (4) kg provides comparable systemic exposure to that of adult dose of 15 mg.	submission), and the population PK analysis can serve as the basis for extrapolation of efficacy for morphine sulfate solution and tablets and support an initial dose of 0.15 mg/kg to 0.3 mg/kg in pediatrics, not to exceed the adult dose of 20 mg for morphine oral solution and adult dose of 30 mg for morphine oral tablets.
Risk and Risk Management	• The safety of morphine sulfate oral solution or oral tablet was evaluated in 81 patients aged 2 to ≤ 17 years of age who received morphine sulfate solution for the treatment of postoperative acute pain. A total of 63 patients aged 2 to 17 years old received morphine oral solution and 18 patients aged 12 to 17 years old received morphine tablets. • A total 43 patients received initial dosing of 0.15 mg/kg to 0.3 mg/kg, 33 patients received initial dosing more than 0.3 mg/kg and 5 patients received dosing less than 0.15 mg/kg. • The median treatment duration was 20 hours with a maximum treatment duration of 36 hours. • There were no deaths. Five patients experienced six serious adverse events, all determined to be unrelated or unlikely related to morphine sulfate. One subject discontinued due to an AE of procedural pain, unrelated to morphine sulfate. • The most frequently reported adverse reactions with an incidence >5% were nausea, vomiting, constipation, decreased oxygen saturation, and flatulence. • Incidence of TEAEs was higher in older age group (12-17 years old) than younger age group (2-6 years old). • There are clear dose dependent treatment-emergent adverse events associated with morphine treatment. Patients receiving	It is not acceptable to extrapolate safety from adult to pediatric patient population. Given the differences in patient populations between acute and chronic pain, as well as unknown development of opioid tolerance and opioid-induced hyperalgesia regarding chronic use of morphine sulfate in the pediatric population, it is not acceptable to extrapolate safety from an acute pain population to a chronic pain population. Opioids should be used at the lowest dose for the shortest duration. The submission did not contain safety data to support use in a chronic pain population. The safety database submitted in this NDA efficacy supplement for acute pain is small, but is adequate to support acute pain indication, taken together with the literature and the publicly available documented well-established

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	initial dosing of more than 0.3 mg/kg had the higher incidence of treatment emergent adverse events than patients in the 0.15-0.3 mg/kg group. Dose-dependent adverse events included nausea, vomiting, constipation, and decreased oxygen saturation. • There is clear dose response for adverse events related to respiratory or CNS depression including oxygen saturation decreased, hypoxia and sedation. The incidence of AEs related to respiratory /CNS depression in the high dosing (>0.3 mg/kg) group was 18.8% which was higher than 4.6% in the initial dose of 0.15 - 0.3 mg/kg group. Respiratory/CNS-related adverse events were dose-dependent considering that concomitant medications such as peri-and post-operative opioids and anesthetics may contribute to respiratory- depression related adverse events.	clinical use of morphine in pediatric patient populations. No new safety signal has been identified for short term use of morphine oral solution or tablets in pediatric patients aged 2-17 years old. Safety data submitted in this NDA pediatric efficacy supplement, in combination with literature, are adequate to support the safety of initial dosing of 0.15-0.3 mg/kg in pediatric patients aged 2-17 years old for morphine oral solution short term use. Safety data submitted in this NDA pediatric efficacy supplement, in combination with literature, are adequate to support the safety of short-term use of morphine tablets in pediatric patients aged 12-17 years old with a minimum weight of 50 kg. Morphine sulfate is currently approved for use in adults. The label includes a Risk Evaluation and Mitigation Strategy (REMS). Approval of morphine sulfate for use in pediatrics age 2-17 years will have the same REMS as used for adult labeling.

APPEARS THIS WAY ON ORIGINAL

2.Therapeutic Context

2.1 Product Information

Morphine sulfate, a Schedule II controlled substance, is a full opioid receptor agonist that is relatively selective for the mu-opioid receptor and has a principal therapeutic action of analgesia.

Morphine sulfate oral solution is available in three concentrations: 10 mg/ 5 mL, 20 mg /5 mL, and 100 mg/ 5 mL. Morphine sulfate tablets are available in 15 mg and 30 mg strengths. Both solution and tablet are labeled for the indication of relief of moderate to severe acute and chronic pain where use of an opioid analgesic is appropriate.

Morphine sulfate 100 mg/5 mL strength is approved for adult patients who are opioid tolerant. When morphine sulfate 100 mg/5 mL strength oral solution was approved in 2010, pediatric studies were waived for this strength because it was determined that necessary studies are impossible or highly impracticable due to the small number of pediatric patients requiring this medication. Morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL) may cause fatal respiratory depression when administered to patients not currently taking opioids who are opioid tolerant. Adult patients considered to be opioid tolerant are those who are taking at least 60 mg oral morphine per day, or at least 30 mg of oral oxycodone per day, or at least 12 mg hydromorphone per day, or an equianalgesic dose of another opioid, for a week or longer immediately prior to initiating dosing.

Only the 10 mg/5 mL and 20 mg/5 mL solutions and the 15 mg and 30 mg tablets will be approved for the pediatric population. The 100 mg/5 mL concentration will not be approved for pediatric use and will be labeled to be used in opioid-tolerant adults only.

2.2 Analysis of Condition

Pain is a serious medical condition in pediatric patients that needs to be managed effectively to minimize suffering and the impact on day-to-day functioning, and the potential for long-term negative consequences. There are many therapeutic options available to manage pain including non-pharmacologic and pharmacologic options. The two major pharmacologic classes of analgesics for treating pain include opioid and non-opioid analgesics. Opioid analgesics or opioid-containing combination products are indicated for the management of severe pain when alternative treatments are inadequate. Prescription medications are often a component of a multimodal analgesic approach. Opioid analgesics are important in treating severe pain conditions such as post-operative pain after major surgery, sickle cell pain crisis, extensive trauma, and invasive medical procedures.

Therapies available to treat moderate to severe pain predominantly consist of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. Use of these

products in the pediatric population can be broadly categorized into "on"- or "off"- label use of approved products or use of marketed unapproved products.

Acute pain: Morphine sulfate has been used off-label in the pediatric population for many years. The following starting doses for immediate-release orally administered morphine sulfate are recommended:

- Harriet Lane[2]: Children greater than one month (tablets and solution) 0.2-0.5 mg/kg every 4-6 hours as needed
- Berde[3]: Child <50 kg give 0.3 mg/kg every 3-4 hours. Child >50 kg give 15-20 mg every 3-4 hours

Chronic pain: The World Health Organization (WHO) defines chronic pain as pain that persists or recurs for longer than three months, can be primary (independent of any identified biological or psychological contributing factor) or secondary to a clear, underlying etiology. The WHO recently issued new guidelines on the management of chronic pain in children[4] which state that chronic pain in children differs from that in adults for a number of physiological, developmental, and social reasons and data/research/clinical experiences with adults may not be directly applicable to children. The WHO guidelines state the following:

- There were no comparative studies identified in the systematic review of the evidence on the use of morphine or other opioids in children with chronic pain.
- The pharmacokinetics of morphine in children are not well studied, and there is variability in children's individual sensitivity to morphine and their pain perceptions. It is therefore essential that all healthcare providers involved in the management of children receiving morphine are trained in the assessment and monitoring of these children.
- Children who are appropriately prescribed morphine for chronic pain in the context of end-of-life care or in children with life-limiting conditions, may require morphine for the management of intercurrent, acute or breakthrough severe pain (e.g. sickle cell crisis). Time-limited use of morphine in these contexts should be at the lowest appropriate dose and duration possible and must be regularly reviewed in order to ensure the fewest possible adverse events. Healthcare providers and caregivers need to perform frequent and repeated reassessments of pain and other symptoms, and the principles and relevant guidelines for acute pain management should be followed, including having an opioid stopping plan and adhering to other aspects of opioid stewardship.

Although opioids, including morphine, have historically been used off-label in the pediatric population for both acute and chronic cancer and non-cancer pain and dosing

[2] Harriet Lane Handbook, Mosby, Unbound Medicine; accessed online May 7, 2021. http://www.unboundmedicine.com/harrietlane/view/Davis-Drug-Guide/51518/all/morphine

[3] Berde CB, Sethna NF. Analgesics for the treatment of pain in children, N Eng J Med. 2002; 347:1094-1103

[4] https://www.who.int/news/item/01-02-2021-who-issues-new-guidelines-on-the-management-of-chronic-pain-in-children; accessed online May 1, 2021

recommendations are readily available from clinical sources, it remains vitally important to establish the safety and effectiveness (including proper dosing) of these products in the pediatric population.

The products that are the subject of this Application are currently approved for use in adults. Injectable morphine sulfate products are also approved in the United States.

The list below contains opioid analgesics with and without pediatric labeling.

Table 1. Opioid Analgesics with and without Pediatric Labeling

Opioid analgesics and opioid-containing combination products with pediatric labeling or indications	Opioid analgesics without pediatric labeling
Opioids • Fentanyl transdermal (≥2 y) (chronic pain) • Buprenorphine injection • Fentanyl citrate injection • Meperidine • OxyContin (>11 y) (chronic pain) • Morphine sulfate injection **Combination Products** • Codeine/APAP (≥3 y) • Hydrocodone/APAP (≥2 y) • Pentazocine/APAP • Dihydrocodeine/ASA/Caffeine • Codeine/ASA/Butalbital/Caffeine • Oxycodone/Ibuprofen • Pentazocine/Naloxone • Carisoprodol/ASA/Codeine • Butalbital/APAP • Butalbital/APAP/Caffeine	**Single-Entity Opioids** • Fentanyl oral transmucosal • Hydrocodone ER • Hydromorphone IV/IR/ER • Methadone • Morphine sulfate IV/IR/ER • Morphine/Naltrexone ER • Oxycodone IR/ER • Oxycodone/Naltrexone ER • Oxymorphone IV/IR/ER • Tramadol IR/ER • Tapentadol IR/ER • Buprenorphine transdermal • Butorphanol • Levorphanol • Nalbuphine • Pentazocine • Oliceridine

Source: Agency NDA reviews as of May 9, 2021

3.Regulatory Background

3.1 Summary of Regulatory History

Over the years, there has been a considerable amount of correspondence and communication between the Division and the Sponsor/Applicant. The following highlights major regulatory issues as related to this NDA submission and PMR 204-3 (2-17 years).

- 3/17/2008 – Morphine sulfate oral solution and tablets were previously marketed, unapproved. On 3/17/2008 the NDAs were approved for the indication of relief of moderate-to-severe acute and chronic pain where an opioid analgesic is appropriate. There was deferral for the pediatric study required under PREA for the treatment of moderate to severe acute and chronic pain where an opioid analgesic is appropriate in patients 0 to 17 years of age. Final report March 31, 2013
- 5/17/2010 – After approval, the Agency determined that efficacy can be extrapolated from adults to pediatric patients age 2 to <17 years, based on demonstrating comparable drug exposures between the two groups. The NDAs were released from the original PREA requirement and replaced with PK and safety study for ages 2-17 years and PK, safety, and efficacy study for birth to 2 years as below:
    - Deferred pediatric study of pharmacokinetics and safety under PREA for the treatment of moderate to severe pain where an opioid analgesic is appropriate in pediatric patients ages 2 to 17 years. Final Protocol Submission Date: July 1, 2010; Final Report Submission Date: October 1, 2012
    - Deferred pediatric study of pharmacokinetics, safety and efficacy under PREA for the treatment of moderate to severe pain where an opioid analgesic is appropriate in pediatric patients ages birth to 2 years. Final Protocol Submission Date: April 1, 2013; Final Report Submission Date: July 1, 2015
- 3/23/2015 – The Sponsor submitted a pediatric efficacy supplement to fulfill the PREA PMR for ages 2-17 years and conducted one PK and safety study, MORP-OS+T-(2-17)-SPK-1
- 1/21/16 – The Agency issued a Complete Response (CR) letter with the following deficiencies:
    1. The postmarketing studies required under the PREA for morphine sulfate tablets and oral solution were required to assess the safety and effectiveness of the products for the claimed indication in pediatric patients. The Division has determined that there is scientific support for efficacy to be extrapolated from adults to pediatric patients two years of age and older for certain analgesics, including opioids, provided that comparable systemic exposure is demonstrated between adults and that pediatric age group. However, the pharmacokinetic results from Study MORPOS+ T-(2-17)-SPK-1 did not demonstrate comparable systemic exposure to morphine between adults and pediatric patients 2 to <17 years of age and, therefore, could not solely serve as the basis for extrapolation of efficacy or allow for an adequate assessment of safety. The results of the study, in combination with the pharmacokinetic findings, were further inadequate to allow for an extrapolation of efficacy to the proposed pediatric population because concomitant use of analgesics were not reliably captured in the study (i.e. errors in collecting and/or reporting the use concomitant analgesics, including continuous and bolus patient controlled analgesia) and pain intensity was not regularly assessed in all age groups over the course of the treatment period as specified in the protocol.

2. You must demonstrate comparable systemic exposure to morphine between adults and the proposed pediatric population in order to extrapolate efficacy from adults to the proposed pediatric population or, as opioids are titrated to effect, you must establish that the morphine doses utilized in the study represent a reasonably effective starting dose, to serve as a basis for extrapolating efficacy and assessing safety in combination with the pharmacokinetic findings.
3. Because the dosing in Study MORPOS+ T-(2-17)-SPK-1 did not achieve the expected exposure, and in fact, resulted in morphine levels below the limit of quantification in numerous patients, the assessment of safety of morphine in pediatric patients from this study is inadequate. The assessment of safety must be based on exposure to a dose expected to provide efficacy.
4. You have not provided a dosing device capable of delivering accurate dosing for use in the proposed pediatric population. Because small dosing errors in the proposed population could have serious consequences, you must propose a dosing device to be provided with the product that can accurately deliver the full range of anticipated doses in the proposed pediatric population.
    a. The dosing devices co-packaged with drug product must be appropriate for the dosages to be measured. Oral liquid drug products packaged with dosage delivery devices must bear markings that are consistent with labeled dosage directions in order to facilitate proper dispensing of the product by patient, parent, or caregiver. The lowest labeled dose must be considered when determining appropriate dosing devices.
    b. Multiple dosing devices may be required. Development of an appropriate dosing device must account for the dosing ranges used when doses are calculated based on the weight range of intended users. These calculations will determine whether appropriate dosing can be achieved with a single dosing device. Multiple volume oral dosing devices may be required to allow patients and caregivers to measure the dose needed. If your risk analysis determines that multiple dosing devices are required, careful consideration should be given to develop risk mitigation strategies to avoid confusion regarding which device to use. For example, if a caregiver needs to administer a 0.5 mL dose, they will need to understand which dosing device should be utilized for the greatest dosing accuracy.
    c. Provide a mechanism to obtain additional dosing devices as needed. A single bottle of morphine sulfate oral solution may be used to fill several prescriptions each of quantities less than an entire bottle. If the co-packaged oral dosing devices are only sufficient for a single patient, an alternate means for ordering additional dosing devices should be available.
    d. If you plan to replace the 5 mL dose cup with a 5 mL oral syringe, provide the information (CMC information, DMF reference, or 510K clearance number, with data to demonstrate dose accuracy) necessary to support the change. If you plan to continue to use the 5 mL dosing cup (not prefilled), provide the CMC information for the 5 mL dose cup as a dosing device. Alternatively, you can provide a DMF reference. Provide data to demonstrate the dose accuracy of

the 5 mL dose cup for both the 10 mg/5 mL and 20 mg/5 ml strengths.

- 6/30/2016 – The Sponsor submitted Protocol MORP-OS+T-(2-17)-SPK-2, Version 1.0 for Agency review to IND 75041
- 8/4/2016 – The Sponsor submitted Protocol MORP-OS+T-(2-17)-SPK-2 synopsis incorporating PK simulation data for proposed starting doses for Agency review
- 2/27/2017 – The Division issued an Advice Letter for proposed study MORP-OS+T-(2-17)-SPK-2 regarding protocol design as follows:
    - Pain Scales: The Division gave advice related to the proposed pain rating scales for the Sponsor to clarify in the protocol how pain will be assessed for subjects >7 years of age. The Sponsor's response was that three different age-appropriate pain rating scales will be used to ensure subjects are experiencing moderate-to-severe pain, including those with limited verbal skills. The study drug can only be administered if the age-appropriate pain score is ≥4. For subjects <6 years old, the Face, Legs, Activity, Cry, and Consolability (FLACC) scale will be used. For subjects age 6 to 11 years, the Faces Pain Scale - Revised (FPS-R) pain scale will be used, and for subjects >11 years old, the Numeric Rating Scale (NRS) will be used. The Division determined that the Sponsor's proposal was acceptable.
    - Rescue medication: All supplemental opioid or non-opioids used for analgesia must be recorded in relation to scheduled dosing for morphine and analyzed expressed as total morphine equivalents of other opioids compared to morphine sulfate. Analyses should include the percentage of patients using rescue, the amount of rescue in morphine equivalent dose per day, and the number of doses of rescue per day. The Applicant revised the protocol accordingly.
- 2/10/2020 – The Sponsor submitted Complete Response considered Incomplete
- 3/10/2020 – The Division issued an Incomplete Response Letter – Deficiency #4 had not been adequately addressed.
- 12/2/2020 – The Applicant submitted second Complete Response

4. Product Quality

Dr. Rohit Kolhatkar determined that there are no Chemistry Manufacturing Controls (CMC) issued identified for this submission. See Dr. Kolhatkar's review for full discussion.

5. Nonclinical Pharmacology/Toxicology

Dr. Carlic Huynh's pharmacology/toxicology review determined that there are no pharmacology/toxicology issues identified for this submission. See Dr. Huynh's review for full discussion.

As taken from Dr. Huynh's review:

> NDA 22-207 (tablet): The approved immediate-release oral tablet formulation of morphine sulfate was utilized in the pediatric study. No pediatric-specific toxicologic concerns were identified for any of the excipients for this pediatric

population (~6 to 17 years of age), therefore the evaluation of the excipients in the original NDA review is sufficient to support the safety of the formulation in this population. The drug substance and drug product impurity/degradant specifications have already been determined to be acceptable by the pharmacology toxicology review team and are therefore considered acceptable for this supplement. No changes to the product label in the nonclinical sections are proposed by either the Applicant or the Reviewer. Pharmacology Toxicology review team has no outstanding issues with this supplement.

NDA 22-195 (solution): No pediatric-specific toxicologic concerns were identified for any of the excipients in the 2 mg/mL or 4 mg/mL formulations under consideration for the proposed pediatric population (2 to 17 years of age), therefore the evaluation of the excipients in the original NDA review is sufficient to support the safety of the formulation in this population. The drug substance and drug product impurity/degradant specifications have already been determined to be acceptable by the pharmacology toxicology review team and are therefore considered acceptable for this supplement. No changes to the product label in the nonclinical sections are proposed by either the Applicant or the Reviewer. Pharmacology Toxicology review team has no outstanding issues with this supplement.

6 Clinical Pharmacology

Based on an understanding of neurodevelopment, the physiology of pain, and the pharmacology of opioid analgesics, it is reasonable to extrapolate a finding of efficacy for morphine as an analgesic from adults to pediatric patients over the age of 2 years. Pharmacokinetic data from pediatric studies MORP-OS+T-(2-17)-SPK-1 (reviewed in 2015) and MORP-OS+T-(2-17)-SPK-2 (reviewed in this submission), and the population PK analysis can serve as the basis for extrapolation of efficacy for morphine sulfate solution and tablets and support an initial dose of 0.15 mg/kg to 0.3 mg/kg in pediatrics, not to exceed the adult dose of 20 mg for morphine oral solution and adult dose of 30 mg for morphine oral tablets. Safety data submitted in this NDA confirmed that 0.15 -0.3 mg/kg is a safe and tolerable initial dose for pediatric patient population aged 2-17 years old.

From a clinical perspective, although PK data may support a minimum weight of (b) (4) kg for the tablet, given the dose-dependent profile of respiratory/CNS depression adverse events, the clinical reviewers recommend that the minimum weight is 50 kg for 12-17 years old for the tablet so that the initial dosing will not exceed 0.3 mg/kg.

See Dr. Srikanth Nallani's clinical pharmacology review for a full discussion of the clinical pharmacology aspects of this submission.

As taken from Dr. Nallani's review:

> Based on clinical pharmacology comment provided in the CR letter for the first cycle of pediatric morphine sulfate oral solution and oral tablet supplement, the

sponsor conducted a second PK study in pediatric patients of >2 to 17 years of age. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAAP at the time) had determined that findings of efficacy for morphine sulfate in adults can be extrapolated to pediatric patients ages 2 through 17 years. Matching plasma morphine exposure in pediatric patients receiving morphine sulfate oral solution and oral tablets with adult patients was the primary approach to establish efficacy. Additional safety data as required by the division are also submitted to support this supplement.

Results of the second pediatric PK study MORP-OS+T-(2-17)-SPK-2 are reviewed in this submission. Results of the first pediatric PK study MORP-OS+T-(2-17)-SPK-1 were previously reviewed in 2015. Pharmacokinetic data from the two pediatric studies, taken together with adult PK data and the population PK analysis form the pivotal evidence for establishing efficacy in pediatrics >2 to 17 years of age. Specifically, pharmacokinetic analysis established similar systemic exposure of morphine in pediatric and adult patients with acute and chronic pain that require an opioid analgesic and for which alternative treatments are inadequate.

As adult efficacy can be extrapolated to pediatric patients, the PK simulations support the selection of the 0.3 mg/kg oral solution dose level (maximum recommended dose level of 20 mg oral solution) as an initial dose in pediatric patients. In addition, for the same reason, the PK simulations support the selection of the 15 mg tablet as the initial dose in pediatric patients (b) (4) kg and heavier.

Table 2 Single dose and multiple dose (steady-state) pharmacokinetics of morphine in pediatric patients compared to adults receiving oral solution or oral tablets of morphine sulfate.

Weight Category	Recommended Dose (Per Protocol)	Actual Dose (Range)	n	Single-dose (Geomean, Range)		Multiple-dose (Geomean, Range)	
				Cmax_pred (ng/mL)	AUCinf_pred[1] (ng*h/mL)	Cmax_pred (ng/mL)	AUCtau,ss_pred[2] (ng*h/mL)
>10-12 kg	3 mg	2.7 mg (1.6 - 3)	4	7.81 (1.46 - 22.7)	56.7 (42.8 - 83.9)	12.8 (11.3 - 14.5)	51.8 (43.0 - 68.7)
>12-19 kg	5 mg	4.6 mg (2.4 – 5)	15	5.55 (0.577 - 30.9)	53.0 (30.5 - 124)	15.5 (5.49 - 34.9)	52.4 (30.5 - 133)
>19-30 kg	7.5 mg	5.2 mg (3 - 7.6)	3	11.0 (2.98 - 22.4)	79.0 (58.3 - 96.6)	16.6 (10.2 - 25.4)	72.2 (62.1 - 91.9)
>30-38 kg	10 mg	12 mg (10 - 15)	5	6.69 (2.44 - 15.9)	59.5 (43.4 - 107)	16.5 (9.93 - 33.5)	57.1 (36.8 - 107)
>38-55 kg	15 mg	16.4 mg (7.6 – 30)	17	8.81 (4.37 - 25.1)	64.6 (38.5 - 181)	18.8 (8.78 - 62.4)	62.7 (35.3 - 198)
Adults	10 to 20 mg Oral Solution	10 to 20 mg Oral Solution	100	7.42 – 14.8 (2.77 – 41.6)[5]	36.9 – 73.9 (17.8 – 175)[5]	13.5 – 27.0 (5.43 – 77.3)[5]	36.6 – 73.2 (17.2 – 177)[5]

>55 kg	15 to 30 mg	17.5 mg (5-30)	22	11.2 (2.28 - 36.1)	74.8[3] (24.8 - 258)	21.2 (4.90 - 53.4)	74.3[3] (22.2 - 258)
Adults	15 to 30 mg tablets	15 to 30 mg tablets	*100*	12.5 - 25.0 (4.23 - 72.7)[4]	51.4 - 102.8 (22.8 – 254)[4]	20.1 - 40.2 (8.4 – 116)[4]	50.9 - 101.9 (21.2 – 253)[4]

[1]AUC0-inf calculated as follows: Dose*Frel/CL; where CL=V (after first dose) * Kel; [2]AUCtau,ss calculated as: Dose*Frel/CL; where CL=V (average of all IOVs) * Kel; [3]As recommended dose is 15 to 30 mg, predictions were based on the average of the two (i.e., 22.5 mg); [4]5% percentile of 15 mg dose to 95% percentile of 30 mg dose; [5]5% percentile of 10 mg dose to 95% percentile of 20 mg dose; pred: predicted. See details of modeling approach in section 4.2 Clinical PK assessments).

Dr. Nallani's Clinical Pharmacology Review

7 Clinical Microbiology

Not applicable

8 Clinical/Statistical- Efficacy

Efficacy: This open-label PK and safety study was not designed to assess efficacy in the 2 to ≤17-year age group as efficacy is to be extrapolated based on PK findings. The Applicant's submission states that pain scores were collected prior to dosing to confirm that pain intensity required morphine dosing. During development, in prior advice, the Agency advised the Applicant to collect pain intensity scores and analyze rescue medication use to provide supportive evidence that the doses administered were safe and effective.

Table of Clinical Studies
The Applicant submitted one clinical study MORP-OS+T-(2-17)-SPK-2, titled, "A Multicenter, Open- Label, Safety and Pharmacokinetic Study of Oral Morphine Sulfate Administration in Pediatric Subjects 2 years old through 17 years old with Postoperative Pain," in support of this supplement to fulfill PREA requirements. The table below summarizes the key features of the study.

Table 3 Clinical Study Contributing Toward Safety and PK

Study	Population	Formulation	Number Enrolled	Relevance/Study Design
MORP-OS+T-(2-27)-SPK-2	Acute post-op pain aged 2-17 years	Morphine Solution or Tablets	N=88 enrolled	Open-label, safety and PK. Inpatients (post-op) received morphine sulfate up to every four hours for a maximum of five days. Rescue analgesics were allowed.

Reviewer

Review Strategy: There was one safety and PK study submitted to support approval of the NDA. The full NDA submission and the Applicant's responses to Agency information requests were reviewed. The clinical review team also read relevant pediatric research articles to provide support for current best practices in pediatric medical practice. The labels of the currently approved morphine sulfate solution and tablet were also reviewed, as well as relevant documents from the first review cycle.

PK findings are summarized in Review Section 6. The study design is found in Appendix A. Study results including patient disposition, demographic and baseline characteristics are summarized in Review Section 8. Safety findings are summarized in Review Section 9.

DAAP consulted the Division of Pediatrics and Maternal Health (DPMH) who attended many of the internal meetings for this NDA submission and also provided input throughout the review cycle.

8.1 Study Results

8.1.1 Compliance with Good Clinical Practice
Section 5.1 of the Clinical Study Report, (Institutional Review Board), states the following: The protocol (and Amendment 1), the patient information sheet/informed consent form, and any information provided to subjects were approved by an Institutional Review Board (IRB) prior to each center's initiation.

Section 5.2 of the Clinical Study Report, (Ethical Conduct of the Study), states the following: This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and current Good Clinical Practice (GCP) and in compliance with local regulatory requirements and 21 Code of Federal Regulation (CFR) 312.

8.1.2 Financial Disclosure

The submission contained Form FDA 3454, which states the following: "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

8.1.3 Office of Scientific Investigations (OSI) Audits

No OSI inspections were conducted since this was an open-label study that did not meet regulatory definition of a covered clinical study CFR 21 Section 54.2.

The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Study Integrity (DNDSI), inspected one site. The following is taken from Dr. Li-Hong Yeh's OSIS April 14, 2021 review:

> *OSIS conducted a remote record review of the clinical portion of study MORP-OS+T-(2-17)-SPK-2 conducted at Shoals Medical Trials, Inc. (operating within Helen Keller Hospital), Sheffield, Alabama and submitted in support of NDA 022195/S010 (morphine sulphate oral solution) and NDA 022207/S005 (morphine sulphate tablets). An on-site inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic. I did not observe any observations during the remote record review that impact reliability of study data.*
>
> *Based on my review of the remote record review observations, I conclude that the clinical data from study MORP-OS+T-(2-17)-SPK-2 are reliable. Clinical data from other studies of similar design conducted by the site between May 2019 and the end of the current surveillance interval should be considered reliable without an inspection.*

8.1.4. Patient Disposition

Ten sites originally enrolled patients. However, Site 106 had early termination due to investigator noncompliance. The Agency was notified at the time of the early site termination. This affected 3 subjects (one enrolled; one enrolled and discontinued; and one was screen failure). As a result, these 3 subjects were excluded from the Applicant's analyses.

After excluding site 106, a total of 103 subjects were screened and 88 were enrolled from nine sites. The safety database, defined as subjects who received at least one dose of morphine solution or tablet, consisted of 81 subjects. The PK population consisted of 80 subjects who contributed 66 PK observations (PK data from 14 subjects were excluded because the samples did not meet adequate PK criteria).

The clinical review team noted that the reasons for discontinuation for many subjects was due to the designation of "other." The Agency sent information requests to the Applicant to further describe the category of "other" and to clarify the number of subjects completing at least 24 hours of dosing, completing the study, and discontinuing.

In response to Agency Information Requests, the Applicant clarified that there were some errors in the initial disposition table because the data were analyzed based on the Electronic Data Capture (EDC). The Applicant, therefore, conducted a post-hoc analysis which was based on actual treatment start and end times and dates instead of the EDC. As a result of this re-analysis, the Applicant determined that a total of 33 subjects (40.74% of the subjects in the Safety population) completed at least 24 hours of dosing.

A total of 32 out of 81 subjects in the safety database or 39 out of 88 subjects who enrolled discontinued. This difference reflects 7 subjects who were enrolled and discontinued before receiving a dose of study drug (therefore were not part of the safety database).

The Applicant's table below contains one error which shows that no subjects discontinued due to an adverse event when, in fact, Subject (b) (6) (12-17-year-old, morphine sulfate solution) discontinued due to an AE. Otherwise, the table is consistent with the Agency's internal analysis of the Applicant's raw datasets.

Table 4 Disposition of Subjects

Disposition Category	2 to <4 years	4 to <6 years	6 to <12 years	12 to ≤17 years	Overall
Subjects Screened	18	13	20	52	103
Site 100 [1]	1 (5.6%)	0	1 (5.0%)	4 (7.7%)	6 (5.8%)
Site 102	0	0	1 (5.0%)	2 (3.8%)	3 (2.9%)
Site 103	0	0	0	3 (5.8%)	3 (2.9%)
Site 104	3 (16.7%)	3 (23.1%)	4 (20.0%)	9 (17.3%)	19 (18.4%)
Site 105	10 (55.6%)	4 (30.8%)	5 (25.0%)	18 (34.6%)	37 (35.9%)
Site 108	0	0	0	1 (1.9%)	1 (1.0%)
Site 109	0	1 (7.7%)	3 (15.0%)	13 (25.0%)	17 (16.5%)
Site 112	0	0	0	1 (1.9%)	1 (1.0%)
Site 114	4 (22.2%)	5 (38.5%)	6 (30.0%)	1 (1.9%)	16 (15.5%)
Subjects Enrolled	14	12	17	45	88
Site 100 [2]	0	0	0	2 (4.4%)	2 (2.3%)
Site 102	0	0	1 (5.9%)	2 (4.4%)	3 (3.4%)
Site 103	0	0	0	3 (6.7%)	3 (3.4%)
Site 104	2 (14.3%)	3 (25.0%)	2 (11.8%)	8 (17.8%)	15 (17.0%)
Site 105	9 (64.3%)	4 (33.3%)	5 (29.4%)	17 (37.8%)	35 (39.8%)
Site 108	0	0	0	1 (2.2%)	1 (1.1%)
Site 109	0	1 (8.3%)	3 (17.6%)	10 (22.2%)	14 (15.9%)
Site 112	0	0	0	1 (2.2%)	1 (1.1%)
Site 114	3 (21.4%)	4 (33.3%)	6 (35.3%)	1 (2.2%)	14 (15.9%)

Subjects in the Safety Population	14 (100%)	10 (100%)	14 (100%)	43 (100%)	81 (100%)
Subjects in the PK Population	14 (100%)	10 (100%)	14 (100%)	42 (97.7%)	80 (98.8%)
Subjects Completing at Least 24 Hours of Dosing [3]	3 (21.4%)	1 (10.0%)	5 (35.7%)	24 (55.8%)	33 (40.7%)
Subjects Completing the Study Treatment [4]	8 (57.1%)	2 (20.0%)	7 (50.0%)	32 (74.4%)	49 (60.5%)
Subjects Discontinuing Study	6 (42.9%)	10 (100%)	10 (71.4%)	13 (30.2%)	39 (48.1%)
Reasons for Study Discontinuation					
Adverse Event	0	0	0	0	0
Abnormal Laboratory Result	0	0	0	0	0
Lost to Follow-Up	0	0	0	0	0
Protocol Deviation	0	0	0	0	0
Withdrawal by Subject	1 (7.1%)	3 (30.0%)	3 (21.4%)	1 (2.3%)	8 (9.9%)
Physician Decision	0	1 (10.0%)	1 (7.1%)	1 (2.3%)	3 (3.7%)
Other	5 (35.7%)	6 (60.0%)	6 (42.9%)	11 (25.6%)	28 (34.6%)

Note: Percentages are based on the number of subjects in the Safety Population unless otherwise specified. The Safety Population includes all subjects who are treated with study drug.
[1] Percentages are based on the overall number of subjects screened in each group.
[2] Percentages are based on the number of subjects enrolled in each group.
[3] Number of subjects who took their last dose at least 24 hours after their first dose.
[4] Number of subjects who completed study treatment per the disposition page on the case report form.

Applicant's Table, response to Agency Information Request received 5/4/2021.

In an effort to determine if subjects discontinued due to safety issues not previously captured or due to lack of efficacy, the primary clinical reviewer analyzed the subjects who discontinued by looking at Pain Intensity (PI) scores and whether they had experienced an AE as listed on the Case Report Forms (CRF) or line listings. Most subjects who discontinued had a decrease in pain score with many scores "0" after dosing, suggesting that morphine sulfate was no longer needed as supported by the reason for discontinuation as "no longer required opioid" or "did not complete 24 hours of dosing." Although 11 of 32 subjects who discontinued did have AEs listed in the CRFs or line listings, these AEs were generally common AEs of nausea and vomiting and all were reported as resolved. A determination of an AE is made by the investigator at the time and only one case (b) (6) was reported as discontinuation due to AE. There is no clear evidence to support that any other subjects discontinued as a result of AEs.

The primary clinical reviewer also analyzed discontinuations based on surgical type and whether rescue medication was received. Many surgeries for subjects who discontinued were tonsillectomy and adenoidectomy. Overall, 16 of the 32 subjects who discontinued received rescue analgesics. Most received non-opioid rescue such as ibuprofen (IB) or APAP (acetaminophen). Only a few of these subjects required opioid rescue analgesic. This further supports the reasons for discontinuation which stated that the subject no longer required opioid or dosing was less than 24 hours.

Demographics: As shown in the table below, overall, there was a slightly higher proportion of female subjects (approximately 53%) compared to male subjects (approximately 47%), and the majority of subjects were white (76%). Although the 2-<4 years enrolled considerably more males (approximately 79%) compared to females (approximately 21%) and the 12-≤17 years oral solution enrolled considerably more females (approximately 76%) to males (approximately 24%), the overall proportion of males to females was similar. There was a higher incidence of nausea and vomiting in females (28% and 16%, respectively) compared to males (5% and 3%, respectively). Otherwise, there were no significant differences in the incidence of AEs by gender or race.

Table 5 Demographic and Baseline Characteristics (Safety Population)

Variable Statistic or Category	2 to <4 years (N=14)	4 to <6 years (N=10)	6 to <12 years (N=14)	12 to ≤17 years (oral solution) (N=25)	12 to ≤17 years (tablet) (N=18)	Overall (N=81)
Age (years) [1]						
n	14	10	14	25	18	81
Mean (SD)	2.6 (0.50)	4.6 (0.52)	9.3 (1.54)	14.6 (1.73)	14.4 (1.61)	10.3 (5.08)
Median	3.0	5.0	9.0	14.0	15.0	12.0
Min, Max	2, 3	4, 5	6, 11	12, 17	12, 17	2, 17
Gender						
Male	11 (78.6%)	4 (40.0%)	8 (57.1%)	6 (24.0%)	9 (50.0%)	38 (46.9%)
Female	3 (21.4%)	6 (60.0%)	6 (42.9%)	19 (76.0%)	9 (50.0%)	43 (53.1%)
Race						
American Indian or Alaska Native	0	0	0	0	0	0
Asian	1 (7.1%)	0	1 (7.1%)	0	0	2 (2.5%)
Black or African American	3 (21.4%)	0	3 (21.4%)	5 (20.0%)	2 (11.1%)	13 (16.0%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	10 (71.4%)	10 (100%)	10 (71.4%)	17 (68.0%)	15 (83.3%)	62 (76.5%)
Other	0	0	0	0	0	0
Multiple	0	0	0	3 (12.0%)	1 (5.6%)	4 (4.9%)
Ethnicity						
Hispanic or Latino	3 (21.4%)	5 (50.0%)	3 (21.4%)	4 (16.0%)	2 (11.1%)	17 (21.0%)
Not Hispanic or Latino	11 (78.6%)	5 (50.0%)	11 (78.6%)	21 (84.0%)	16 (88.9%)	64 (79.0%)
Height (cm)						
n	14	10	14	25	18	81
Mean (SD)	91.51 (10.781)	104.02 (6.921)	142.65 (14.932)	160.62 (10.605)	166.08 (10.851)	139.79 (31.299)
Median	94.60	107.20	144.10	161.00	165.70	152.40
Min, Max	66.0, 109.2	91.0, 111.7	121.9, 173.9	129.0, 184.0	147.3, 186.0	66.0, 186.0
Weight (kg)						
n	14	10	14	25	18	81
Mean (SD)	14.03 (2.016)	17.41 (2.587)	39.04 (17.327)	61.65 (14.773)	63.46 (17.579)	44.45 (24.770)
Median	14.40	16.95	35.60	57.00	59.10	46.40
Min, Max	10.5, 17.0	13.8, 22.0	24.0, 91.6	38.8, 101.0	37.7, 94.2	10.5, 101.0
BMI (kg/m^2)						
n	14	10	14	25	18	81
Mean (SD)	17.13 (3.695)	16.11 (1.932)	18.84 (6.292)	24.20 (6.728)	22.88 (5.523)	20.76 (6.286)
Median	16.45	16.10	17.10	22.10	21.35	18.70
Min, Max	12.2, 27.5	13.5, 18.4	13.8, 37.8	15.0, 39.7	14.4, 32.8	12.2, 39.7

CSR, Applicant's Table 14.1.3.1, p. 90-91.

Initial dosing was weight-based but ultimately the investigator's decision. The weights of subjects ranged from 10.5 kg to 101 kg. The minimal weight for 12-17-year age

group (solution or tablet) was 37.7 kg. The minimal weight for the 2-4-year age group was 10.5 kg.

Demographics by Surgical Procedure are included in Appendix C. There were a variety of different types of surgical procedures with different levels of pre- and peri-surgical anesthesia and post-operative medications received. Because of the wide variety of the types of procedures (from tonsillectomy and circumcision to spinal fusions), post-operative pain intensity levels and duration of requirement of pain medication may have varied considerably.

8.1.5. Protocol Deviations and Violations

The protocol and statistical analysis plan did not distinguish the definitions of the terms protocol violation versus protocol deviation and the terms were used interchangeably as protocol deviation/violation. More than half (56.8%) of subjects experienced a protocol deviation/violation.

As shown in the table below, the two most common types of deviations/violations were related to laboratory/PK (34.6%) and safety assessment/other (21%). Laboratory/PK violations included examples such as the PK being collected outside of the protocol-defined time frames or missed. Safety assessment/other violations included examples such as screening assessments being completed postoperatively and pain intensity scale scores or University of Michigan Sedation Scale (UMSS) being completed out of sequence or out of the time frame. The Applicant's determination was that none of these deviations/violations were deemed to impact study results or subject safety. After review of the protocol deviations/violations in detail, the Agency clinical reviewers agree with the Applicant's assessment that these deviations/violations do not impact study results or subject safety. Examples of the types of protocol deviations/violations are shown in the table in Appendix F.

Table 6 Protocol Deviations/Violations (Safety Population)

	2 to <4 years (N=14) n (%)	4 to <6 years (N=10) n (%)	6 to <12 years (N=14) n (%)	12 to ≤17 years (oral solution) (N=25) n (%)	12 to ≤17 years (tablet) (N=18) n (%)	Overall (N=81) n (%)
Subjects with Any Protocol Deviation/Violation	11 (78.6)	4 (40.0)	6 (42.9)	12 (48.0)	13 (72.2)	46 (56.8)
Assessment - safety - Laboratory / PK	0	0	0	1 (4.0)	0	1 (1.2)
Assessment - safety - Other	6 (42.9)	1 (10.0)	1 (7.1)	7 (28.0)	2 (11.1)	17 (21.0)
Assessment - safety - Vital Signs	0	0	0	4 (16.0)	3 (16.7)	7 (8.6)
Informed Consent / Assent - ICF	2 (14.3)	0	0	1 (4.0)	2 (11.1)	5 (6.2)
Laboratory / PK - Laboratory / PK	7 (50.0)	4 (40.0)	3 (21.4)	8 (32.0)	6 (33.3)	28 (34.6)
Other - Other	0	1 (10.0)	2 (14.3)	5 (20.0)	4 (22.2)	12 (14.8)
Study Drug - Dosing	1 (7.1)	0	3 (21.4)	0	0	4 (4.9)
Violation of Inclusion Criteria - Other	0	0	0	1 (4.0)	0	1 (1.2)
Visit Window - Dosing	0	0	0	0	1 (5.6)	1 (1.2)

Source: Section 14.1, Table 14.1.2
Abbreviations: ICF = informed consent form; n = number of subjects in that category; N = number of subjects; PK = pharmacokinetic
Note: percentages are based on the number of subjects in the Safety Population as displayed in column header 'N.' Subjects with one or more deviation within a type of protocol deviation were counted only once.

Applicant's table CSR, p. 45.

By site, the largest number of subjects with protocol deviations was site 105 with 22 subjects. Site 104 had the largest number of individual types of deviations/violations.

Prophylactic Naloxone Use: Upon reviewing line listings, the Agency reviewer noted that 13 of the 14 subjects from Site 109 received naloxone HCL as a concomitant medication or prior medication. The Division sent an Information Request to the Applicant to provide narratives for these subjects and the rationale for why naloxone was administered. In response to the IR, the Applicant stated that, "During the study, it was mentioned by some sites or hospitals that their standard practice is to use naloxone or methadone intra-operatively or post-operatively to reverse the effects of opiates and thereby prevent narcotic overdose." Although naloxone was not specifically prohibited per protocol and, therefore, does not constitute a protocol deviation/violation, the use of naloxone in the context of opioid safety and effectiveness must be taken into consideration. The narratives revealed that all subjects who received naloxone prophylactically were at site 109 and were s/p spinal surgery. The dose of naloxone varied (presumably weight-based but a clear rationale for dosing was not provided). No naloxone appeared to be administered in response to an opioid-related AE as the naloxone was received prior to morphine administration in most cases.

Although the Division could not determine the exact reason for naloxone administration at site 109, based on a literature search conducted by the primary reviewer, post-operative administration of naloxone has been reported but is not considered standard of care.

- One study by Monitto[5] found that naloxone infusion rates ≥1 ug/kg/h significantly reduced but did not eliminate the incidence of opioid-induced side effects, primarily pruritus in 59 children and adolescents after major surgery. This effect was not associated with a significant increase in opioid consumption or impairment of analgesia.
- A randomized, controlled trial of 46 pediatric patients using postoperative patient-controlled analgesia (PCA) found less pruritus with low-dose (0.25 mg/kg/h) naloxone infusion than placebo and that pain control was not adversely affected[6].

[5] Monitto, C., et al, The optimal dose of prophylactic intravenous naloxone in ameliorating opioid-induced side effects in children receiving intravenous patient-controlled analgesia morphine for moderate to severe pain: a dose-finding study, Anesthesia Analg. 2011 Oct: 113(4): 834-842.
[6] Cravero, J, et al, The society for pediatiric anesthesia recommendations for the use of opioids in children during the perioperative period; Paediatric Anaesth. 2019 June; 29 (6): 547-571.

The primary clinical reviewer analyzed adverse events for the 13 subjects from Site 109 who received naloxone. Three subjects experienced no AEs. The only AE that occurred in more than one subject was oxygen saturation decreased, experienced by four subjects. One subject each experienced an AE of sedation; hypoesthesia/pruritus; nausea; pleural effusion; ventricular hypertrophy; and spinal cord injury (SCI). It is unknown if these AEs would have been worse without naloxone or if naloxone prevented these or other AEs from occurring in these subjects. However, despite the fact that data from these subjects are confounded, the data still contribute to an overall understanding of the safety of morphine sulfate use in the pediatric population. Four of the total 7 subjects who experienced respiratory-related TEAEs were from site 109 and all were spinal surgeries. The clinical significance of this is unclear.

Reviewer's assessment of Prophylactic Naloxone use: It is impossible to determine if naloxone may have prevented or minimized respiratory events and other opioid-related AEs in subjects from site 109, and therefore, these data are confounded. However, the safety findings regarding the respiratory depression or CNS depression may be underreported in those patients who received naloxone.

Efficacy: Efficacy was not a primary endpoint in this open-label study as efficacy was extrapolated from adults based on PK simulation modeling. The age-appropriate pain scale was to be administered prior to and after each dose of study drug according to the site's standard of care (but at least at approximately 2 hours post-dose), and pain scores were to be obtained in all subjects to ensure that moderate-to-severe pain was being experienced and, hence, study drug administration was appropriate. The first dose of the study drug could only be administered if the age-appropriate pain score was ≥4 (i.e., consistent with pain of at least moderate severity).

Pain Intensity Assessment: Three different age-appropriate pain rating scales (Appendix B) were used to ensure subjects were experiencing moderate-to-severe pain including those with limited verbal skills.

- Age <6 years: The Faces, Legs, Activity, Cry, and Consolability Scale was used. Each category was scored 0-2 which results in a total score of 0-10. 0=relaxed and comfortable; 1-2=mild discomfort; 4-6=moderate pain; 7-10=severe discomfort or pain or both.
- Age 6-11 years: The Faces Pain Scale-Revised (FPS-R) was used. Subjects were required to point to the face that showed the amount of pain they were in.
- Age >11 years: The Numeric Rating Scale was used. Subjects rated their pain on a scale from 0-10. 0=none; 1-3=mild; 4-6=moderate, and 7-10=severe.

Across all age groups, the pooled baseline mean pain score overall was 6.2 (minimum score of 4 and maximum score of 10). Two hours after the first dose, the overall mean change from baseline was -3.4 (minimum score change -10 and maximum score change 2). Overall, most subjects had a mean decrease of 3 points from baseline or prior dose when assessed 2 hours after dosing through Dose 10.

Reviewer's assessment of Pain Intensity Scores: There were no major differences in pain intensity change from baseline by age group or whether solution or tablet. Without a comparator, efficacy based on pain scores alone is not possible. Additionally, most subjects used opioid or non-opioid rescue medication, so it is difficult to determine any treatment effect from morphine alone. This open-label study was not designed for pain scores to serve as efficacy endpoints.

8.1.6. Rescue Medication Use

As per the protocol, supplemental pain medication was permitted as rescue medication during the oral treatment period if the study drug did not provide adequate pain relief as assessed by the investigator or an appropriately qualified designee. Supplemental pain medication was also permitted as pre-emptive/prophylactic treatment when a potentially painful procedure was to be performed in the post-operative period. All supplemental opioid or non-opioids used for analgesia were analyzed expressed as total morphine equivalents of other opioids compared to morphine sulfate. Summaries include the percentage of subjects using rescue medication, the amount in morphine equivalent dose per day, and the number of doses per day.

As shown in the table below, rescue medication was used by 71.6% of subjects overall. The highest rescue medication use was in the 12 to ⩽17-year tablet group (17 subjects, 94.4%), followed by the 12-17 year oral solution group (21 subjects, 84.0%). For the other age groups, the incidence of rescue medication, in descending order, was for the 4 to <6-year group (7 subjects, 70%), the 2 to <4-year group (7 subjects, 50%), and the 6 to <12 years group (6 subjects, 42.9%).

The mean cumulative rescue medication usage was 108.6 mg/day in the 12 to ≤17-year tablet group and 33.3 mg/day in the 6 to <12-year group, followed by 15.9 mg/day in the 12 to ≤17-year oral solution group.

Table 7 Summary of Rescue Medication Use

Variable Parameter/Statistic	2 to <4 years (N=14)	4 to <6 years (N=10)	6 to <12 years (N=14)	12 to ≤17 years (oral solution) (N=25)	12 to ≤17 years (tablet) (N=18)	Overall (N=81)
Rescue Medication Use						
Yes	7 (50.0%)	7 (70.0%)	6 (42.9%)	21 (84.0%)	17 (94.4%)	58 (71.6%)
No	7 (50.0%)	3 (30.0%)	8 (57.1%)	4 (16.0%)	1 (5.6%)	23 (28.4%)
Cumulative Rescue Medication Usage (mg/day) [1]						
n	7	7	6	21	16	57
Mean (SD)	1.713 (1.2310)	2.529 (3.4603)	33.285 (61.4255)	15.931 (24.3044)	108.627 (278.7699)	40.386 (152.6154)
Median	1.001	0.991	7.367	4.000	15.725	4.000
Min, Max	0.63, 3.42	0.72, 10.20	1.76, 158.10	0.80, 94.40	1.80, 1068.82	0.63, 1068.82
Number of Rescue Medication Doses (per day) [2]						
n	7	5	6	19	16	53
Mean (SD)	3.570 (1.8610)	3.274 (1.3432)	8.406 (6.9457)	9.065 (14.1524)	7.348 (14.2979)	7.200 (11.7550)
Median	2.994	3.462	6.500	2.855	3.598	3.462
Min, Max	1.44, 5.81	1.25, 4.94	1.01, 21.55	0.97, 44.34	0.79, 60.23	0.79, 60.23

Source: Listing: 16.2.9.2
Note: Percentages are based on the number of subjects in the Safety Population as displayed in column header 'N'. SD = standard deviation.
[1] Reported in cumulative total morphine milligram equivalent (MME) dose per day. Chloraseptic Spray, Diazepam, Ropivicaine and Lidocaine 5% were administered as rescue medications but not included in the calculation of cumulative rescue medication usage due to the absence of MME conversion factors. Rescue medications with frequencies reported as "Other", "Unknown", "Continuous", "Intermittent" and "Occasional" were included in the calculation assuming a frequency of a single administration.
[2] Number of Rescue Medication Doses (per day) = (the sum across all rescue medications of (Frequency x duration [in days])) / treatment duration. For rescue medcations with a frequency of once per day, the duration of administration was rounded up to the nearest day for calculation purposes. Rescue medications with a frequency less than the reported duration were assumed to be administered once.

Applicant's table 14.3.6.5, CSR p. 342.

A variety of opioid rescue medications were used. The most frequently used was hydromorphone. Of the subjects who received opioid rescue medication, approximately 70% of pediatric patients 2-17 years old received hydromorphone IV (intravenous) or PCA (patient-controlled analgesia) as the rescue medication for pain relief.

There was no clear correlation between rescue medication use and the initial morphine dose received. Some subjects who received initial dosing of 0.15 -0.3 mg/kg had low cumulative dosing of rescue medication use. Conversely, some subjects who received higher initial dosing such as 0.3 to 0.4 mg/kg received a high amount of rescue medication.

8.1.7. Concomitant Medications

Concomitant medications were defined as those medications that were initiated prior to the start of the study drug and maintained during the study. As expected in a post-operative setting, there were many concomitant medications. With regard to concomitant analgesics, the most frequently received were paracetamol (approximately 48%) and oxycodone/oxycodone HCL (approximately 27%). Although morphine was prohibited, three subjects (3.7%) received IV morphine as follows: Subject (b) (6) (12-17 year solution) received IV morphine once; Subject (b) (6) (12-17 years solution) received oral morphine once described as "standard of care for post-op pain"; and Subject (b) (6) (12-17 years tablet) received IV morphine once as pre-emptive to the procedure of "pulling out chest tube." One subject (b) (6) (2-<4 years) received IV morphine on 2 occasions as rescue medication.

Reviewer's assessment of rescue medication use: Rescue medication was given based on the investigator's judgment and a pre-specified pain score was not required. Parenteral hydromorphone or fentanyl was to be used as the preferred supplemental analgesic, although other analgesics were also allowed per protocol. Many of these post-operative subjects received opioid rescue alone, non-opioid rescue such as acetaminophen or NSAID, or a combination of opioid and non-opioid rescue. Without pre-rescue pain scores, it is difficult to determine the effect of opioid vs non-opioid rescue on efficacy of morphine sulfate in the pediatric population in this open-label study where morphine was dosed every four hours as needed.

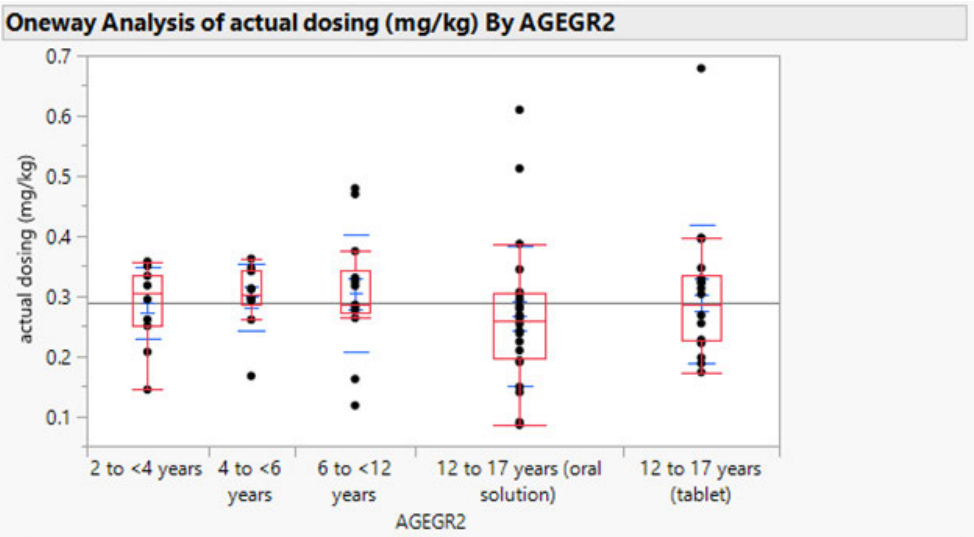
9. Safety

9.1 Review of Safety database

The safety database included 81 post-operative pediatric patients aged 2-17 years old who received at least one dose of morphine oral solution or tablets. Among them, 6 patients received single dose and 75 patients received multiple dosing up to 10 doses. A total of 63 patients aged 2- 17 years old received morphine oral solution stratified by age groups of 2-<4 years (N=14), 4-<6 years(N=10), 6-<12 years (N=14), 12-≤17 (N=25) years. A total of 18 patients aged 12-≤17 years old received morphine tablet. The starting doses recommended in the study were provided by weight-band and approximated 0.3 mg/kg. However, the study allowed the actual dose administered to the patient to be based upon investigator judgement. As indicated in Figure 1, the actual initial dosing ranged from 0.08 mg/kg to 0.68 mg/kg. A total of 43 patients (53%) received initial dosing of 0.15-0.3 mg/kg, 33 patients (41%) received dosing >0.3 mg/kg initial starting dose and 5 patients (6%) received initial dosing <0.15 mg/kg.

Among 63 subjects aged 2-17 years who received morphine oral solution, the initial dosing ranged from 0.08 mg/kg to 0.61 mg/kg. Initial dosing range was wider in the older age group compared to the younger age group. The mean initial dosing across age groups were from 0.26 mg/kg to 0.30 mg/kg. Approximately 80% of subjects in the less than 6 years received initial dosing from 0.17 to 0.36 mg/kg. Approximately 80% of subjects in the older age group received initial dosing from 0.11 to 0.42 mg/kg. There were some outlier patients who received dosing higher than 0.5 mg/kg and a few outlier subjects who received dosing less than 0.1 mg/kg. Among 18 subjects who received morphine tablets, 14 patients received 15 mg and 4 patients received 30 mg tablet as initial dosing with a range of 0.17 mg /kg to 0.67 mg /kg. The minimum weight in this age group is 37. 8 kg.

Figure 1 Actual initial dosing distribution by age group



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2 to <4 years	0.144144	0.17552	0.25	0.305789	0.333333	0.353397	0.357143
4 to <6 years	0.166667	0.176042	0.284402	0.303208	0.342348	0.360381	0.361905
6 to <12 years	0.117647	0.13961	0.272972	0.285443	0.341393	0.474224	0.478964
12 to 17 years (oral solution)	0.085393	0.114736	0.196717	0.258483	0.305235	0.449272	0.609756
12 to 17 years (tablet)	0.17301	0.186051	0.225506	0.285444	0.333858	0.425016	0.678733

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2 to <4 years	14	0.2877149	0.0597345	0.0159647	0.2532252	0.3222045
4 to <6 years	10	0.2981996	0.0551493	0.0174397	0.2587482	0.3376511
6 to <12 years	14	0.3035045	0.0973539	0.0260189	0.247294	0.359715
12 to 17 years (oral solution)	24	0.2669151	0.1174241	0.0239691	0.2173312	0.3164989
12 to 17 years (tablet)	18	0.3024937	0.1147895	0.0270561	0.2454102	0.3595772

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As indicated in Table 8 the median treatment duration was 20 hours with a maximum treatment duration of 36 hours. The average treatment duration was between 10 hours and 22 hours. The treatment duration in the older age group was longer than in the younger age group. The average cumulative doses received were from 16 mg to 129 mg. The older age group received higher cumulative doses compared with the younger age group as shown in the graphic below. The maximum cumulative doses of morphine received was 270 mg over 35 hours for tablets and 210 mg over 36 hours for oral solutions.

Overall, the mean (SD) average time between consecutive doses of study drug was 4.85 (1.328) hours and slightly lower for subjects 12 to ≤17 years (4.57 [0.663] hours and 4.20 [0.368] hours for the oral solution and tablet, respectively).

Table 8 Summary of Study Drug Exposure (Safety Population)

Parameter (unit) Statistics	2 to <4 years (N=14)	4 to <6 years (N=10)	6 to <12 years (N=14)	12 to ≤17 years (oral solution) (N=25)	12 to ≤17 years (tablet) (N=18)	Overall (N=81)
Number of doses of study drug, n	14	10	14	25	18	81
Mean (SD)	4.1 (1.51)	3.1 (1.91)	4.8 (2.55)	5.2 (2.01)	6.4 (1.82)	5.0 (2.19)
Median	4.0	2.5	5.0	5.0	7.0	5.0
Min, Max	2, 7	1, 7	1, 10	1, 9	1, 9	1, 10
Treatment duration (hours)[a], n	14	10	14	25	18	81
Mean (SD)	16.48 (6.431)	10.32 (8.624)	18.17 (10.279)	18.83 (8.208)	22.55 (7.545)	18.08 (8.788)
Median	16.88	9.57	21.95	20.48	24.06	20.25
Min, Max	4.0, 25.0	0.0, 25.7	0.0, 36.2	0.0, 35.9	0.0, 34.2	0.0, 36.2
Total drug exposure (mg), n	14	10	14	25	18	81
Mean (SD)	16.37 (6.083)	16.58 (10.729)	51.71 (33.142)	85.99 (52.386)	129.17 (65.915)	69.06 (61.067)
Median	15.00	12.50	50.00	75.00	105.00	50.00
Min, Max	6.0, 28.0	2.4, 30.4	15.0, 103.6	15.0, 210.0	15.0, 270.0	2.4, 270.0
Number of missed doses, n	14	10	14	25	18	81
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.1 (0.40)	0.1 (0.24)	0.0 (0.25)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 0	0, 0	0, 0	0, 2	0, 1	0, 2
Average time between consecutive doses (hours), n	14	8	13	23	17	75
Mean (SD)	5.58 (2.085)	5.13 (1.173)	5.26 (1.661)	4.57 (0.663)	4.20 (0.368)	4.85 (1.328)
Median	5.43	4.66	4.73	4.25	4.02	4.27
Min, Max	4.0, 12.1	4.0, 6.9	4.0, 9.3	4.0, 6.7	3.8, 5.1	3.8, 12.1

Source: Section 14.1, Table 14.3.6.1
Abbreviations: Max = maximum; Min = minimum; n = number of subjects in that category; SD = standard deviation
a Treatment duration (hours) = date/time of last intake of study drug – date/time of first intake of study drug.

Applicant's table CSR.

Determination of adequacy of safety database

The safety database submitted in this NDA efficacy supplement is small but is typical for a pediatric PK/ safety study. The sample size meets the agency's advice for at least 50 pediatric patients (10 patients per age group). Most patients received multiple dosing up to 10 doses with a median treatment duration of 20 hours. Given that oral morphine has been widely used in clinical practice for acute pain management in the pediatric patient population, taken together with literature review data, there was adequate exposure to inform safety of morphine sulfate solution and tablets at the starting dose range of 0.15-0.3 mg/kg as proposed in the label for acute pain management.

9.2 Safety Results

9.2.1 Deaths

There were no deaths reported in the study.

9.2.2. Serious Adverse Events

The reader is referred to Appendix D for the definitions of SAEs and adverse events grading scale. Five subjects experienced 6 SAEs with preferred terms: Pericardial

effusion; Postoperative fever/Failure to thrive; Influenza; Spinal cord injury (SCI); and Pyelonephritis acute. As determined by the clinical reviewer, all SAEs were unrelated or unlikely related to study drug, morphine sulfate. All SAEs were rated as moderate in severity except for spinal cord injury and acute pyelonephritis which were rated severe. The SAE of spinal cord injury occurred before study drug was given, pyelonephritis occurred two days after the last dose of study drug, and pericardial effusion occurred four days after the last dose of study drug.

Table 9. Summary of serious adverse events

Site-Subject	AE Preferred Term	Start Date End Date	Outcome	Severity	Relatedness	Study Drug Action Taken
(b) (6)	Pericardial effusion	(b) (6)	Recovering/ Resolving	Moderate	Unrelated	Not applicable
	Postoperative fever		Resolved	Moderate	Unrelated	Dose not changed
	Failure to thrive		Resolved	Moderate	Unrelated	Dose not changed
	Influenza		Resolved	Moderate	Unrelated	Not applicable
	Spinal cord injury		Resolved with sequelae	Severe	Unrelated	Dose not changed
	Pyelonephritis acute		Resolved	Severe	Unrelated	Not applicable

Source: Applicant's table 12-5, CSR p. 60; Appendix 16.2, Listing 16.2.7.2.

A summary of the SAE narratives is provided below.

Table 10. SAE Narratives

Patient ID Demographics	Brief Narrative	Reviewer's comment
(b) (6) 15-year old M s/p spinal fusion	Preferred term: Spinal cord injury (SCI) SAE onset of spinal cord injury occurred on (b) (6) on the same day as his spinal fusion and before his first dose of morphine which was on (b) (6)	The SAE appears unrelated to morphine since it occurred before the 1st dose of study drug. Transient neuromotor changes are a possible known risk after spinal surgical procedures.
(b) (6) 2-year-old M s/p vesicoureteral reflux repair	Preferred term: Pyelonephritis SAE onset of pyelonephritis occurred 2 days after last dose of morphine sulfate. The medical history was significant for hypospadias and cryptorchism. He was discharged home with a Foley catheter in place. The symptoms subsequently resolved with antibiotic treatment.	The SAE appears unrelated or unlikely related to morphine since it occurred 2 days after the last dose of study drug. The patient had risk factors of pre-existing ureteral condition and an indwelling Foley catheter. Morphine is labeled to cause urinary retention.

(b) (6) 3-year-old F s/p T&A	Preferred term: Influenza SAE onset of influenza occurred on Day 2 of treatment. On Day 1, the subjected started vomiting and developed a postoperative fever. The subject tested positive for Influenza A. She was started on Tamiflu and over time, began to improve.	The SAE appears unrelated to morphine. Given that this subject tested positive for influenza and that symptoms improved with treatment for influenza, it is not likely that morphine sulfate use was causally contributive and appears unrelated.
(b) (6) 16-year-old M s/p aorta repair	Preferred term: Pericardial effusion SAE onset of pericardial effusion occurred 4 days after last dose of morphine. The PMH was significant for aortic aneurysm and aortic root dilation and gene mutation.	The SAE appears unrelated to morphine since it occurred 4 days after the last dose of morphine sulfate. Pericardial effusion is reported after cardiopulmonary surgery.
(b) (6) 3-year-old M s/p T&A	Preferred terms: Post-op fever; Failure to thrive SAE onset was on Day 1 of his first dose of study drug. Throughout his hospital stay, the subject developed fever, difficulty eating and drinking, and developed dehydration. He had diagnostic work-up, was managed medically and ultimately discharged home and recovered.	The SAE of post-op fever and failure to thrive appears unrelated to morphine since there was associated elevated WBC suggesting underlying infection possibly related to post-operative sequalae. The subject had a risk factor of asthma.

Reviewer; M=male; F=female; T&A=tonsillectomy & adenoidectomy; CBP=cardiopulmonary bypass.

9.2.3. Adverse Events leading to drug discontinuation

During the study, one subject (1.2%) discontinued from the study due to an AE. Subject (b) (6) in the 12 to ≤17-year (oral solution) group experienced an AE of severe procedural pain and the study drug was withdrawn. This TEAE was considered unrelated to the study drug.

Table 11. Discontinuation due to AE Narrative

Patient ID and Demographics	Narrative	Reviewer's comment
(b) (6) 14-year-old F s/p T5-L4 instrumented fusion of thoracic and lumbar spine	Preferred term: Procedural pain AE onset Day 1. On Day 1, the subject experienced a severe AE of procedural pain, which started out as moderate two days prior. She was discontinued from the study on Day 2 before completing 24 hours with the study drug and given oxycodone for pain management.	Causality of this AE of procedural pain appears unrelated to morphine sulfate. The event was considered recovering/resolving.

Reviewer; F=female.

9.2.4. Adverse Events by Severity

As shown in the table below, most AEs were moderate severity. One subject experienced an AE of procedural pain rated as severe intensity.

Table 12 Treatment-emergent Adverse Events by Severity

Preferred Term	2 to <4 years (N=14) n (%)	4 to <6 years (N=10) n (%)	6 to <12 years (N=14) n (%)	12 to ≤17 years (oral solution) (N=25) n (%)	12 to ≤17 years (tablet) (N=18) n (%)	Overall (N=81) n (%)
Number of Subjects with at Least 1 TEAE	5 (35.7)	2 (20.0)	4 (28.6)	13 (52.0)	9 (50.0)	33 (40.7)
Mild	3 (21.4)	1 (10.0)	2 (14.3)	2 (8.0)	4 (22.2)	12 (14.8)
Moderate	2 (14.3)	1 (10.0)	2 (14.3)	10 (40.0)	5 (27.8)	20 (24.7)
Severe	0	0	0	1 (4.0)	0	1 (1.2)
Procedural pain	0	0	0	1 (4.0)	0	1 (1.2)

Source: Section 14.1, Table 14.3.1.8
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in that category; N = number of subjects; TEAE = treatment-emergent AE
Note: All AEs were coded using MedDRA Version 20.1. At each level of summarization (preferred term), subjects who reported more than 1 AE were only counted once for the maximum severity. If a particular event was missing the severity then the strongest possible severity was assumed for analysis (severity = severe), unless the start date of the event was before the date of the first study drug administration. Preferred terms are sorted in descending order of frequency of overall.

Applicant's Table 12-3, CSR p. 57.

9.2.5. Treatment Emergent Adverse Events and Adverse Reactions

The adverse reaction profile was similar to adults in that they were typically opioid-related. The most common adverse reactions reported in at least 5% of patients across all age groups were: nausea (17%), vomiting (10%), constipation (6%), decreased oxygen saturation (5%), and flatulence (5%).

The table below includes a summary of the incidence of treatment-related adverse reactions reported in at least 1% of the population stratified by age group and overall.

Table 13. Incidence of Adverse Reactions Reported in > 1% Patients Stratified by Age-Group and Overall

Dictionary-Derived Term	2 to <4 years N=14	4 to <6 years N=10	6 to <12 years N=14	12 to 17 years (oral solution) N=25	12 to 17 years (oral tablet) N=18	Overall N=81
Patients with any TEAE (%)	35.7	20	28.6	52	50	40.7
Nausea	7.1	10	21.4	24.0	16.7	17.3
Vomiting	14.3	10	.	16.0	5.6	10
Constipation	7.1	.	.	8.0	11.1	6.2
Flatulence	.	.	.	12.0	5.6	4.9
Oxygen saturation decreased	.	.	7.1	4.0	11.1	4.9
Pyrexia	7.1	.	.	.	11.1	3.7
Sedation	.	.	.	4.0	5.6	2.5
Pruritus	.	.	.	4.0	5.6	2.5
Hypoxia	.	.	.	.	5.6	1.2
Vertigo	.	.	.	.	5.6	1.2
Muscle spasms	.	.	.	.	5.6	1.2

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9.2.6. Dose-response Relationship Exploration

A total of 43 subjects (53%) received initial dosing of 0.15 mg/kg to 0.30 mg/kg (N=34 oral solution and N=9 tablet). There were 33 subjects (41%) who received initial starting dose >0.3 mg/kg and 5 subjects (6%) received initial dosing <0.15 mg.

The protocol allowed for dose adjustment of up titration up to 25% of the subjects starting dose or down titration by 25% based on clinical assessments or use of supplemental analgesia. Seven subjects required up or down titration. Two of these subjects experienced respiratory-related adverse events (Subject (b) (6) [hypoxia] and Subject (b) (6) [oxygen saturation decreased] which required dose adjustment. There were otherwise no trends in the types of AEs or clinical presentations requiring dose adjustment based on starting dose or cumulative exposure.

As shown in the table below, the incidence of AEs overall for morphine sulfate solution was higher in the dosing group >0.3 mg /kg (41.7%) than the dosing group of 0.15 -0.3 mg/kg (32.4%). As only 5 subjects received dosing less than 0.15 mg/kg, comparison with this group is not meaningful. Excluding <0.15 mg/kg group, there is a clear dose-response for opioid related adverse events including nausea, vomiting, oxygen saturation decreased, sedation and pruritis.

Table 14. AE Incidence by Initial Starting Dose – Morphine Oral Solution

Treatment Emergent Adverse Events by Preferred Term within Initial Dose Subgroups Safety Population Initial Dose: Solution				
	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=5)	0.15 to 0.3 mg/kg (N=34)	>0.3 mg/kg (N=24)	Overall (N=63)
Number of Subjects with at least one TEAE	3 (60.0%)	11 (32.4%)	10 (41.7%)	24 (38.1%)
Nausea	2 (40.0%)	4 (11.8%)	5 (20.8%)	11 (17.5%)
Vomiting	2 (40.0%)	2 (5.9%)	3 (12.5%)	7 (11.1%)
Constipation	1 (20.0%)	2 (5.9%)	0	3 (4.8%)
Flatulence	0	3 (8.8%)	0	3 (4.8%)
Oxygen saturation decreased	0	0	2 (8.3%)	2 (3.2%)
Postoperative fever	0	2 (5.9%)	0	2 (3.2%)
Procedural pain	2 (40.0%)	0	0	2 (3.2%)
Abdominal pain	0	1 (2.9%)	0	1 (1.6%)
Anxiety	0	0	1 (4.2%)	1 (1.6%)
Electrocardiogram T wave inversion	0	1 (2.9%)	0	1 (1.6%)
Failure to thrive	0	1 (2.9%)	0	1 (1.6%)
Influenza	0	1 (2.9%)	0	1 (1.6%)
Pleural effusion	0	0	1 (4.2%)	1 (1.6%)
Pruritus	1 (20.0%)	0	0	1 (1.6%)
Pyrexia	0	1 (2.9%)	0	1 (1.6%)
Sedation	0	0	1 (4.2%)	1 (1.6%)
Tachycardia	1 (20.0%)	0	0	1 (1.6%)
Ventricular hypertrophy	0	1 (2.9%)	0	1 (1.6%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; TEAE = treatment emergent adverse event.
Note: A TEAE is defined as any AE with an onset date after the first intake of the study drug and before the last intake of the study drug plus 24 hours, having been absent pretreatment, or worsens relative to the pretreatment state. All AEs are coded using MedDRA Version 20.1. Within each level of summarization, subjects who reported more than one adverse event were only counted once. Preferred Term is sorted in descending order of frequency of overall and then alphabetically

Applicant's table, response to IR received 4/27/2021.

The AE incidence for the tablet for the initial starting dose revealed the highest incidence was in the >0.3 mg/kg dose group. Dose-dependent adverse events included nausea, vomiting, constipation, oxygen saturation decreased, sedation and hypoxia.

Table 15. AE Incidence by Initial Starting Dose – Morphine Oral Tablet

Treatment Emergent Adverse Events by Preferred Term within Initial Dose Subgroups Safety Population Initial Dose: Tablet				
	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=0)	0.15 to 0.3 mg/kg (N=9)	>0.3 mg/kg (N=9)	Overall (N=18)
Number of Subjects with at least one TEAE	0	2 (22.2%)	7 (77.8%)	9 (50.0%)
Nausea	0	0	3 (33.3%)	3 (16.7%)
Constipation	0	1 (11.1%)	1 (11.1%)	2 (11.1%)
Oxygen saturation decreased	0	0	2 (22.2%)	2 (11.1%)
Pyrexia	0	0	2 (22.2%)	2 (11.1%)
Flatulence	0	0	1 (11.1%)	1 (5.6%)
Hypoxia	0	0	1 (11.1%)	1 (5.6%)
Muscle spasms	0	0	1 (11.1%)	1 (5.6%)
Pruritus	0	1 (11.1%)	0	1 (5.6%)
Sedation	0	0	1 (11.1%)	1 (5.6%)
Vertigo	0	0	1 (11.1%)	1 (5.6%)
Vomiting	0	0	1 (11.1%)	1 (5.6%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; TEAE = treatment emergent adverse event.
Note: A TEAE is defined as any AE with an onset date after the first intake of the study drug and before the last intake of the study drug plus 24 hours, having been absent pretreatment, or worsens relative to the pretreatment state. All AEs are coded using MedDRA Version 20.1. Within each level of summarization, subjects who reported more than one adverse event were only counted once. Preferred Term is sorted in descending order of frequency of overall and then alphabetically

Applicant's response to IR received 4/27/2021.

Adverse Events by cumulative dose: As shown in the table below, most subjects received cumulative dosing between >0 to 50 mg (N=41). However, the highest incidence of AEs by cumulative dosing was in the >150-200 mg group at 67% but only two subjects received that cumulative dose. As expected, consistent with opioid AEs, the higher incidence of AEs appears in the higher dose ranges, overall. The number of subjects in those highest ranges were very few so interpretability of these findings is limited.

Table 16. Treatment Emergent Adverse Events by Cumulative Dose

Dose Group (mg)	Age Group					Overall
	2-<4	4-6	6-<12	12-<17 soln	12-<17 tab	
>0 to 50	**N=14**	**N=10**	**N=8**	**N=7**	**N=2**	**N=41**
At least 1 TEAE [N (%)]	5 (36)	2 (20)	1 (12)	4 (57)	0	12 (29)
>50 to 100	**N=0**	**N=0**	**N=4**	**N=10**	**N=3**	**N=17**
At least 1 TEAE [N (%)]	0	0	2 (50)	5 (50)	1 (33)	8 (47)
> 100 to 150	**N=0**	**N=0**	**N=2**	**N=6**	**N=7**	**N=15**
At least 1 TEAE [N (%)]	0	0	1 (50)	3 (50)	4 (57)	8 (53)
> 150 to 200	**N=0**	**N=0**	**N=0**	**N=0**	**N=3**	**N=3**
At least 1 TEAE [N (%)]	0	0	0	0	2 (67)	2 (67)
>200 to 250	**N=0**	**N=0**	**N=0**	**N=2**	**N=2**	**N=4**

At least 1 TEAE [N (%)]	0	0	0	1 (50)	1 (50)	2 (50)
>250 to 300	**N=0**	**N=0**	**N=0**	**N=0**	**N=1**	**N=1**
At least 1 TEAE [N (%)]	0	0	0	0	1 (100%)	1 (100%)

Reviewer; TEAE=treatment emergent adverse event; based on Applicant's table modified by reviewer.

9.2.7 Adverse events related to Respiratory or CNS Depression

All opioids induce respiratory or CNS depression in a dose-dependent manner. The safety findings regarding the respiratory depression or CNS depression in this NDA may be underreported in that 13 patients from the site 109 received naloxone as prophylaxis therapy. To explore dose-response relationship for AE related to respiratory /CNS depression, patients with a preferred term of "hypoxia", " oxygen saturation decreased" and "sedation" were included in the table below. A total of 8 (9.8%) patients developed adverse events related to respiratory or CNS depression including oxygen desaturation (N=5), hypoxia (N=1) and sedation (N=2). These adverse events were dose-dependent, 2 (4.6 %) patients were from the initial dosing of 0.15-0.3 mg/kg group and 6 patients (18.8%) were from the high dosing >0.3 mg/kg group. It is worth to note that these 6 patients who received initial dosing of more than 0.3 mg/kg also were from site 109 and received naloxone as prophylaxis therapy. Among four patients who received the tablets, three with weight ranging between 40 kg to 50 kg received the initial dosing of 15 mg. Given that the lowest dosing strength for morphine tablets is 15 mg and there is significant safety concern for patients with an initial dosing of more than 0.3 mg/kg, the recommended minimum weight is 50 kg so that the initial dosing will not exceed 0.3 mg /kg. Since it is not feasible to accurately adjust the dose for morphine tablets and potential swallowing issues for the less than 12 years old age group, morphine tablets are not recommended for patients younger than 12 years old or weight less than 50 kg.

Table 17. Adverse events related to respiratory /CNS depression

Subject ID	***Initial dose received (mg/kg)***	***Age group***	***Dictionary derived term***
(b) (6)	0.28	12 to 17 years (oral solution)	Oxygen saturation decreased
	0.3	12 to 17 years (tablet)	Hypoxia
	0.32	12 to 17 years (tablet)	Sedation
	0.39	12 to 17 years (tablet)	Oxygen saturation decreased
	0.4	12 to 17 years (tablet)	Oxygen saturation decreased
	0.48	6 to <12 years	Oxygen saturation decreased
	0.51	12 to 17 years (oral solution)	Sedation
	0.61	12 to 17 years (oral solution)	Oxygen saturation decreased

CDTL reviewer JMP clinical

9.2.8. Adverse Events of Special Interest (AESI)

Based on the known safety profile of morphine sulfate, an opioid analgesic, the protocol pre-defined AEs of special interest as follows: Sedation, respiratory depression, nausea, vomiting, and pruritus of moderate-to-severe intensity/grade.

Overall, approximately 23% of subjects experienced an AESI, all of which were of moderate intensity. The most common AESIs by preferred term were nausea, experienced by 18.5% and vomiting, experienced by 4.9% of subjects, respectively. Two subjects experienced sedation (2.5%) that met the criteria of an event of special interest. None of these AESIs was serious or led to discontinuation from the study. No subjects met the Applicant's pre-defined criteria of an adverse event of special interest in the respiratory depression or pruritus category, although mild pruritus was experienced by some subjects. Treatment-emergent adverse events of special interest by preferred term are shown in the table below.

Table 18. Treatment-emergent adverse events of special interest

System Organ Class Preferred Term	2 to <4 years (N=14) n (%)	4 to <6 years (N=10) n (%)	6 to <12 years (N=14) n (%)	12 to ≤17 years (oral solution) (N=25) n (%)	12 to ≤17 years (tablet) (N=18) n (%)	Overall (N=81) n (%)
Number of Subjects with at Least 1 AESI	1 (7.1)	1 (10.0)	2 (14.3)	9 (36.0)	6 (33.3)	19 (23.5)
Gastrointestinal disorders	1 (7.1)	1 (10.0)	2 (14.3)	8 (32.0)	5 (27.8)	17 (21.0)
Nausea	1 (7.1)	1 (10.0)	2 (14.3)	7 (28.0)	4 (22.2)	15 (18.5)
Vomiting	1 (7.1)	0	0	2 (8.0)	1 (5.6)	4 (4.9)
Nervous system disorders	0	0	0	1 (4.0)	1 (5.6)	2 (2.5)
Sedation	0	0	0	1 (4.0)	1 (5.6)	2 (2.5)

Source: Section 14.1, Table 14.3.2.3.2
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in that category; N = number of subjects; TEAE = treatment-emergent AE
Note: Adverse events of special interest include sedation, respiratory depression, nausea, vomiting and pruritis of moderate to severe intensity grade. All AEs are coded using MedDRA Version 20.1. At each level of summarization (system organ class and preferred term), subjects who reported more than one AE of special interest (AESI) were only counted once for the maximum severity. System organ class and preferred term are sorted in descending order of frequency of overall.

Applicant's Table 12-6, CSR, p. 62.

Sedation: The University of Michigan Sedation Scale (UMSS) is a 5-point scale which measures sedation/arousal as follows: 0= Awake and Alert; 1= Minimally Sedated: tired/sleepy, appropriate response to verbal conversation and/or sound; 2=Moderately Sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command; 3=Deeply Sedated: deep sleep, arousable only with significant physical stimulation; and 4=Unarousable.

The UMSS was administered at the following time points: 1) Immediately before and 30 minutes, one hour, and two hours after the first two doses of study drug, and 2) Immediately before and one hour after each subsequent dose of study drug. As a result of the frequent assessment of UMSS, a subject had the opportunity to have multiple UMSS scores obtained during the study.

The Applicant provided a Summary table of UMSS scores by age group and Timepoint (Baseline through Dose 10 pre- and post-dose). UMSS scores by individual subject were also provided in the submission.

Across all groups and time points, most UMSS scores were 0, 1, or 2. Five subjects had at least one sedation scale score of 3. No subject had a score of 4. No definite trends were noted with regard to timing of scores of 2 or greater in relation to dosing and no age group appeared to have a higher number of scores of 3 or greater.

The five subjects with at least one sedation scale score of 3 are summarized below:

- (b) (6) (12-17 years tablet): AE of sedation with a sedation score of 3 on 14 out of 18 scores at multiple time points. See brief narrative in the table below.
- (b) (6) (2-<4 years): AE of pyelonephritis; see SAE narrative; subject discontinued early; sedation score of 3 on 3 out of 14 scores at 30 minutes post-dose 1, 1 hour post-dose 1, and 2 hours post-dose 1. All other scores were 0 or 1 except for one score of 2 at 30 minutes post-dose 2. All oxygen saturation levels were ≥97%.
- (b) (6) (4-<6 years): No AEs; sedation score of 3 on 2 out of 14 scores at 1 hour post-dose 3 and 1 hour post-dose 4; remainder of scores 0 or 1 except for one score of 2 pre-dose 3. All oxygen saturation levels were ≥97%.
- (b) (6) (6-<12 years solution): AE of nausea; sedation score of 3 on 1 out of 17 scores at 2 hours post-dose 1; remainder of scores 0 or 1. All pulse oximetry scores were ≥98%.
- (b) (6) (6-12 years solution): No AEs; sedation score of 3 on 1 out of 11 scores at 2 hours post-dose 2; remainder of scores 0 or 1. All pulse oximetry scores were ≥97%.

Two subjects (b) (6) had sedation TEAEs, as shown in the narrative table below.

Table 19. Narratives of Subjects with TEAEs of Sedation

Subject ID; Age group	# of times UMSS Score 3	Reviewer's Comments
(b) (6) 12-17 tablet	14 out of 18 scores	This subject had baseline sedation score of 3 and remained 3 until pre-dose number 4, when the score improved to 2. The scores then went back and forth between 2 and 3. The sedation AE was rated as moderate. Reported action was that gabapentin was stopped and clonidine patch was removed. Therefore, concomitant medications may have been a contributor. There was not associated decreased oxygenation. The AE resolved. No other AEs were reported for this subject.
(b) (6) 12-17 solution	0 out of 18 scores	All sedation scores were 2 or less. No scores of 3. The AE was rated as moderate sedation. Morphine dosing was interrupted. This subject received hydromorphone for rescue medication x 4 which may have been a contributor to the sedation AE. Pulse oximetry scores were ≥92 throughout. This subject from site 109 did not receive prophylactic naloxone. The subject received 5 doses of morphine and completed the study. No other AEs were reported.

Reviewer; UMSS=University of Michigan Sedation Scale

Reviewer's assessment of UMSS scores: It is not unexpected in a post-operative patient population who have received opioids and anesthetics during surgery to have UMSS scores of 1-2. Additionally, many subjects received concomitant medications (including opioid rescue analgesics) which may have impacted their UMSS scores. Overall, a UMSS score of 3 did not appear to be associated with increased risk of other adverse events or associated with respiratory-related events in this study. No subject experienced a UMSS of 4. No definite trends with regard to change from baseline of UMSS scores based on timing of morphine dosing were identified.

Respiratory-Related Adverse Events*:* Based on the Agency's clinical reviewer analysis, a total of 7 subjects (8.6%) experienced a respiratory-related treatment emergent adverse event with the preferred terms oxygen saturation decreased (5 subjects) or hypoxia (2 subjects).

The Applicant analyzed respiratory-related events in the following categories: a) clinically significant decreases in oxygenation, b) oxygen saturations <92%, c) TEAE of hypoxia and d) TEAE of oxygen saturation decreased.

The percentage of subjects with clinically significant decreases in SpO2 was a secondary safety endpoint in this study. Per protocol, pulse oximetry was to be >92% for all subjects during the study. Although the investigator determined clinical significance, it was usually reached when the subject needed an intervention (e.g., administration of oxygen for low SpO2). The Applicant identified seven (8.6%) of subjects who met the protocol-defined criteria of clinically significant decreases in

SpO_2. All seven of these subjects were also identified in the TEAE categories of oxygen saturation decreased or hypoxia and are consistent with the Agency's findings of respiratory-related TEAEs. Two subjects (b) (6) each experienced one isolated pulse oximetry value <92%. These two subjects did not meet the protocol-defined criteria of clinical significance or experience a respiratory-related AE.

The table below provides a summary of TEAE with preferred terms oxygen saturation decreased or hypoxia, which were dose dependent. A total of 7 subjects experienced oxygen saturation or hypoxia, 5 received an initial dosing of more than 0.3 mg/kg and 4 of them from study site 109 also received naloxone as prophylaxis therapy per the clinical investigator.

Table 20. Treatment Emergent Respiratory-Related Adverse Event Narratives

Subject ID	Age Group	Initial Dose	AE Terms and Oxygen Desaturation Values	Reviewer's comments
TEAE Oxygen saturation decreased				
(b) (6)	12-<17 y soln	0.15-0.3 mg/kg	Oxygen saturation decreased 97, 97, 96, 95, 94, 95, 96, 96, 93, 98, 98, 98, 97, 95, 99, 98, 98, 98, 97, 97, 97	Lowest oxygen desaturation of 93 occurred 2 hours post-dose 2 of morphine. Treated with 0.5-2 L/min oxygen via nasal cannula. The subject also experienced significant emesis.
	12-17 y tablet	>0.3 mg/kg	Oxygen saturation decreased 97, 97, 95, 95, 97, 93, 93, 92, 93, 91, 93, 89, 96, 94, 92, 97, 95, 95, 95, 98, 98	Lowest desaturation of 89 was 12 hours after dose 1 and predose 4 of morphine. Dose was titrated down. Patient received 1 L oxygen via nasal cannula. Received concomitant rescue hydromorphone.
	12-17 y tablet	>0.3 mg/kg	Oxygen saturation decreased 100, 98, 97, 96, 96, 97, 98, 98, 93, 95, 96, 99, 96, 100, 99, 95, 98, 97, 96, 96, 98	Lowest oxygen desaturation of 93 was 2 hours after dose 2 of morphine. Patient received 10 L blow-by oxygen. Rescue medication included hydromorphone via PCA which coincided with oxygen desaturation.
	6-<12 y	>0.3 mg/kg	Oxygen saturation decreased 100, 98, 98, 100, 95, 99, 99, 97, 100, 97, 99, 94, 93, 98, 98, 95, 94, 97, 95, 96, 97	Lowest desaturation was 93, 1 hour after dose 4 of morphine. RR=10-13 breaths/min. No dose adjustments. Blow-by oxygen was given for the AE. Concurrent rescue medication

				of hydromorphone confounds causality. AE resolved.
(b) (6)	12-<17 y soln	>0.3 mg/kg	Oxygen saturation decreased 99, 96, 98, 98, 99, 97, 99, 97, 98, 96, 96, 94, 92, 96, 95, 94, 97, 96, 93, 96, 98	Prior to dose 4, oxygen saturation decreased to 94 with a further decrease to 92 one hour later. No dose adjustments. Prior history of asthma. No treatment was given. The first decreased oxygenation occurred 14 hours after morphine was started. Gabapentin and hydromorphone were relevant concomitant medications.
	TEAE Hypoxia			
	12-17 soln	<0.15 mg/kg	Hypoxia 100, 98, 97, 98, 96, 96, 97, 96, 96, not done; missing, 95, missing, 94, 98	Lowest oxygen desaturation was 94. Hypoxia coincided with concomitant medications which included gabapentin, diazepam, and oxycodone. Subject received 2 L oxygen via nasal cannula. The onset of the AE occurred before morphine was administered.
	12-17 y tablet	>0.3 mg/kg	Hypoxia 99, 97, 97, 98, 97, 97, 97, 97, 95, 96, 96, 94, 96, 95, 95, 95, 98, 98, 96, 97, 98	Lowest oxygen desaturation of 94 began about 40 minutes after receiving dose 5 of morphine. Oxygen was given. Concomitant medications included hydromorphone.

Reviewer; RR=respiratory rate; Note: Subjects above from site 109 received prophylactic naloxone

Respiratory Rate (RR): Clinically significant decreases in RR (as assessed by the investigator) was a secondary safety endpoint in this study. Per the Applicant, normal ranges for respiratory rates are: 20-30 breaths/min for ages 1-2, 20-25 breaths/min for ages 3-5, 14-22 breaths/min for ages 6-12 and 12-18 breaths/min for ages 13-17.

Overall, 29 (35.8%) subjects experienced decreases in RR during the study; however, no clinically significant decreases were reported. Per the CSR, clinical significance was assessed by the investigator, but usually was reached when the subject needed an intervention.

One subject (Subject (b) (6) [12-17 years tablets]) s/p right frontal external ventricular drain and Chiari decompression experienced an AE of bradypnea, mild, resolved, dose not changed. This subject also experienced AEs of post-op procedural pain, nausea, constipation and muscle spasms. The expected respiratory rate range for this age group would be 12-18 breaths/minute. This subject had

several recordings of RR less than 12, with the lowest RR of 7.0 at one hour post-dose 3 and a RR of 8.0 pre-dose 4. UMSS scores were 2 or less throughout and pulse oximetry did not show clinically significant respiratory events. He received multiple concomitant medications including diazepam and rescue medication of oxycodone and was an outlier who received multiple doses of hydromorphone. Therefore, there are numerous confounders which make it impossible to determine if bradypnea was due to morphine alone.

Overall, more subjects in the younger age groups had decreases in RR during the study than in the older age groups with 13 (92.9%) subjects aged 2 to <4 years and 10 (100%) subjects aged 4 to <6 years) experienced decreases in RR. In a post-operative population of subjects receiving multiple concomitant medications, considerable variation in respiratory rate may be observed.

9.2.9. Other Safety Findings

- *Vital signs:* Vital sign measurements included systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), SpO_2 (determined by pulse oximetry), and body temperature. Vital signs were recorded at screening after the subject had been in a sitting or resting position for 5 minutes. If screening was prior to Day 1, vital signs were repeated before surgery on Day 1. In addition, for the first 2 doses of study drug, vital signs were measured immediately before as well as at 30 minutes, 1 hour, and 2 hours after administration. For all subsequent doses, vital signs were measured immediately before and 1 hour after study drug administration. Vital signs were also measured 8 hours after the last dose of study drug and again prior to discharge or 24 hours after the last dose of study drug, whichever occurred first. There were no clinically significant vital signs reported.
- *Laboratory:* Clinical laboratory tests were performed at screening to confirm subject eligibility. They were not collected at study completion or any other time during the study unless deemed necessary by the investigator (e.g., in case of an adverse event). There were no abnormal clinically significant values in hematology test results. On subject (Subject (b) (6), a screen failure) had a clinically significant high ALT value at baseline. There were no abnormal clinically significant urinalysis values.
- *ECG:* A 12-lead ECG or 12-second rhythm strip (a minimum of 2 leads was preferred) was recorded at screening (i.e., any time during the interval from Day -13 until just before initiation of surgery on Day 1) and at any time during the 24-hour posttreatment period. Every ECG or rhythm strip was interpreted by the investigator (signed and dated). All ECG results (normal/abnormal) were listed by subject. ECG results were provided by individual subject in Line Listing 16.2.9.7. Although the clinical reviewer noted that there were some abnormal ECG results at Screening and 24-hour post-dosing, the Investigators did not consider these to be clinically significant. The approved morphine sulfate labels list the following cardiac-related adverse events in the

cardiovascular system: Bradycardia, hypertension, hypotension, palpitations, syncope, and tachycardia.

Reviewer's assessment of other safety findings: Acknowledging the limitation in interpreting AEs in a post-operative population, there were no clinically important AEs in the vital signs, laboratory values, or ECG that could be solely attributed to morphine. No subject experienced an SAE or discontinuation related to vital sign, laboratory, or ECG abnormalities and no trends were noted, overall.

9.3. Applicant's literature to support safety

Given that there is extensive clinical experience for morphine use in the pediatric population, the Applicant submitted the following literature to support the safety of the proposed initial dosing of 0.15 mg/kg to 0.3 mg/kg in pediatric patient population aged 2-17 years old.

Table 21. Applicant's Literature Supporting Proposed Morphine Sulfate Initial Starting Dose

First Author	Type of Study	Population	Study Overview	Author's conclusions	Reviewer's comments
Poonai[7]	Randomized, blinded superiority trial comparing oral morphine (0.5 mg/kg; maximum 20 mg) with ibuprofen (10 mg/kg; maximum 600 mg) every 6 h as needed	N=65 received morphine; Ages 5 to 17 years for up to 8 doses	The primary outcome was pain & secondary outcomes were additional analgesic requirements, adverse effects, unplanned health care visits and pain scores for doses 2 to 8.	Both drugs decreased pain with no apparent difference in efficacy, although more participants in the morphine treatment arm experienced adverse events.	Dosing used in the study was higher than proposed labeled dosing for this product. AEs in the study were opioid-related. No unexpected safety events were identified.
Wille[8]	Prospective study evaluating oral morphine administered as 0.5 mg/kg	N=91 received morphine; Efficacy N=74 Ages 6 months to 16 years	Compliance of prescription, pain scores and adverse events were studied in pediatric patients who presented with fractures in Emergency Department.	There were few adverse events. No AEs were severe. Efficacy was reached after 30 to 60 minutes as measured on the Visual Analog Scale.	Dosing used in the study was higher than proposed labeled dosing for this product. AEs in the study were opioid-related. No unexpected major safety events were identified.
Dahlstrom[9]	PK	N=53 total; Ages Birth to 15 years	Morphine kinetics in children to induce anesthesia based on	No significant difference in morphine kinetics was observed in premedication	The minimum morphine plasma PK concentration to suppress clinical signs of

[7] ClinicalTrials.gov, no. NCT01686802. Poonai, N, etal, Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial, Canadian Medical Association Journal, 2017 October 10; 189(40): p. 1252-1258.
[8] Wille C, etal, Oral morphine administration for children's traumatic pain, Archives de pediatrie Volume 12 (2005), pages 248-253.
[9] Dahlstrom, B, etal, Morphine kinetics in children, Clinical Pharmacology & Therapeutics, Vol 26, Issue 3, September 1979, pages 354-365.

			paradigms for IV morphine.	vs surgical dosing.	pain during surgery was not different in ages 7-15 years.

Reviewer; N=number; h=hour; PK=pharmacokinetic

Although these articles cited by the Applicant have limitations (all non-US), they provide additional support for the safety of the Applicant's proposed dosing for the use of morphine sulfate in an acute pain setting.

Healthcare providers who are prescribing for the pediatric population should be aware of the risk of special populations. According to the Applicant's analysis, patients enrolled in this study did not represent a "high-risk" group of severe neurological impairment or other risk groups identified in the literature as being potentially more vulnerable to respiratory-related effects of opioids.

9.4 Safety Conclusions

It is not acceptable to extrapolate safety from adults to pediatric patient population. Based upon the review of the data in the NDA submission, the clinical review team determined that the Applicant's submitted data, along with literature, provide support for use of morphine on an acute, short-term basis in pediatric patients ages 2-17 years for morphine sulfate oral solution and in pediatric patients 12 years and older with a minimum weight of 50 kg for 15 mg oral tablets. The data or literature do not provide support for a chronic pain indication for the pediatric population ages 2-17 years. Study MORPOS+ T-(2-17)-SPK-2 was an open-label study.

1. The study provided sufficient data to establish the effectiveness of morphine sulfate oral solution and tablets in the proposed age range of 2-17 years, based on PK extrapolation, for short-term (acute) indication.
2. Safety data submitted in this NDA are not adequate to support the morphine tablets or oral solutions for long-term (chronic) use. The Applicant did not submit data to define the pediatric patient population whose benefits will outweigh the risks of long-term morphine use.
3. The review of safety was consistent with the known safety profile of labeled morphine and did not identify any new safety signals in the proposed patient population.
4. Approximately 53% of subjects received initial dosing in the proposed labeled dosing range of 0.15-0.3 mg/kg and approximately 40% received an initial dose higher than that. As expected, opioid related side effects such as nausea, vomiting and oxygen saturation decreased are dose-dependent. Initial dosing of 0.15-0.3 mg/kg is a safe and tolerable dose for pediatric patients aged 2-17 years old.
5. The lowest strength for morphine tablets is 15 mg and the minimum weight of 50 kg is required for pediatric patients so that the initial dosing does not exceed 0.3 mg/kg. This NDA supplement does not include safety data for

morphine tablets use in pediatric patients less than 12 years old. Given that swallowing a tablet may be an issue for pediatric patients less than 12 years old and it is not feasible to accurately adjust dosage of tablet, morphine tablets are not recommended for patients less than 12 years old who weigh less than 50 kg.

10. Clinical Summary

This study was conducted to fulfill the Pediatric Research Equity (PREA) Act Postmarketing Requirements (PMRs) for NDA 22195 (morphine sulfate solution) and NDA 22207 (morphine sulfate tablet). The postmarketing studies required under PREA for morphine sulfate tablets and oral solution were conducted to assess the safety and effectiveness of the products for the claimed indication in pediatric patients. The Division allows efficacy to be extrapolated from adults to pediatric patients two years of age and older for certain analgesics, including opioids, provided that comparable systemic exposure is demonstrated between adults and that pediatric age group. The Division's clinical pharmacology review team determined that the pharmacokinetic results from study MORPOS+ T-(2-17)-SPK-2 demonstrate comparable systemic exposure to morphine between adults and pediatric patients 2 to <17 years of age and, therefore, can serve as the basis for extrapolation of efficacy.

The Applicant addressed the clinical deficiencies cited in the first review cycle (listed below) during this second review cycle as follows:

1. The postmarketing studies required under the PREA for morphine sulfate tablets and oral solution were required to assess the safety and effectiveness of the products for the claimed indication in pediatric patients. The Division has determined that there is scientific support for efficacy to be extrapolated from adults to pediatric patients two years of age and older for certain analgesics, including opioids, provided that comparable systemic exposure is demonstrated between adults and that pediatric age group. However, the pharmacokinetic results from Study MORPOS+ T-(2-17)-SPK-1 did not demonstrate comparable systemic exposure to morphine between adults and pediatric patients 2 to <17 years of age and, therefore, could not solely serve as the basis for extrapolation of efficacy or allow for an adequate assessment of safety. The results of the study, in combination with the pharmacokinetic findings, were further inadequate to allow for an extrapolation of efficacy to the proposed pediatric population because concomitant use of analgesics were not reliably captured in the study (i.e. errors in collecting and/or reporting the use concomitant analgesics, including continuous and bolus patient controlled analgesia) and pain intensity was not regularly assessed in all age groups over the course of the treatment period as specified in the protocol.

   Second cycle clinical review conclusion: This deficiency is resolved. Concomitant use of analgesics was captured in a manner to allow for the data to be analyzed. Pain intensity scores were regularly assessed in all groups over the course of treatment period using an age-

appropriate PI scale. However, the clinical review team has determined that due to the study design, these data cannot provide supportive efficacy. But efficacy can be determined based on PK extrapolation alone.

2. You must demonstrate comparable systemic exposure to morphine between adults and the proposed pediatric population in order to extrapolate efficacy from adults to the proposed pediatric population or, as opioids are titrated to effect, you must establish that the morphine doses utilized in the study represent a reasonably effective starting dose, to serve as a basis for extrapolating efficacy and assessing safety in combination with the pharmacokinetic findings.

   Second cycle clinical review conclusion: This deficiency is resolved. The clinical pharmacology team determined that systemic exposure in pediatrics is comparable to adults, therefore efficacy can be extrapolated. The safety database is adequate to assess safety at the initial starting doses proposed.

3. Because the dosing in Study MORPOS+ T-(2-17)-SPK-1 did not achieve the expected exposure, and in fact, resulted in morphine levels below the limit of quantification in numerous patients, the assessment of safety of morphine in pediatric patients from this study is inadequate. The assessment of safety must be based on exposure to a dose expected to provide efficacy.

   Second cycle clinical review conclusion: This deficiency is resolved. Doses studied appeared to be in a dose range expected to provide efficacy based on pharmacokinetic extrapolation.

4. You have not provided a dosing device capable of delivering accurate dosing for use in the proposed pediatric population. Because small dosing errors in the proposed population could have serious consequences, you must propose a dosing device to be provided with the product that can accurately deliver the full range of anticipated doses in the proposed pediatric population.
   a. The dosing devices co-packaged with drug product must be appropriate for the dosages to be measured. Oral liquid drug products packaged with dosage delivery devices must bear markings that are consistent with labeled dosage directions in order to facilitate proper dispensing of the product by patient, parent, or caregiver. The lowest labeled dose must be considered when determining appropriate dosing devices.
   b. Multiple dosing devices may be required. Development of an appropriate dosing device must account for the dosing ranges used when doses are calculated based on the weight range of intended users. These calculations will determine whether appropriate dosing can be achieved with a single dosing device. Multiple volume oral dosing devices may be required to allow patients and caregivers to measure the dose needed. If your risk analysis determines that multiple dosing devices are required, careful consideration should be given to develop risk mitigation

strategies to avoid confusion regarding which device to use. For example, if a caregiver needs to administer a 0.5 mL dose, they will need to understand which dosing device should be utilized for the greatest dosing accuracy.

c. Provide a mechanism to obtain additional dosing devices as needed. A single bottle of morphine sulfate oral solution may be used to fill several prescriptions each of quantities less than an entire bottle. If the co-packaged oral dosing devices are only sufficient for a single patient, an alternate means for ordering additional dosing devices should be available.
d. If you plan to replace the 5 mL dose cup with a 5 mL oral syringe, provide the information (CMC information, DMF reference, or 510K clearance number, with data to demonstrate dose accuracy) necessary to support the change. If you plan to continue to use the 5 mL dosing cup (not prefilled), provide the CMC information for the 5 mL dose cup as a dosing device. Alternatively, you can provide a DMF reference. Provide data to demonstrate the dose accuracy of the 5 mL dose cup for both the 10 mg/5 mL and 20 mg/5 ml strengths.

Second cycle clinical review conclusion: The dosing device deficiency #4 is resolved through labeling. In response to an Agency IR, the Applicant agreed to update the carton and container labels for morphine sulfate oral solution to include a note to pharmacists instructing to dispense morphine sulfate oral solution with an appropriately graduated oral syringe to ensure the dose can be accurately measured. In conjunction to the carton and container label revisions, the Applicant agreed to update the prescribing information (PI) to describe dose rounding so that prescribed weight-based doses will align to graduation marks on commonly dispensed oral dosing syringes graduated in 0.1 mL and 0.2 mL increments.

See the CMC and DMEPA reviews for additional discussion.

11. Advisory Committee Meeting

This supplemental Application did not go to an Advisory Committee Meeting as the review teams determined that there were no issues that required Advisory Committee input. The Agency recognizes the potential public health concern in approving an opioid for the pediatric population.

12. Pediatrics

With initial dosing of 0.15 mg to 0.3 mg/kg for oral solution or tablets, comparable exposure levels have been established between adults and the pediatric population ages 2 to 17 years. The pediatric dose range the Division is approving is based on pharmacokinetic data, over the dose and duration investigated, showing similar

exposures to that observed in adults at the approved dose(s). The number of patients in each age subgroup who received the oral solution in the trial were reasonably distributed and showed comparable exposures to that observed in adults at the dose to be approved. The population PK model was designed by the applicant based on FDA input and included single- and multiple- dose BA data obtained in adults along with adult and pediatric PK data. The oral solution represents the age-appropriate formulation that would have been needed to fulfill the PREA PMR for the tablet dosage form down to 2 years of age. Collectively, the data provided from both dosage forms in this trial support adult efficacy extrapolation for morphine sulfate down to 2 years of age, thereby fulfilling PMR 204-3 (PK and safety for 2 to 17 years).

This NDA was presented at the Pediatric Review Committee (PeRC) on April 27, 2021. The PeRC members agreed with the Division that the completed study included in the submission fulfilled the PREA PMR 204-3 for ages 2-17 years.

13.Other Relevant Regulatory Issues

No additional regulatory issues were addressed.

14. Labeling

The labeling negotiations are still ongoing and have not been finalized at the time of this review. It is anticipated that there will be major changes to the label to the following sections:

I) Section 1 Indications and Usage
II) Section 2 Dosage and Administration
III) Section 6 Adverse Reactions
IV) Section 8.4 Pediatric Use

15. Postmarketing Recommendations

Risk Evaluation and Management Strategies (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 (PPI), communication plan, elements to assure safe use (ETASU), and/or an implementation system.

All immediate-release opioids require a REMS. We will recommend the same Risk Evaluation and Mitigation Strategy for pediatric labeling as is required for adults in the currently approved morphine sulfate oral solution and oral tablets labels as follows:

Section 5. (b) (4) Opioid Analgesic Risk and 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 1-800-5030784, 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.

16. Recommended Comments to the Applicant

The Division has no comments to be communicated to the Applicant.

Appendix

Appendix A. Review of Relevant Individual Trial Used to Support Safety

Protocol Number: MORP-OS+T-(2-17)-SPK-2; Version Amendment 1; dated June 22, 2018

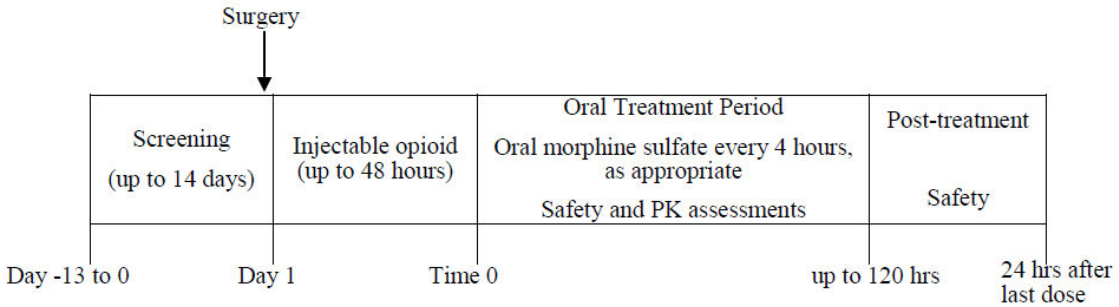
Title: A Multicenter, Open-Label, Safety and Pharmacokinetic Study of Oral Morphine Sulfate Administration in Pediatric Subjects 2 years old through 17 years old with Postoperative Pain

Objectives:

- To evaluate the tolerability and safety of oral morphine sulfate in the treatment of post-operative pain in different pediatric age groups following multiple-dose administration
- To determine multiple-dose pharmacokinetics (PK) of morphine sulfate in pediatric subjects
- To compare plasma concentration of morphine sulfate in each age group of pediatric subjects with adult plasma morphine sulfate concentrations

Study Overview: This study was to have been conducted in pediatric surgical patients anticipated to require inpatient hospitalization postoperatively and to have moderate-to- severe postoperative pain requiring the use of oral opioids for treatment. Morphine sulfate could be administered every 4 hours, as determined by the investigator, up to a maximum of 120 hours. Although pain scores were to be obtained prior to dosing, the protocol stated that pain scores were to determine if dosing was needed, as the open-label protocol design did not require pain scores to serve as a basis for determination of efficacy. Opioid and non-opioid rescue analgesics were allowed. In subjects who have reached the end of the oral treatment period (i.e., they no longer have moderate-to-severe pain), analgesia was to have been managed according to the local standard of care, however, not with codeine or morphine and preferably not with an opioid. The last dose of study drug was defined when 8 hours have elapsed without the subject requiring study drug for pain (i.e., the last dose will be the dose that was taken prior to this 8-hour period).

Schematic Design for Protocol MORP-OS+T-(2-17)-SPK-2



NOTE: Injectable opioid will be preferably hydromorphone or fentanyl; other analgesics are also allowed. Intravenous morphine should not be given post-operatively.

Protocol, Figure 1, p. 25.

Inclusion Criteria

1. Has a parent or guardian providing written parental permission/informed consent, with subject assent (if required by local IRB).
2. Has an age-appropriate pain score of ≥4 prior to receiving first dose of study drug.
3. Is a child 2 years old through 17 years old, inclusive (at the time of informed consent signing).
4. Weighs at least 10 kg.
5. Has a routine pediatric procedure that is expected to require inpatient hospitalization postoperatively.
6. Must be an inpatient for the study treatment period.
7. Is expected by the investigator to have moderate to severe postoperative pain requiring the use of oral opioids for treatment.
8. Has the ability to read and understand the study procedures and has the ability to communicate meaningfully with the study investigator and staff (if the subject is of preverbal age or cannot read or communicate meaningfully, then the subject's parent or guardian must meet this criterion).
9. Is able to tolerate oral medications within 48 hours of surgery.
10. If female subject is of childbearing potential, she must have a negative urine pregnancy test result on the day of surgery prior to surgery. In this population, female of childbearing potential is defined by the onset of menarche, i.e., menstruation, whether at irregular or regular intervals (periods).
11. Female subjects of childbearing potential and male subjects with partners capable of reproduction must agree to use an effective contraceptive method as follows from the time of Screening through 30 days after the last dose of study drug:
    - A highly effective method of contraception, including hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants), intrauterine device or intrauterine system OR
    - An effective double-barrier contraceptive method (2 of the following: male condom, female condom, cervical cap, diaphragm, or contraceptive sponge) OR
    - Abstinence

12. Must have vascular access to facilitate blood draws.

Exclusion Criteria

1. Has significant medical disease(s), laboratory abnormalities, or conditions(s) that in the investigator's judgment could compromise the subject's welfare, ability to communicate with study staff, complete study activities, or would otherwise contraindicate study participation. There is no minimum value for SpO_2 for inclusion in the study; this should be based on the investigator's judgment.
2. Has used opioids chronically (e.g., codeine, morphine, oxycodone, or hydromorphone), for >7 calendar days within the previous 30 days prior to surgery.
3. Has received codeine, hydrocodone, morphine, or oxycodone in any form in the previous 7 calendar days prior to surgery.
4. Is undergoing procedure for treatment of acute burns.
5. Has known hypersensitivity or contraindication to receiving oral opioid(s).
6. Has a current active enteral malabsorption disorder.
7. Has impaired liver function (e.g., alanine aminotransferase [ALT] ≥3 times the upper limit of normal [ULN], or total bilirubin ≥2 times ULN [except patients with evidence of Gilbert's syndrome]), known active hepatic disease (e.g., hepatitis), evidence of clinically significant chronic liver disease or other condition affecting the liver (e.g., chronic hepatitis) that may suggest the potential for an increased susceptibility to hepatic toxicity with oral morphine exposure. Subjects with no previous history of liver function impairment may be enrolled prior to receipt of screening laboratory testing results.
8. Has significantly impaired renal function or disease, as evidenced by an estimated glomerular filtration rate (i.e., from creatinine levels using the Schwartz formula) calculated to be less than one-third of normal for the applicable age of this study population. Subjects with no previous history of kidney function impairment may be enrolled prior to receipt of screening laboratory testing results.
9. Has a history of substance abuse or there is evidence of current substance abuse, in the investigator's opinion.
10. Has received epidural or regional anesthesia within 12 hours prior to the first dose of study drug.
11. Has participated in an interventional clinical study (investigational or marketed product) within 30 days before screening or plans to participate in another clinical trial in the next 30 days.

Treatments to be Administered:

- All subjects were to have received the study drug (oral morphine sulfate) for up to 5 days (i.e., 120 hours), administered as an oral solution or tablet. The study drug was to have been administered every 4 hours as long as this schedule is considered appropriate by the investigator based on safety assessments and/or the subject's analgesic needs.
- Subjects in the following age categories will be administered the oral solution:

- ≥2 to <4 years, ≥4 to <6 years, and ≥6 to <12 years.

- There were 2 groups of ≥12 to 17 years old subjects:
  - One was to be given the oral solution and the other was to be given the tablet.
  - The dose for each subject was to have been determined by the investigator and based on the subject's body weight.

Drugs in Study

- *Study drug: Oral morphine sulfate solution or tablets*
  - Formulation: Oral morphine sulfate will be provided as an oral solution (10 mg/5 mL or 20 mg/5 mL) or as tablets (15 mg).
  - Dosing: Weight-based with recommended initial dosing of 0.3 mg/kg as shown in the table below.

Study Drug Dosing Guidelines

Mean weight (kg)	Recommended Starting Doses
10-12	3 mg*
> 12 – 19	5 mg*
> 19 – 30	7.5 mg*
> 30 – 38	10 mg*
> 38 – 55	15 mg**
> 55	15 mg to 30 mg**
Adult (reference)	15 mg to 30 mg

Note: The actual body weight-derived dose is 0.3 mg/kg.[5]

*Oral solution only

** Oral solution or 15-mg tablets

Applicant's table 3, Protocol, p. 101.

- *Rescue (supplemental) analgesic:* Parenteral hydromorphone or fentanyl should be used at the preferred supplemental analgesic, although other analgesics are also allowed. Oral and parenteral morphine are prohibited as a supplemental pain analgesic.
  - *Oral Treatment Period: Permitted during the oral treatment period if the study drug does not provide adequate pain relief as assessed by the investigator or an appropriately qualified designee.*
  - *Pre-emptive/Prophylactic treatment: When a potentially painful procedure is to be performed in the post-operative period (e.g., thoracostomy tube removal). Parenteral*

- *Allowed Concomitant Medications:* Antipyretics, laxatives, anti-emetics, and all other medications not prohibited by the protocol and considered necessary for the subject's welfare can be given and/or continued under the investigator's supervision.
- *Prohibited Concomitant Medications: In addition to medications already listed in Exclusion Criteria, the following are also prohibited:*
    - Subjects should not receive epidural or regional anesthesia within 12 hours prior to the first dose of study drug.
    - Subjects cannot receive oral morphine sulfate (other than the study drug) at any time during the study.

Study Procedures

Time	Screening[a]	Surgery (Day 1)	Oral Treatment Period									Post-treatment		
			0 h[b] (Dose 1)	0.5 h (Dose 1 + 0.5 h)	1 h (Dose 1 + 1 h)	2 h (Dose 1 + 2 h)	4 h (Dose 2)	4.5 h (Dose 2 + 0.5 h)	5 h (Dose 2 +1 h)	6 h (Dose 2 +2 h)	Every 4 h from 8 h (Dose 3) up to last dose (max:120 h)	8h after last dose	24 h after last dose or prior to discharge/ ET	7-14 day follow-up phone call
Window	Day -13 to Day 0			±15 min	±5 min	±15 min	±15 min	±5 min	±5 min	±15 min		+2 h	±2 h	
Written parental permission/informed consent and assent (as required by local IRB)	X													
Inclusion/exclusion criteria	X	X[a]	X											
Demographics	X													
Medical history[c]	X	X[a]												
Physical examination[d]	X												X	
Height	X													
Weight	X	X[a]											X	
Vital signs (BP, HR, temp, RR, SpO_2)[e,f,g]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	
UMSS scale for arousal/sedation[e,g]			X	X	X	X	X	X	X	X	X			
Pain scale[h]			X		X	X	X	X	X	X	X			
Clinical laboratory tests (hematology, chemistry, urinalysis)[i,j]	X													
Pregnancy test for females of childbearing potential[k]	X	X												
Surgical procedure		X[l]												
PK blood sample collection[e,i,m]	See study protocol (Appendix 16.1.1)													
Study drug administration[n]			X				X				X			
Concomitant medications	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]
12-lead ECG or 12-second rhythm strip	X[q]											X[q]		
Study completion[r]													X	

Abbreviations: AE = adverse event; BP = blood pressure, CRO = contract research organization; ECG = electrocardiogram; ET = early termination; FLACC = Face, Legs, Activity, Cry, and Consolability; FPS-R = Faces Pain Scale - Revised; h = hour; HR = heart rate; IRB = institutional review board; min = minute; NRS = numerical rating scale; PK = pharmacokinetic; RR = respiratory rate; SAE = serious adverse event; SpO_2 = oxygen saturation by pulse oximetry; temp = temperature; UMSS = University of Michigan Sedation Scale.

Note: items in the table in parenthetical notation were optional.

a. Screening was also permitted on Day 1. Assessments shown for screening did not need to be repeated at the surgery visit if both visits occurred within 24 hours.
b. Assessments shown for Time 0 were performed prior to (i.e., within 30 minutes before) study drug administration. Time 0 was to occur within 48 hours after surgery.
c. Medical history was updated on Day 1. The planned surgical procedures were also recorded.
d. A complete physical examination was performed at screening and prior to study completion (to record only changes from baseline).
e. When assessments were scheduled at the same time point, they were performed in the following order: sedation assessment (UMSS), pain rating scale, vital signs, and PK blood sample collection.
f. Vital signs (BP, HR, temperature, RR, and SpO_2) were measured after the subject had been in a sitting or resting position for 5 minutes.
g. For the first 2 doses of study drug, vital signs and UMSS were measured immediately before administration, as well as at 30 minutes, 1 hour, and 2 hours after administration. For all subsequent doses, vital signs and UMSS were measured immediately before and 1 hour after study drug administration.
h. The FLACC scale was only assessed in subjects aged <6 years old. The FLACC score was required to be ≥4 for study drug to be administered. The FPS-R was used to determine pain of at least moderate severity in subjects aged 6 to 11 years and the NRS was used in subjects aged >11 years. The age-appropriate pain scale was used prior to and after administration of study drug according to the site's standard of care (but at least at approximately 2 hours post-dose).
i. Samples for clinical laboratory tests were collected at screening to establish eligibility and were not collected at study completion unless deemed necessary by the investigator (i.e., in case of an AE).
j. The approximate blood volume collected per subject for PK and laboratory assessments could not exceed 3% of the estimated total blood volume by age.
k. If screening occurred on a day separate from Day 1, females of childbearing potential would have a serum pregnancy test at screening and a urine pregnancy test on Day 1 prior to the start of surgery (i.e., prior to the first incision). If screening occurred on Day 1, both a serum and urine pregnancy test were performed. Blood collection for the serum pregnancy test could occur after initiation of local practice anesthesia but was required to occur prior to the start of surgery (i.e., prior to the first incision). Regardless of what day screening occurred, the urine pregnancy test (using the kit provided by the local laboratory) had to be reviewed prior to the start of surgery, and was required to be negative for the subject to continue in the study.
l. Subjects could receive an injectable opioid (preferably hydromorphone or fentanyl and excluding morphine) for up to 48 hours after surgery.
m. Pharmacokinetic blood samples were collected at the time points as described in the study protocol.
n. The first dose of study drug was administered within 48 hours after surgery when, in the investigator's estimation, pain intensity was moderate to severe and the subject could tolerate oral medication. Subsequent doses were administered every 4 hours, assuming that this schedule was considered appropriate by the investigator based on safety assessments and/or the subject's analgesic needs.
o. Adverse events that were ongoing at study completion were followed until resolution. Subjects were contacted by phone 7 to 14 days after study completion to collect information about SAEs and resolution of any AEs that were ongoing at study completion. All SAEs that occurred after the subject completed the clinical study were also reported to the CRO within 30 days of the last dose of study drug.
p. Subjects or their guardians were contacted by telephone within 7 to 14 days after study completion to collect information about SAEs and follow-up on any AEs that were ongoing at study completion.
q A 12-lead ECG or 12-second rhythm strip (a minimum of 2 leads was preferred) was recorded at screening (i.e., any time during the interval from Day -13 until just before initiation of surgery on Day 1).
r. Subjects were considered to have completed the study after 24 hours of dosing and all post-operative treatment period assessments had been completed.

- *Screening (Day -13 to Day 1)*
  - Informed consent, vital signs, physical examination, concomitant medications
- *Surgery (Day 1)*
  - Subjects undergo their scheduled surgical procedure using local practice anesthesia (but with restrictions on epidural and regional anesthesia)
  - While subjects are NPO after surgery, they may receive an IV opioid (preferably hydromorphone or fentanyl and excluding morphine) for initial post-operative pain. Subjects who require an injectable opioid for more than 48 hours will not be eligible to receive the study drug.
- *Oral Treatment Period*
  - Subjects who are able to tolerate oral medication and who experience or are expected to experience moderate-to-severe pain will be eligible to enroll in the study.
  - Subjects whose pain intensity, as determined by the age-appropriate pain scale, does not meet the minimum entry criterion of ≥4 on the appropriate pain scale within 48 hours after the end of surgery or those who cannot tolerate oral medication within 48 hours after surgery will not be eligible for enrollment and pain will be managed using standard of care methods.
  - Enrolled subjects will receive the study drug until it is no longer required for pain management up to a maximum of 120 hours.

  - Last dose of study drug will be defined when 8 hours have elapsed without the subject requiring study drug for pain (i.e., the last dose will be the dose that was taken prior to this 8-hour period).
  - In subjects who reach the end of the oral treatment period, analgesia will be managed according to the local standard of care, however, not with codeine or morphine and preferably not with an opioid.

- *Post-Treatment (Follow-Up) Period:* Parents or guardians and, if age-appropriate, subjects were contacted within 7 to 14 days to collect any SAEs that may have occurred and to follow-up on any AEs that were ongoing at study completion.

Statistical Analysis Plan: No formal statistical testing was performed for this study. Descriptive statistics were provided for all demographic and safety parameters. The safety analysis was based on the safety population defined as all subjects who received study drug.

Protocol Amendment: The original protocol was modified by a single amendment Amendment 1, dated 22-Jun-2018, made the following changes:

- A 7- to 14-day follow-up period was added to allow collection of information on AEs and SAEs that were ongoing at study completion; this increased the subjects' study duration to approximately 4 weeks.
- The timing of the 12-lead ECG or 12-second rhythm strip conducted on Day 1 was changed from just before initiation of local anesthesia to just before initiation of surgery, with the condition that the results be reviewed before administration of the first dose of study drug.
- A maximum daily dose of 248 mg was added.
- Acetylsalicylic acid and acetaminophen were added as permissible anti-pyretics to facilitate enrollment; acetylsalicylic acid and acetaminophen had previously been prohibited because they could impact the analysis of morphine.

Reviewer's comment: The protocol was reviewed by the Division prior to initiation of the study and was, overall, consistent with prior Agency advice. The protocol amendment changes should not have impacted safety or PK assessments, monitoring, or results of the study.

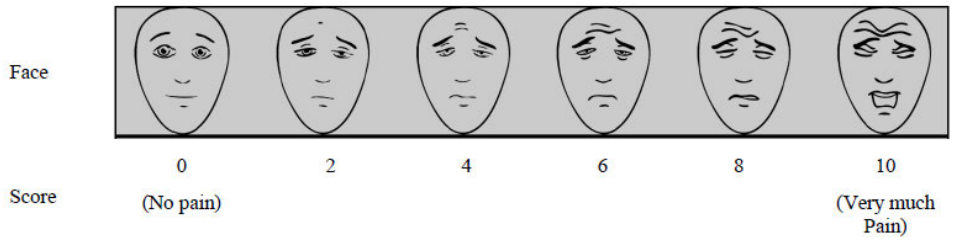
Appendix B: Pain Intensity Scales

FLACC (Faces, Legs, Activity, Cry, and Consolability)

	FLACC Behavioral Pain Assessment Scale		
Categories	**Scoring**		
	0	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Abbreviations: FLACC = Faces, Legs, Activity, Cry, and Consolability

FPS-R (Faces Pain Scale-Revised)



NRS (Numeric Rating Scale) 10 - point scale scored from 0-10

Appendix C Surgical procedures performed by age group

2 to <4 years	4 to <6 years	6 to <12 years	12 to 17 years (oral solution)	12 to 17 years (tablet)
Adenoidectomy	Tetralogy of Fallot repair	Aortic arch repair	adenoidectomy	ADENOIDECTOMY
BILATERAL EAR TUBE PLACEMENT	FOREIGN OBJECT REMOVED FROM NASAL PASSAGE	ASD closure	Bilateral myringotomy	Adenotonsillectomy
BILATERAL MYRINGOTOMY	BILATERAL MYRINGOTOMY WITH TUBE PLACEMENT	Bicuspidization of truncal valve	cerebral embolization	APPENDECTOMY
BILATERAL MYRINGOTOMY AND TUBE INSERTION	Post Hemivertebral Excision	Casting of Scoliosis	Cervical Spinal Fusion	Bilateral Myringotomy
CIRCUMCISION	Post Vertebral Fusion & Instrumentation	CATH ballooning of branch PA	CLOSED REDUCTION RIGHT ARM FRACTURE	BILATERAL MYRINGOTOMY TUBE PLACEMENT
FULL DENTAL EXTRACTION		Closure of ventricular septal defect	Duodenal Hernia Repair	Dental Restoration
LABIAL FRENECTOMY		Craniotomy Posterior Fossa	Hemiepiphyseal arrest distal femur proximal tibia & fibula-Left	EXCISION OF LEFT AXILLA LESION
LEFT HYDROCELECTOMY		Halo Cervical Traction Placement	Incision and drainage of abscess around the AICD	Expansion VEPTR
Neck dissection, left		Interupter aortic arch repair	Knee Surgery	Posterior Fossa Craniotomy

Parotidectomy, left Pulmonary artery banding RIGHT HYDROCELECTOMY Tonsillectomy Tracheostomy dependent		nephrectomy PDA ligation Repair of Diaphragmatic hernia- Morgagni type RV-PA conduit replacement Spica Cast Subclavian artery stenosis repair Tibial guided growth plating Tracheostomy dependent Truncal valve repair VSD closure	Ligament Repair Mitral valvuloplasty posterior fusion cervical spine PRBC transfusion pressure equalizer tubes (bilateral) inserted PYLOROMYOTOMY REPAIR OF ANTERIOR CRUCIATE LIGAMENT RIGHT KNEE Tonsillectomy & Adenectomy WISDOM TEETH EXTRACTION	Prosthetic Titanium Rib device implantation Rev. Prosthetic Rib Device Rev. VEPTR RIGHT WRIST FRACTURE REPAIR WITH HARDWARE SKIN GRAFT Spinal Fixation status post circumcision status post dental surgery TONSILLECTOMY

Appendix D: Adverse Events Definitions

The CSR states that adverse events were coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA), Version 20.1. The Applicant's raw data sets were analyzed by the Agency's clinical reviewers using JMP and JMP clinical Agency analysis tools.

Protocol Definitions of Adverse Events (AE): Per protocol, the investigator is responsible for monitoring and recording all AEs observed from the time parental permission/informed consent is obtained until study completion (at discharge or 24 hours after the last dose of study drug, whichever occurs first). Adverse events were defined in the protocol as follows:

- AE: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.
- Serious Adverse Event (SAE): An SAE, experience, or reaction is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:
    - Results in death.
    - Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
    - Requires inpatient hospitalization or prolongation of existing hospitalization:
    - Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
    - Results in persistent or significant disability/incapacity.
    - Is a congenital abnormality/birth defect.
    - Other: Medically significant events that do not meet any of the criteria above but may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the previous definition.
- Treatment-emergent adverse event (TEAE): An event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state."

Statistical Analysis Plan (SAP) Definitions of Adverse Event

- TEAE: Any AE with an onset date after the first intake of the study drug and before the last intake of the study drug plus 24 hours, having been absent pretreatment, or worsens relative to the pretreatment state.
- Treatment-related adverse event: Any AE with a relationship to the study drug of possible or probable.

AE Severity: The severity of the AE was characterized as "mild," "moderate," or "severe," according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities
- Severe events interrupt the subject's usual daily activities

Appendix E: Adverse Events by Initial dosing & age group

Treatment Emergent Adverse Events by Preferred Term within Initial Dose Subgroups Safety Population				
Age group: 2 to <4 years	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=0)	0.15 to 0.3 mg/kg (N=7)	>0.3 mg/kg (N=7)	Overall (N=14)
Number of Subjects with at least one TEAE	0	4 (57.1%)	1 (14.3%)	5 (35.7%)
Postoperative fever	0	2 (28.6%)	0	2 (14.3%)
Vomiting	0	1 (14.3%)	1 (14.3%)	2 (14.3%)
Abdominal pain	0	1 (14.3%)	0	1 (7.1%)
Constipation	0	1 (14.3%)	0	1 (7.1%)
Failure to thrive	0	1 (14.3%)	0	1 (7.1%)
Influenza	0	1 (14.3%)	0	1 (7.1%)
Nausea	0	1 (14.3%)	0	1 (7.1%)
Pyrexia	0	1 (14.3%)	0	1 (7.1%)
Age group: 4 to <6 years	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=0)	0.15 to 0.3 mg/kg (N=5)	>0.3 mg/kg (N=5)	Overall (N=10)
Number of Subjects with at least one TEAE	0	0	2 (40.0%)	2 (20.0%)
Nausea	0	0	1 (20.0%)	1 (10.0%)
Pleural effusion	0	0	1 (20.0%)	1 (10.0%)
Vomiting	0	0	1 (20.0%)	1 (10.0%)

Applicant's table, response to clinical IR received 4/27/2021.

Treatment Emergent Adverse Events by Preferred Term within Initial Dose Subgroups				
Safety Population				
Age group: 6 to <12 years	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=1)	0.15 to 0.3 mg/kg (N=7)	>0.3 mg/kg (N=6)	Overall (N=14)
Number of Subjects with at least one TEAE	0	1 (14.3%)	3 (50.0%)	4 (28.6%)
Nausea	0	1 (14.3%)	2 (33.3%)	3 (21.4%)
Anxiety	0	0	1 (16.7%)	1 (7.1%)
Oxygen saturation decreased	0	0	1 (16.7%)	1 (7.1%)

Age group: 12 to ≤17 years (oral solution)	Initial Starting Dose			
Preferred Term	<0.15 mg/kg (N=4)	0.15 to 0.3 mg/kg (N=15)	>0.3 mg/kg (N=6)	Overall (N=25)
Number of Subjects with at least one TEAE	3 (75.0%)	6 (40.0%)	4 (66.7%)	13 (52.0%)
Nausea	2 (50.0%)	2 (13.3%)	2 (33.3%)	6 (24.0%)
Vomiting	2 (50.0%)	1 (6.7%)	1 (16.7%)	4 (16.0%)
Flatulence	0	3 (20.0%)	0	3 (12.0%)
Constipation	1 (25.0%)	1 (6.7%)	0	2 (8.0%)
Procedural pain	2 (50.0%)	0	0	2 (8.0%)
Electrocardiogram T wave inversion	0	1 (6.7%)	0	1 (4.0%)
Oxygen saturation decreased	0	0	1 (16.7%)	1 (4.0%)
Pruritus	1 (25.0%)	0	0	1 (4.0%)
Sedation	0	0	1 (16.7%)	1 (4.0%)
Tachycardia	1 (25.0%)	0	0	1 (4.0%)
Ventricular hypertrophy	0	1 (6.7%)	0	1 (4.0%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; TEAE = treatment emergent adverse event.
Note: A TEAE is defined as any AE with an onset date after the first intake of the study drug and before the last intake of the study drug plus 24 hours, having been absent pretreatment, or worsens relative to the pretreatment state. All AEs are coded using MedDRA Version 20.1. Within each level of summarization, subjects who reported more than one adverse event were only counted once. Preferred Term is sorted in descending order of frequency of overall and then alphabetically

Applicant's table, response to clinical IR received 4/27/2021.

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Appendix F. Protocol Deviation/Violation Examples

Parameter	Protocol Deviation/Violation	Reviewer's Assessment
PK	PK collected outside of window or missed	Did not affect PK results or interpretability since the PK modeling takes these variations into account per clinical pharmacology review team.
Dosing	▪Dose 2 given 45 min out of window due to patient pain ▪More than 8 hours elapsed between doses. Dose 4 was 9 h 45 min after dose 3 ▪More than 8 h elapsed between doses. Dose 3 was 9 h 25 min after dose 2	Unlikely effect on overall safety results or interpretability if dosing was approximately 1 hour later than scheduled for 4 subjects.
Safety Assessment	UMSS, NRS, vital signs collected out of window, out of order, or may have been missed.	Given the frequency of assessments, a missing collection or collection out of order would likely not have affected the safety reports of individual subjects or overall safety findings.
Informed Consent	▪IC page 21 of 22, second parent permission field was not completed; parent listed as "mother" on page 17 and "dad" on page 21 ▪IC page 9, participant ID field was not completed and obtained post start of surgical procedure ▪IC signed by 1 parent only	These are primarily administrative/procedural issues and should not have affected the quality of the data or interfere with ability to interpret results.
Screening Deviations	ECG completed post operative Screening PE completed post-operative Screening labs completed post op	Given that these were surgical patients who would have received pre-; peri-, and post-surgical cardiac monitoring and laboratory evaluations, these out-of-order screening assessments do not affect overall safety of subjects or interpretability of results.

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/

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05/11/2021 04:42:35 PM

FANG E DENG
05/11/2021 04:47:10 PM