Office of Clinical Pharmacology Review

NDA or BLA Number	22195 S-010 and 22207 S-005
Link to EDR	\\CDSESUB1\evsprod\NDA022195\0095 \\CDSESUB1\evsprod\NDA022207\0070
Submission Date	12/2/2020
Submission Type	*[Standard review]*
Brand Name	Morphine Sulfate Oral Solution Morphine Sulfate Tablets
Generic Name	Morphine Sulfate Oral Solution Morphine Sulfate Tablets
Dosage Form and Strength	Oral Solution: 10 mg per 5 mL (2 mg/mL); 20 mg per 5 mL (4 mg/mL); 100 mg per 5 mL (20 mg/mL). Tablets: 15 mg and 30 mg.
Route of Administration	Oral
Proposed Indication	Management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Applicant	Hikma
OCP Division:	*Division of Neuropsychiatry Pharmacology*
OND Division:	*Division of Anesthesiology, Addiction Medicine, and Pain Medicine*
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1. EXECUTIVE SUMMARY

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal evidence of effectiveness	Morphine systemic exposure is similar (Cmax and AUC) after first dose and steady-state between pediatric patients with proposed pediatric dosing regimen and adult patients with recommended dosing regimen in approved label of acute pain.
General dosing instructions (Adults)	Initiating Treatment with Morphine Sulfate Oral Solution (NDA 022195): Do not initiate treatment with Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg per mL) in patients who are opioid naïve. Select an alternate product with lower concentration. Initiate treatment with Morphine Sulfate Oral Solution in a dosing range of 10 mg to 20 mg every 4 hours as needed for pain. Initial Dosage in adult patients with Morphine Sulfate Oral Tablets (NDA 022207): Use of Morphine Sulfate Tablets as the First Opioid Analgesic (Opioid-naïve or Opioid-non-tolerant Patients): Initiate treatment with Morphine Sulfate Tablets in a dosing range of 15 mg to 30 mg every 4 hours as needed for pain.
Dosing in patient subgroups (Pediatrics)	A bodyweight-based dosing regimen that considers 0.15 – 0.3 mg/kg of morphine sulfate oral solution and oral tablets is proposed. Note: Maximum dose limits are set in bodyweight cohorts to not exceed a safe starting dose.
Labeling	Section 2: Bodyweight based dosing. Section 8.4: Effectiveness of morphine oral tablets and solution in pediatric patients with acute pain. Section 12.3: Pharmacokinetics of morphine in pediatric patients with acute pain.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.
Other (specify)	None.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

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.

2.1 Pharmacology and Clinical Pharmacokinetics

Clinical Pharmacology of Morphine in adults:

The absolute bioavailability of morphine tablet or oral solution was 35 –55% with regard to AUC (0-inf) (Study PLFS-1 submitted in support of the NDA's 22195 and 22207). The same dose of morphine oral tablet and oral solution have similar exposure in terms of AUC (0-t) but exposure is not equivalent in terms of Cmax (tablet has 30% higher Cmax vs. oral solution). Morphine oral tablet had limited (11% decrease in Cmax) food-effect which may not be clinically relevant. There was a dose proportional increase in Cmax and AUC between the 15 mg and 30 mg tablet in adults (Study PVFS-2); and similar exposure is expected with morphine oral solution. The sponsor had previously conducted study PVFS-3 (MORP-T30-PVFS-3) evaluating multiple dose PK of morphine in adults. Bioavailability of morphine solution and tablet were compared in study PVFS-3 following administration of 30 mg dose every 6 hours (120 mg total daily dose) for 5 days. On Day 5, plasma morphine exposure (AUC24 hours) was similar following tablet and solution administration, although Cmax was 25% higher for tablet compared to solution.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

In adult patients requiring opioid treatment for acute and chronic pain the following are the dose initiation instructions in the morphine oral sulfate solution and oral tablet labels. Morphine Sulfate oral solution or tablets are indicated for the management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Initiating Treatment with Morphine Sulfate Oral Solution (NDA 022195): Do not initiate treatment with Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg per mL) in patients who are opioid naïve. Select an alternate product with lower concentration. Initiate treatment with Morphine Sulfate Oral Solution in a dosing range of 10 mg to 20 mg every 4 hours as needed for pain.

Initial Dosage in adult patients with Morphine Sulfate Oral Tablets (NDA 022207): Use of Morphine Sulfate Tablets as the First Opioid Analgesic (Opioid-naïve or Opioid-non-tolerant Patients): Initiate treatment with Morphine Sulfate Tablets in a dosing range of 15 mg to 30 mg every 4 hours as needed for pain.

2.2.2 Therapeutic individualization

A bodyweight-based dosing regimen that considers 0.3 mg/kg of morphine sulfate oral solution and oral tablets is proposed to match morphine exposure (Cmax and AUC) in pediatric patients to that noted in adult patients. Tablets may not be a suitable formulation for all pediatric age groups, as swallowing a tablet may be an issue in younger children. Therefore, morphine sulfate oral solution may be considered for all pediatric patients >2 to 17 years; morphine sulfate oral tablets should only be administered in pediatric patients >12 years to 17 years and a minimum weight of (b) (4) kg.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Section 2.3 Initial Dosage

Morphine Oral Solution

Opioid Naïve Pediatric Patients 2 Years of Age and Older:

The recommended dosage to initiate treatment in opioid naïve pediatric patients is 0.15 mg/kg to 0.3 mg/kg every 4 hours as needed for pain. Do not exceed 20 mg as an initial dose.

Morphine Oral Tablets

Pediatric Patients Weighing at Least (b) (4) kg: For pediatric patients weighing at least (b) (4) kg who are able to swallow oral tablets, the recommended dosage to initiate treatment in pediatric patients (b) (4) kg and above is 15 mg every 4 hours as needed for pain. Do not exceed 30 mg as an initial dose.

Section 8.4 for morphine oral solution and tablet:

The effectiveness of an initial 0.3 mg/kg dose in pediatric patients is supported by pharmacokinetic modeling and simulation. Pharmacokinetic modeling and simulation indicate that an initial dose of 0.3 mg/kg in pediatric patients 2 years of age and older is expected to produce a C_{max} similar to a single dose of 10 mg Morphine Oral Solution in adults.

Section 12.3 for morphine oral solution and tablet:

Pediatric Patients 2 Years of Age and Older: Morphine pharmacokinetics were analyzed in a population pharmacokinetic analysis of 66 pediatric patients aged 2 years to 17 years. Initially after dosing, the

geometric mean plasma half-life of morphine was up to 1.8 hours. The geometric mean terminal elimination plasma half-life of morphine was 18.6 hours. For both the M3G metabolite and M6G metabolite, the single-dose geometric mean C_{max} in pediatric patients was not greater than in adults.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Hikma Pharmaceuticals PLC (Hikma) acquired Roxane Laboratories Inc., (Roxane) in 2016. Hikma submitted (on 12/2/2020) amended supplement S-010 for NDA 022195 Morphine Sulfate Oral Solution and S-005 for NDA 022207 Morphine Sulfate Tablets. Previously, Hikma had submitted the complete pediatric study report for MORP-OS+T-(2-17)-SPK-2 to the FDA on February 3, 2020 in reply to an Agency request for a summary of the responses to the January 21, 2016 Complete Response Letter. However, the submission was considered incomplete.

After approval of Roxane's morphine sulfate oral solution NDA 22195 and morphine sulfate oral tablet NDA 22207 in 2008, PREA requirements were established in pediatric patients ages 0 to 17 years for the treatment of moderate to severe acute and chronic pain where an opioid analgesic is appropriate. On May 17, 2010, the NDAs were released from the original PREA requirement and replaced with the following: The Division has determined that findings of efficacy for morphine sulfate in adults can be extrapolated to pediatric patients ages 2 through 17 years. Therefore, we are releasing the aforementioned PREA requirement and replacing it with the following required studies:

1. 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

2. 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

On March 23rd 2015, Roxane responded to a Pediatric Research Equity Act (PREA) study issued by the Agency on March 17, 2008 along with approval of NDA 22195 and 22207. The sponsor submitted pediatric PK study report MORP-OS+T-(2-17)-SPK-1 "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." Because of the bodyweight based dosing and other considerations, the pediatric patients in 2 – 12 year age range received low doses (<0.15 mg/kg of morphine oral solution. However, the use of such low doses (<0.15 mg/kg) resulted in low morphine systemic exposure in pediatrics as compared to the observed data for multiple dose morphine regimen in adults. With exposure matching between pediatric patients and adult patients being the goal, it appeared that higher pediatric doses, compared to the up to 0.15 mg/kg dosing used in the current

study may be needed in 2 – 12 year old pediatric patients to achieve systemic exposure comparable to 10 mg morphine IR product administered in adults to steady-state.

Accordingly, the sponsor was advised as follows in the CR letter dated 1/21/2016 (See Appendix 4.3.1).

The sponsor followed the guidance provided above and conducted a second PK study in pediatric patients of >2 to 17 years of age. Results of the second PK study MORP-OS+T-(2-17)-SPK-2 are reviewed in this submission.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Clinical Pharmacology of Morphine in adults: Absolute bioavailability of morphine tablet or oral solution was 35 –55% with regard to AUC (0-inf) (Study PLFS-1 submitted in support of the NDA's 22195 and 22207). The same dose of morphine oral tablet and oral solution have similar exposure in terms of AUC (0-t) but exposure is not equivalent in terms of Cmax (tablet has 30% higher Cmax vs. oral solution). Morphine oral tablet had limited (11% decrease in Cmax) food-effect which may not be clinically relevant. There was a dose proportional increase in Cmax and AUC between the 15 mg and 30 mg tablet in adults (Study PVFS-2); and similar exposure is expected with morphine oral solution. The sponsor had previously conducted study PVFS-3 (MORP-T30-PVFS-3) evaluating multiple dose PK of morphine in adults. Bioavailability of morphine solution and tablet were compared in study PVFS-3 following administration of 30 mg dose every 6 hours (120 mg total daily dose) for 5 days. On Day 5, plasma morphine exposure (AUC24 hours) was similar following tablet and solution administration, although Cmax was 25% higher for tablet compared to solution.

Administration of the 30 mg Morphine Sulfate Tablet and 30 mg of Morphine Sulfate Oral Solution every six hours for 5 days resulted in a comparable 24-hour exposure (AUC). The steady-state levels were achieved within 48 hours for both tablets and solution. The mean steady state Cmax values were about 78 and 58 ng/mL for tablets and solution, respectively.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Pharmacokinetic data from pediatric studies MORP-OS+T-(2-17)-SPK-1 and MORP-OS+T-(2-17)-SPK-2, and the population PK analysis provide pivotal evidence of efficacy of morphine sulfate oral solution and oral tablets in treating acute and chronic severe pain enough to require an opioid analgesic and for which alternative treatments are inadequate. The DAAP Division has determined that findings of efficacy for morphine sulfate in adults can be extrapolated to pediatric patients ages 2 through 17 years.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

In adult patients requiring opioid treatment for acute and chronic pain the following are the dose initiation instructions in the morphine oral sulfate solution and oral tablet labels.

Initiating Treatment with Morphine Sulfate Oral Solution: Do not initiate treatment with Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg per mL) in patients who are opioid naïve. Select an alternate product with lower concentration. Initiate treatment with Morphine Sulfate Oral Solution in a dosing range of 10 mg to 20 mg every 4 hours as needed for pain.

Initial Dosage in adult patients with Morphine Sulfate Oral Tablets (NDA 022207): Use of Morphine Sulfate Tablets as the First Opioid Analgesic (Opioid-naïve or Opioid-non-tolerant Patients): Initiate treatment with Morphine Sulfate Tablets in a dosing range of 15 mg to 30 mg every 4 hours as needed for pain.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

A bodyweight-based dosing regimen that considers 0.3 mg/kg of morphine sulfate oral solution and oral tablets is proposed to match morphine exposure (Cmax and AUC) to that noted in adult patients. Some of surgeries reported in pediatric patients include cardiovascular, cardiac surgery with cardiopulmonary bypass, spinal fusion, orthopedic, head injuries, cranial nerve microdissection, neck dissection, right frontal external ventricular drain, ear, nose and throat (ENT), abdominal (hernia), genitourinary tract surgeries, etc. It is possible that pediatric patients may benefit from 0.15 mg/kg depending on the peri-operative pain management received. As such, the two pediatric studies have clinical experience with pediatric patients receiving morphine sulfate oral solution and tablet doses of 0.15 mg/kg and above.

Oral tablets may not be a suitable formulation for all pediatric age groups as swallowing a tablet may be an issue in younger children. In addition, oral tablet has less flexibility compared to solution in term of dosing adjustment based on body weight. Therefore, morphine sulfate oral solution may be considered for all pediatric patients >2 to 17 years; morphine sulfate oral tablets should only be administered in pediatric patients >12 years to 17 years and a minimum weight of (b) (4) kg.

The proposed pediatric dosing considers the safe starting dose for morphine oral solution and morphine oral tablets for acute and chronic pain (See single dose PK data in Table 1 below). In addition, plasma concentrations at steady-state following morphine oral solution and oral tablets for patients with chronic pain are also considered (See multiple-dose PK data in Table 1 below). Steady-state plasma morphine levels are expected to be reached following 7 doses or 24-28 hours with morphine sulfate oral solution and oral tablet every four hour dosing in pediatric patients (See details in Appendix 4.2 Clinical PK Assessments).

Table 1: 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).

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.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Morphine sulfate oral tablets can be taken without regard to meals.

When morphine sulfate oral tablets were administered with high-fat meal in adults, there was no change in the extent (AUC) of absorption of morphine, an increase in Tmax from median of 0.5 to 0.75 hours was noted, and an 11% decrease in Cmax was noted. Although food effect was not assessed with morphine oral sulfate solution, significant food-effect is not expected.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

All samples were analyzed according to [(b) (4)] Method P1642, entitled "Quantitation of Morphine, Morphine-3β-D-Glucuronide, and Morphine-6β-D-Glucuronide in Human Plasma via UPLC with MS/MS Detection." A maximum of 232 days passed between sample collection and analysis. All samples were analyzed within the 288 days demonstrated long-term storage stability in human plasma containing dipotassium EDTA at -25 °C. This method was validated by [(b) (4)] and the data are acceptable according to the criteria described in the approved method validation plan and applicable [(b) (4)] SOPs. As indicated, the method is applicable to quantitation within nominal concentration ranges of 0.100 to 50.0 ng/mL for morphine, 3.00 to 1500 ng/mL for morphine-3β-D-glucuronide, and 1.00 to 500 ng/mL for morphine-6β-D-glucuronide from a 50-µL human plasma aliquot, containing dipotassium EDTA. The chromatographic sensitivity, specificity, inter-assay and intra-assay accuracy and precision of acceptable runs were within acceptable limits. Reinjection reproducibility, dilution linearity and Incurred sample reanalysis was acceptable.

OSIS scientist Dr. Li-Hong Yeh remotely reviewed records from the clinical portion of the study MORP-OS+T-(2-17)-SPK-2 at Shoals Medical Trials, Inc. (operating within Helen Keller Hospital), Sheffield, Alabama from 04/07/2021 to 04/09/2021. The remote record review included an examination of study records (paper-based), case report forms, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, accountability and storage of the drug products, randomization, study drug administration, adverse events, collection, processing, and storage of study samples, and electronic data and audit trails. The OSIS reviewer concluded that the clinical data from study MORP-OS+T-(2-17)-SPK-2 are reliable.

4.2 Clinical PK and/or PD Assessments

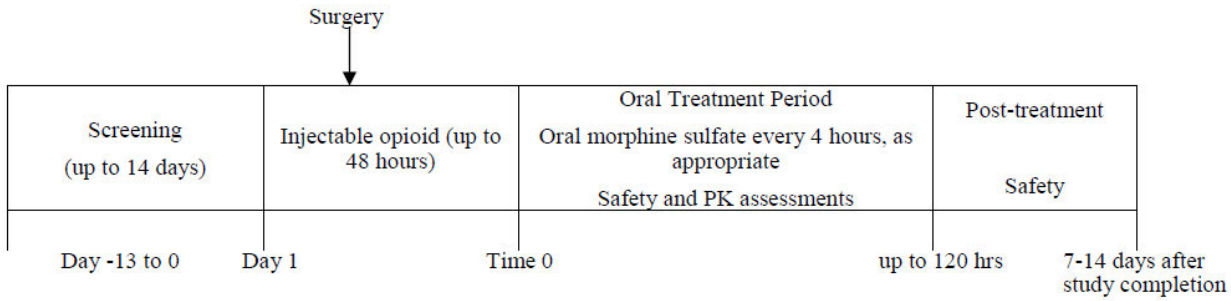
Study MORP-OS+T-(2-17)-SPK-2 was a multicenter, open-label study to evaluate the safety and PK of oral morphine sulfate in pediatric subjects with post-operative pain.

The objectives of this study were:

- 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 PK of morphine sulfate in pediatric subjects.
- To compare plasma concentrations of morphine sulfate in each age group of pediatric subjects with adult plasma morphine sulfate concentrations.

Subjects were inpatients at the study site, with the morning of the scheduled surgery noted as Day 1 and were followed for 7 to 14 days after study completion. On Day 1, local practice anesthesia (i.e., appropriate for the procedure but with restrictions on epidural and regional anesthesia was established, after which subjects underwent their scheduled operative procedure. Subjects received the study drug until, in the investigator's judgment, it was no longer required to manage moderate to severe pain, up to a maximum of 5 days (120 hours after Time 0). The study drug was administered every 4 hours as long as this schedule was considered appropriate by the investigator based on safety assessments and/or the subject's analgesic needs.

Figure 1: Flowchart of Study Design for Protocol MORP-OS+T-(2-17)-SPK-2



Abbreviations: hrs = hours; PK = pharmacokinetic
Note: the injectable opioid was preferably hydromorphone or fentanyl; other analgesics were also allowed. Intravenous morphine was not given post-operatively.

The initial dose range of the study drug was based on the subject's body weight (see Table 2). Investigators were permitted to up- or down-titrate the dose of study drug based on the subject's clinical course and/or changing analgesic requirements. The last dose of study drug was defined when >8 hours had elapsed without the subject needing study drug to manage pain, i.e., the last dose that was taken prior to this 8-hour period. However, the investigators did not strictly adhere with the recommended starting dosage guidelines in some subjects. This is perhaps due to the investigators' judgement based on the surgery type that the pediatric patient underwent, and the post-operative pain experienced.

Table 2: Study Drug Dosing Guidelines in MORP-OS+T-(2-17)-SPK-2.

Mean Weight (kg)	Recommended Starting Doses
10 to 12	3 mg[a]
>12 to 19	5 mg[a]
>19 to 30	7.5 mg[a]
>30 to 38	10 mg[a]
>38 to 55	15 mg[b]
>55	15 mg to 30 mg[b]
Adult (reference)	15 mg to 30 mg

Note: the actual body weight-derived dose is 0.3 mg/kg.[5]
a Oral solution only.
b Oral solution or 15-mg tablets.

Figure 2: Histogram indicating Actual Dose (mg/kg) administered in the pediatric patients (n=66).

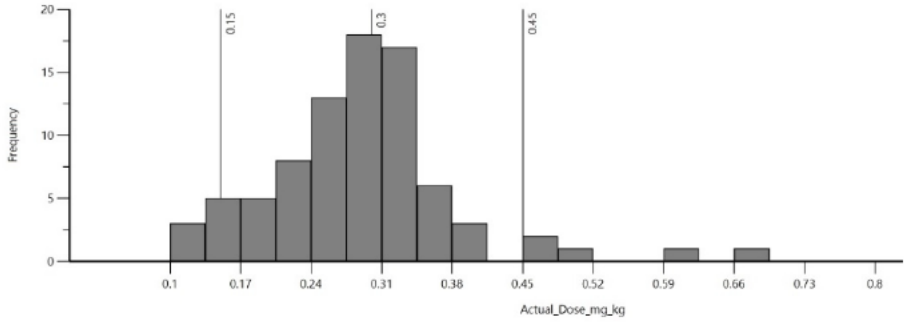
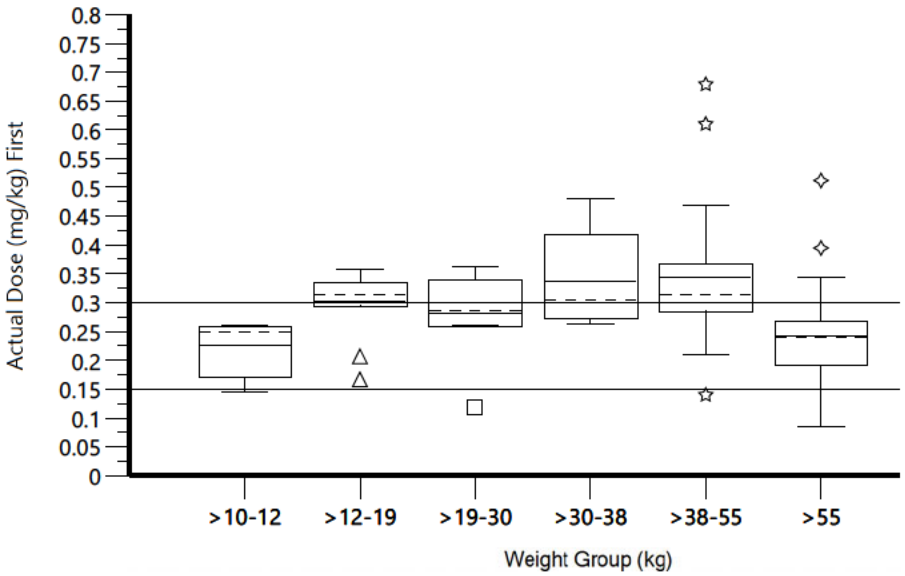


Figure 3: Box-plot of actual first dose (mg/kg) administered in pediatric patients (n=66) categorized by weight group.



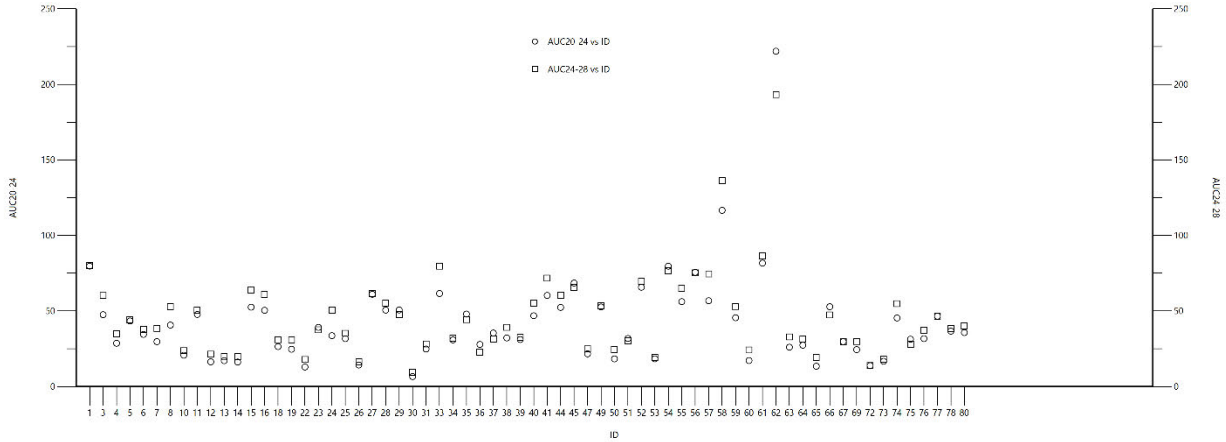
Determination of Sample Size for PK endpoints: A sample size of 60 screened subjects was chosen in order to reach 50 subjects who complete at least 24 hours of dosing. This sample size was selected based on modeling data from adult PK data of morphine, which was used to determine the sample size that would be needed to achieve a coefficient of variation of <20% for apparent clearance and apparent steady-state distribution of volume for each of the 5 age groups included in the study.

Blood Samples (2 mL) of whole blood were obtained for the determination of morphine sulfate and the metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in human plasma. Up to eight PK samples were collected from 66 subjects in the study. Pharmacokinetic blood samples were collected from all subjects at the following time points: 0 hour (Pre-dose 1), 0.25 hours (Dose 1 + 0.25 hours), 0.75 hours (Dose 1 + 0.75 hours), 4 hours (Pre-dose 2), 4.5 hours (Dose 2 + 0.5 hours), 10 hours (Dose 3 + 2 hours), 12 hours (Pre-dose 4), and 24 hours (Pre-dose 7). Pharmacokinetics of morphine in pediatric patients is discussed in section 4.3 below. Since the actual dose administered to the pediatric patient is taken into consideration in the population PK analysis, the overall conclusions derived are not affected by the differences in dosing in pediatric patients.

The POP PK 2020 Report provided the model predicted AUCtau,ss by dose level, which was derived from estimates of clearance (CL), volume of distribution (V) and elimination rate constant (k) provided by the model for each subject. In order to address the FDA's request for estimates of Cmax and AUC after single and multiple doses, supplemental analyses were conducted and are provided below. According to the study protocol, PK samples were to be collected over the first 7 administrations of study drug. Study drug was planned to be administered every 4 hours. However, as the study included pediatric post-operative patients from a wide age range, drug dosing and PK collection were often conducted at different times. Furthermore, up and down titration of study drug occurred for some patients. In order to provide meaningful Cmax and AUC values reflective of single and multiple doses, where all patients have received the same number of doses, single-dose and multiple-dose concentrations were predicted for each patients using the post-hoc PK parameters and where each patient was administered study drug every 4 hours for 7 doses, and PK (i.e., Cmax and AUC) was characterized over the first and last dosing interval. In these predictions, each patient received the actual dose received in the study, but without down or up titrations. These simulated morphine Cmax and AUC values are presented by weight category in Table 8 below in Section 4.3.5 and also Table 1 in section 3.3.3 (Submission dated 3/5/2020).

Additionally, noncompartmental analysis was conducted on population PK analysis derived PK simulation for 66 subjects to compare AUC20-24 after sixth dose and AUC24-28 after seventh dose of morphine in pediatric patients. The similarity in AUC's below show that steady-state is achieved after sixth dose of morphine in pediatric patients when dosed morphine solution or tablets are administered every four hours.

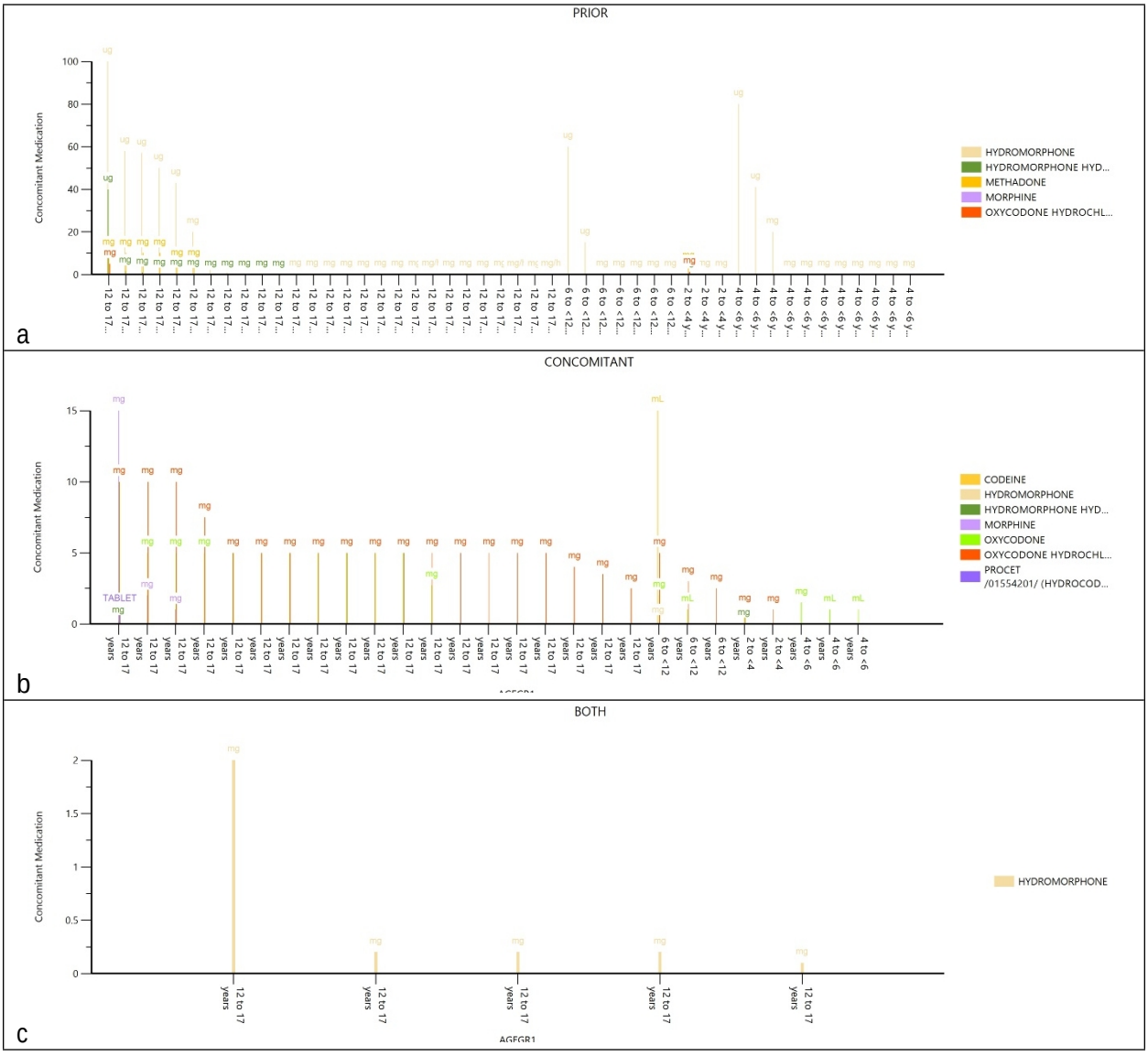
Figure 4: Steady-state exposure of morphine after AUC20-24 and AUC24-28 in pediatric patients.



Some of the surgeries reported in pediatric patients include cardiovascular, cardiac surgery with cardiopulmonary bypass, spinal fusion, orthopedic, head injuries, cranial nerve microdissection, neck dissection, right frontal external ventricular drain, ear, nose and throat (ENT), abdominal (hernia), genitourinary tract surgeries, etc. Please refer to medical officer review by Dr. Elizabeth Kilgore for a comprehensive list of pediatric surgeries involved in this study. The general purpose of the description of surgeries is to suggest the varied need for peri-operative pain management as described in the *Figure 5* below.

Figure 5: Medications administered "PRIOR" to (a), "Concomitant" with (b), and BOTH (c, prior and concomitantly) with morphine sulfate oral tablet/solution in pediatric patients.

To anonymize the data, the age group of the patient is indicated on the X-axis.



The protocol allowed administration of pain medications, other than morphine, to manage pain in pediatric patients. Medications used concomitantly included, hydromorphone, oxycodone, oxymorphone, codeine and Percocet.

4.3 Population PK Analyses

Population PK analysis were conducted by the applicant to characterize the PK of morphine in adult and pediatric patients. Data involved in this modeling exercise came from clinical studies that are described in the table below.

Table 3: Summary of the characteristics of the studies used for PopPK analyses.

Study ID	Subjects	Doses/Route	Description of data
MORP-T30-PLFS-1 (Adults)	Single-dose, 3-way crossover, 3-treatment study in healthy volunteers [n=35]	Treatment A: Single dose 10 mg IV, Duramorph, Baxter Healthcare (30 min infusion) Treatment B: Single 30 mg oral solution (10 mg/5mL), Roxane Treatment C: Single 30 mg oral tablet, Roxane	IV: predose and 5, 15, 30, 32, 35, 40, 45 minutes, and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours postdose (sampling times are relative to the start of the infusion). Oral: predose and 5, 10, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16
MORP-S20-PVFS-1 (Adults)	Single-dose, 2-way crossover study in healthy volunteers [n=34]	Treatment A: Single dose 20 mg oral solution (20 mg/5mL), Roxane Treatment B: Single dose 20 mg oral solution (20 mg/mL), Roxane	Predose and 5, 10, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours postdose
MORP-T30-PVFS-2 (Adults)	Single-dose, 3-way study in healthy Volunteers [n=32]	Treatment A: Single dose 30 mg oral tablet, Roxane, fasting Treatment B: Single dose 15 mg oral tablet, Roxane, fasting Treatment C: Single dose 30 mg oral tablet, Roxane, fed	Predose and 5, 10, 15, 30, 45 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours postdose
MORP-T30-PVFS-3 (Adults)	Multiple-dose, 3-way, 3-treatment study in healthy volunteers [n=27]	Treatment A: 30 mg oral tablet, Roxane Treatment B: 30 mg oral solution (10 mg/5mL), Roxane Treatment C: 120 mg oral controlled release capsules, Avinza®, Ligand Pharmaceuticals Treatment A and B: doses every 6 hours from Days 1 to 5 (inclusive) Treatment C: once a day from Days 1 to 5 (inclusive)	Predose Day 1, 3, 4, and 5, and on Day 5 post-morning dose: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 6.25, 6.5, 6.75, 7, 7.5, 8, 9, 10, 12, 12.25, 12.5, 12.75, 13, 13.5, 14, 15, 16, 18, 18.25, 18.5, 18.75, 19, 19.5, 20, 21, 22, and 24 hours postdose
MORP-OS+T-(2-17)-SPK-1 (pediatric patients)	Multiple-dose PK Study in Subjects 2 to 17 years old with postoperative pain [n=50]	• ≥4 to <10 kg: 0.6 to 2 mg (maximum dose: 3mg) • ≥10 to <25 kg: 1.5 to 5 mg (maximum dose: 7.5 mg) • ≥25 to <50 kg: 3.75 to 10 mg (maximum dose: 15 mg) • ≥50 kg: 15 to 20 mg (maximum dose: 30 mg) The dose was administered every 4 hours, as appropriate, up to a maximum of 5 days.	11 samples total: • Prior to first dose (Hour 0) and 0.5 hours post first dose (Hour 0.5) • Prior to Dose 6 (Hour 20) and 0.5 hours post Dose 6 (Hour 20.5) • Prior to the doses at Hour 24, 48, 72, 96, and 120 • 8 hours after the last dose of study drug • Prior to discharge or 24 hours after the last dose, whichever occurred first

The sample size represents the number of subjects with PK data that were utilized in the population PK analyses.

Source: sequence 0059, module 5311, pediatric-simulation-report.pdf, page 26, 27 of 85

4.3.1 Previous communications to the sponsor

The initial modeling activities discussed in this section of the review are in response to feedback provided by OCP in a complete response letter (please see the complete response letter for NDA 022195 archived on 01/21/2016). The concerns provided by OCP, which were not approvability issues, in the 2016 complete response letter were:

> *"We note that your population pharmacokinetic analysis does not adequately describe the pharmacokinetics of morphine in children and, therefore, cannot be relied upon as the basis for pediatric dosing. This conclusion is based on the finding of a lack of concordance between the predicted pharmacokinetic profiles and the observed data. We acknowledge that the ability of any model to adequately describe pediatric pharmacokinetics of morphine may be limited by the relatively low concentrations observed in MORP-OS+T-(2-17)-SPK-1 and the high proportion of samples below the limit of quantification. We recommend that you repeat the population pharmacokinetic analysis taking into account the following considerations, and include the results in your complete response.*
>
> *a. Include adult and pediatric pharmacokinetic data together in one integrated population pharmacokinetic model.*
>
> *b. The population pharmacokinetic model could be improved if single- and multiple-dose relative bioavailability data were also included along with the pediatric dataset. Therefore, include the following data:*
>
> > *i. Multiple-dose pharmacokinetic data from Study PVFS3.*
> >
> > *ii. Single-dose relative bioavailability data from Study PVFS-1 and absolute bioavailability data from Study PLFS-1.*
>
> *c. Model the relationship between clearance and body size as a continuous relationship. The use of scaling factors based on age groups is arbitrary and can be difficult to interpret. For example, your current analysis results in the internally inconsistent recommendation that pediatric patients from 12 to 17 years of age (who often have similar body weights as adults) should receive 1.7 times the adult dose to achieve comparable exposures.*
>
> *d. Use simulations from the population pharmacokinetic model to derive and justify dosing (using body weight cut-offs, if necessary) in pediatric patients that is expected to achieve exposure similar to adults at the approved dose.*
>
> *e. The derived dose may then be used as a starting dose in a multiple-dose safety and pharmacokinetic study in the target population."*

The Applicant performed additional PPK analyses following receipt of the Complete Response letter. The Applicant submitted subsequent modeling and simulation reports in 2016 and 2020. The 2016 report describes the re-analysis of the PPK data based on the advice in the Complete response letter and PK simulations used to support dose selection for a follow-up PK and tolerability study in pediatric patients,

study SPK-2. The 2020 report addresses analysis of the pediatric PK data from the SPK-2 study. The Applicant also provided a report containing PK simulations intended to support the proposed dosing regimen.

4.3.2 Applicants population PK analyses – 2016 Report

In 2016, Applicant submitted report pediatric-simulation-report.pdf to sequence 0059 in module 5311. This report is titled "*Population Pharmacokinetic Analysis of Roxane's Morphine Sulfate Solutions and Tablet Formulations in Adult and Pediatric Populations Simultaneously to Predict Concentration Profiles and Propose Suitable Doses for Pediatric Populations of Different Age Categories*". The objectives of these analyses were:

1) Develop a morphine PPK model for adults and children simultaneously following the administration of Roxane's solutions and tablet formulations.
2) Simulate morphine concentration profiles for different dosing regimens in pediatric populations between 2 to 17 years of age using the newly developed PPK model.
3) Propose suitable doses for pediatric populations of different age categories based on the simulations in order to achieve systemic PK exposures similar to those seen in adults with the previously approved starting doses.

The final dataset contains 5463 plasma concentration observations from 156 subjects (111 adults, 45 pediatric subjects).

The PK data were modeled using non-linear mixed effects modeling approach with NONMEM software version 6.2. The final structural model consists of 3-compartments parameterized by apparent volume of distribution of a central compartment (Vc/F), rate constants to describe first-order transport into and out of a shallow peripheral compartment (k12, k21), rate constants for first-order transport into and out of a deep peripheral compartment (k13, k31), and a rate constant representing first-order elimination from the central compartment (k10). Absorption was modeled using 2 first-order absorption processes (two ka estimates), one for oral solution and one for the tablet (with a lag time for only the tablet formulation). Each strength of oral solution was assumed to have comparable absorption characteristics.

The final parameter estimates are shown in the table below.

Table 4:Population PK Parameter Estimates Using Final (Model #25) for Adults and Pediatrics following Administrations of Morphine Tablet and Oral Solution: 2016 Report.

Parameter	Geometric Mean	Apparent inter-subject variability (%)	
		Without IOV (within days)	With IOV (between days)
Frel (tablet to solution)	0.93	8.4%	--
ka (h^{-1})			
Solution	1.61	112%	220%
Tablet	2.70	112%	220%
Tlag tablet (h)	0.08	55.1%	--
Vc/F (L/kg of ABW)*	8.18	48.6%	54.3%
k_{10} (h^{-1})	0.45	13.6%	--
k_{12} (h^{-1})	0.39	74.0%	--
k_{21} (h^{-1})	0.07	28.6%	--
k_{13} (h^{-1})	0.69	45.6%	--
k_{31} (h^{-1})	0.87	34.4%	--

**centered around a 76 kg individual, Vc/F for a 76 kg was 622 L. ABW = actual body weight*

Source: sequence 0059, module 5311, pediatric-simulation-report.pdf, page 49 of 85

The Applicant reports that the residual variability estimate is 23.4%.

The Applicant converted the rate constants from the table above to be expressed in terms of Cl/F, Vss/F, and half-lives for absorption, distribution, and elimination (see table below).

Table 5: Secondary Population PK Parameter Estimates (from Model #25 Output) for Adults and Pediatrics following Administrations of Morphine Tablet and Oral Solution: 2016 Report.

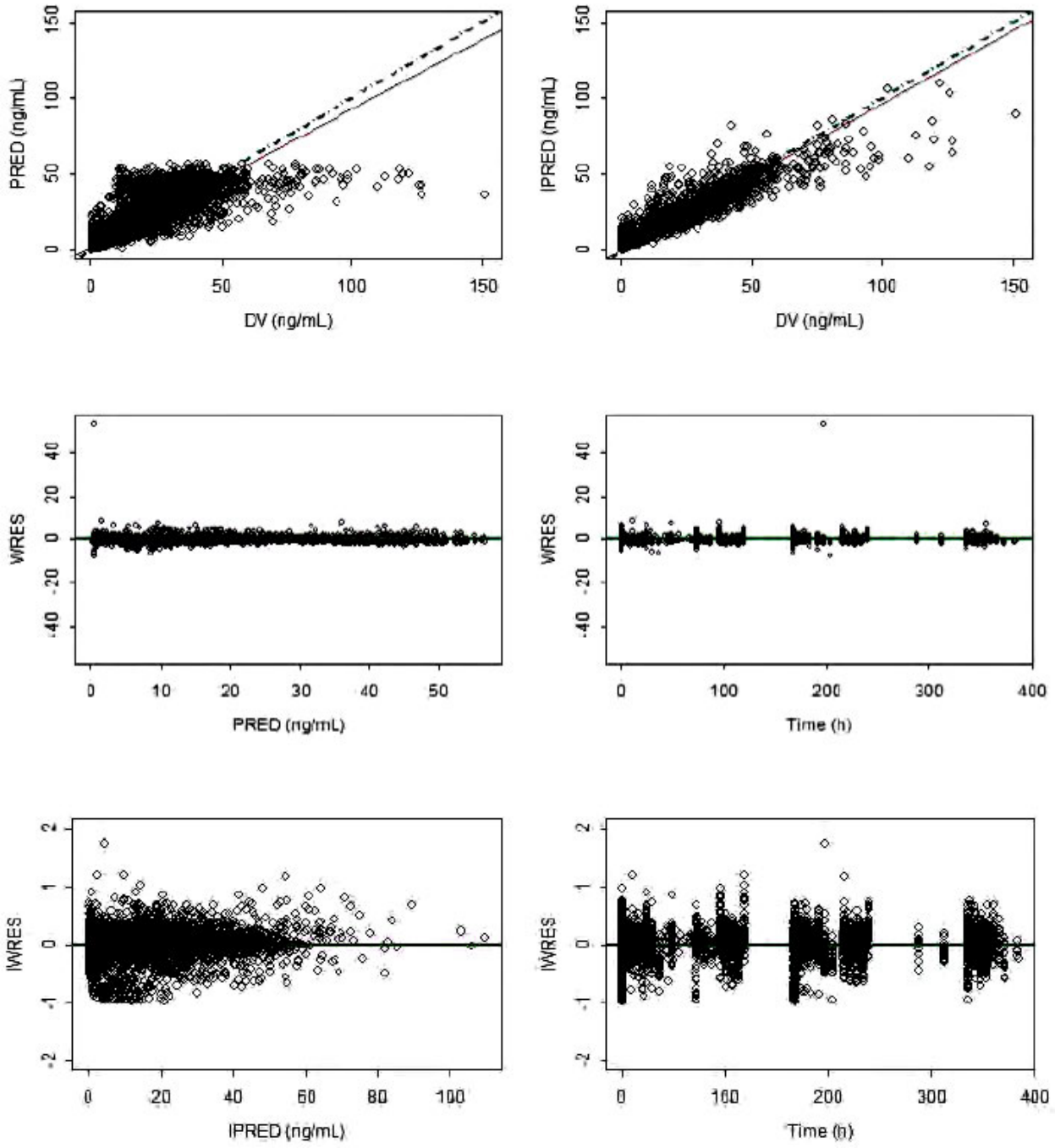
Parameters	From the NONMEM® Fitted Population Values
	Geometric Mean
Absorption half-life (h)	
Solution	0.431
Tablet	0.256
Distribution half-life (h)	
Initial	0.337
Secondary	1.80
Elimination half-life (h)	18.6
CL/F (L/h/kg)[a]	3.71
Vss/F (L/kg)[b]	57.3

a: centered around a 76 kg individual, CI/F for a 76 kg individual is 282 L/h
b: centered around a 76 kg individual, Vss/F for a 76 kg individual is 4352 L

Source: sequence 0059, module 5311, pediatric-simulation-report.pdf, page 49 of 85

The diagnostic plots are presented in the figures below.

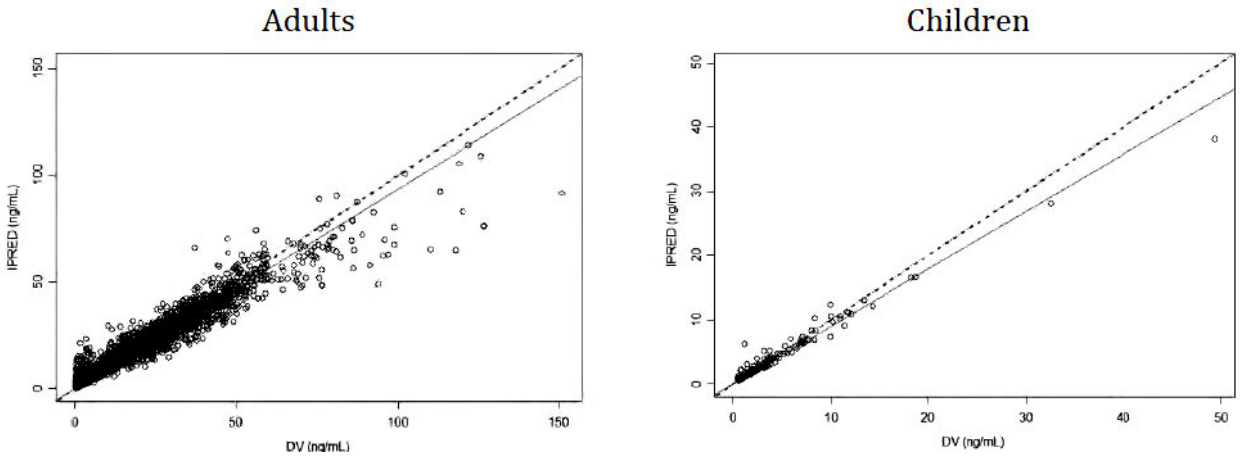
Figure 6: Goodness-of-Fit Plots for the Final PPK model (Model #25) for Adults and Pediatrics Following Administrations of Morphine Tablet and Oral Solution: 2016 Report.



Source: sequence 0059, module 5311, pediatric-simulation-report.pdf, page 52 of 85

The Applicant provided a diagnostic plot comparing the adult population to the pediatric patient population (see figure below).

Figure 7:Individual Prediction versus Observed for Adults and Pediatrics following Administrations of Morphine Tablet and Solution for Model #25: 2016 Report.



Source: sequence 0059, module 5311, pediatric-simulation-report.pdf, page 53 of 85

[*Reviewer comment: Applicant's 2016 PPK model was heavily inspired by the advice provided by OCP in the CR letter regarding the pediatric PK modeling. In the 2016 report, adult data from single-dose and multiple-dose PK studies were pooled with pediatric data, and allometry was applied as a continuous relationship model rather scaling factors based on arbitrary age groups (consistent with OCP's recommendations).*

According to the Applicant, the individual concentration-time profiles from the multiple-dose study appeared to be quite different from one dose to another, which suggested the presence of inter-occasion variability (IOV) in the PK of morphine. Thus, models with IOV were tested to try to improve the model predictions. An occasion was defined as each time a subject received a dose that was followed by the observation of PK samples. It is not clear what factors may be contributing to the apparent IOV in pediatric morphine PK.

Model deconstruction demonstrated that inclusion of weight on volume of distribution provided model stability. However, Applicant's covariate search did not support inclusion of weight as a covariate on clearance, which has been reported in pediatric morphine PK models in the literature[1]. Due to the relatively low number of covariates in the final model, and to pediatric data representing 3.1% of the dataset, performed a sensitivity analysis. The Applicant tested a hypothesis that the small proportion of pediatric PK data in the dataset (3.1%) compared to adult PK data (96.9%) is driving the absence of covariates in the final model. The Applicant tested this hypothesis by creating an artificially "more balanced" dataset in terms of adult and pediatric patients. The "more balanced" dataset was assembled by randomly selecting a subset of adults such that the ~80% of PK samples were from adults and ~20% of the PK samples were from the n=66 pediatric patients. In this artificially balanced dataset, the

[1] Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NHG. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. British Journal of Anaesthesia 2004; 92(2): 208-17.

Applicant then attempted to re-assess covariate testing runs 36, 37, 38, and 39 that assessed height on Vc/F, age on ka, sex on k10, and weight on k10, respectively. The result is that inclusion of additional covariates, including weight on k10 (the rate-constant term associated with morphine clearance), resulted in a failure for the model to converge. As such, the Applicant rejected the hypothesis that the paucity of covariates in the final PPK model was due to the low proportion of pediatric PK data. Overall, the Applicant did not further consider these covariates in the final PPK model.

In order to further assess the performance of the PPK model, the reviewer inspected the Individual predictions versus observations on a patient-by-patient basis (figures not included in this review, can be found on pages 163 to 318 of sequence 0059, module 5311, appendicies.pdf). The individual prediction versus observation plots suggest that the model performs reasonably well. Overall, the PPK model is fit for purpose in terms of being used to derive and justify dosing.

The final request from OCP in the CR letter was for the Applicant to utilize the updated PPK model to justify the starting dose selection to be utilized in a new pediatric PK and safety study, study SPK-2. These PK simulations are described in the next section of this review. This PPK model is referred to as the 2016 PPK model.]

4.3.3 Applicant's PK Simulations to Support the Starting Dose in Study SPK-2

The Applicant utilized the 2016 PPK model (see section 4.3.1 for details) to justify the selection of the starting dose for the next pediatric PK and safety study, study SPK-2. The Applicant conducted numerous PK simulations comparing the mean concentration-time profile for pediatric patients to adults for both oral solution and tablets. These PK simulations (figures 8 to 24 [not shown in review] on pages 57 to 78 of pediatric-simulation-report.pdf, module 5311, sequence 0059) lead the Applicant to select 0.3 mg/kg as the initial dose level for use in the next pediatric PK and safety study they planned to conduct, Study SPK-2. The Applicant implemented the 0.3 mg/kg initial dose via a "flat" mg dosing within multiple weight strata (see table below).

Table 6: Dosing Utilized in Study SPK-2.

Mean Weight (kg)	Recommended Starting Doses
10 to 12	3 mg[a]
>12 to 19	5 mg[a]
>19 to 30	7.5 mg[a]
>30 to 38	10 mg[a]
>38 to 55	15 mg[b]
>55	15 mg to 30 mg[b]
Adult (reference)	15 mg to 30 mg

Source: sequence 0097, module 5312, report-body.pdf, page 25 of 367

The Applicant submitted the SPK-2 protocol to FDA for feedback prior to initiating the study.

4.3.4 External validation of 2016 PPK Model

Upon completion of pediatric PK and safety study SPK-2, the PK data were utilized in additional PK analyses intended to re-assess the 2016 PK model. The Applicant's objectives with the SPK-2 PK data were 1) perform an external validation of the 2016 PPK model using the SPK-2 PK data (which were not available when the 2016 model was developed), and 2) if the external validation was not successful, to rebuild the 2016 PPK model by pooling the SPK-2 PK data with the PK data used to build the 2016 PPK model. The report containing these analyses is entitled "*External Validation of the Previous Morphine Adult/Children PPK 2016 Model in Children with Morphine Data from Hikma's Pediatric Study MORP-OS+T-(2-17)-SPK-2, and PK Characterization of Morphine and its Metabolites (M3G and M6G) in this Pediatric Population*" (report-body-ppk.pdf), submitted to module 5312 in sequence 0089.

The Applicant's external validation method involved estimating individual PK parameters from study SPK-2 subjects using the final 2016 PPK model, simulating PK profiles with the individual parameter estimates, and comparing the observed PK data. The Applicant defined successful external validation as 2/3 (66.67%) of individual predicted concentration observations falling within 25% of the respective mean of observed and fitted concentrations. In other words, $-0.25 < (C_{obs}-C_{fitted})/Mean(C_{obs}, C_{fitted}) < 0.25$, where, for a particular subject at a particular time, C_{obs} is an observed concentration, C_{fitted} is a simulated concentration, and $mean(C_{obs}, C_{fitted})$ is the mean of observed and fitted concentration. The Applicant determined that 25% is the lowest limit that could be realistically utilized since the 2016 PPK model had a residual variability of 23.4%.

Of the 387 morphine observations collected in study SPK-2, 276 observations (71.3% of the data) met the criteria. Thus, the Applicant considers externally validation of the 2016 PPK model successful.

[*Reviewer comment: The Applicant's external validation of the SPK-2 data is acceptable.*]

The mean individual calculated morphine PK parameters of the n=66 subjects in study MORP-OS+T-(2-17)-SPK-2 using the 2016 PPK model are found in the table below.

Table 7: Individual PK Parameters Following Administration of Morphine Tablets and Oral Solution to Pediatric Patients in Study MORP-OS+T-(2-17)-SPK-2 using 2016 PPK Model.

Calculated PK parameter	Geometric Mean	Geometric CV (%)	n
Absorption half-life (h)			
Solution	1.01	138	50
Tablet	1.14	135	16
Distribution half-life (h)			
Initial	0.319	11.1	66
Secondary	1.62	23.0	66
Terminal half-life (h)	21.7	33.9	66
CL/F (L/h/kg)	4.58	40.0	66
Vss/F (L/kg)	78.8	61.6	66

Source: sequence 0089, module 5312, report-body-ppk.pdf, page 52 of 367

[*Reviewer comment: The Applicant indicated that a subset of subjects was not included in the PPK analyses. OCP was asked to comment on how the exclusion of PK data from the subset of subjects may impact on PPK analyses. There were 4 reasons why 14 subjects out of the original 80 subjects were excluded from the PPK analyses (resulting in n=66 subjects in the final dataset).*

1) *"No detectable plasma concentrations". Subjects which have all PK samples either undetectable or missing were excluded.*
2) *"emesis soon after administration". The applicant followed the guideline presented in the FDA guidance document of Bioavailability and Bioequivalence[2] to exclude subjects from PK analyses when emesis occurred within 2 times the median Tmax.*
3) *"Unknown amount of drug administered". Subjects have measurable morphine plasma concentrations, but the amount of drug administered is not available were excluded.*
4) *"non-zero pre-dose levels prior to the first dose of study drug". Subjects that appeared to have prior exposure to morphine prior to surgery were excluded.*

Overall, OCP considers the rationale for excluding the subjects from the PPK analyses acceptable. The resulting n=66 population is an acceptable sample size for conducting the PPK analyses.

OCP was asked to comment on the actual timing of PK samples differing from the nominal PK sampling times described in the protocol for some PK samples. Though there are observations where the actual PK

[2] "Guidance for Industry Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA", page 22 of 24. https://www.fda.gov/files/drugs/published/Bioequivalence-Studies-With-Pharmacokinetic-Endpoints-for-Drugs-Submitted-Under-an-Abbreviated-New-Drug-Application.pdf. Last accessed 2021/04/28.

sample times differ from the planned PK sample times, the resulting PPK model is fit for purpose in terms of being used to derive and justify dosing (see section 4.3.2 for details on the Applicant's PPK model).]

4.3.5 Sponsor's Simulations to Support Proposed Dosing for Label

An information request was sent to the Applicant on 02/26/2020 with numerous requests from the Clinical and Clinical Pharmacology teams. One such request by the Clinical Pharmacology team was that the Applicant provide simulated single-dose and multiple-dose Cmax and AUC values across age groups for the proposed pediatric initiation dose as well as the approved tablet dosing approved for adults (15 mg to 30 mg).

The Applicant provided an initial response to this request from OCP in module 1, sequence 0090, in multiple-module.pdf (Tables 1 through 10). OCP sent a subsequent information request on March 4th, 2021 asking the Applicant to also include simulations of single dose and multiple dose Cmax and AUC of morphine based on adult subjects receiving the 10 to 20 mg oral morphine solution (the labelled oral solution starting dose for adults). The Applicant provided the response in sequence 0101, module 1, question-answer-to-fda-email-20210303-0304.pdf, page 56 of 78, Table 8a. The Applicant provided the following description of their methodology (Submission dated 3/5/2020):

> "The POP PK 2020 Report provided the model-predicted AUCtau,ss by dose level, which was derived from estimates of clearance (CL), volume of distribution (V) and elimination rate constant (k) provided by the model for each subject. In order to address the FDA's request for estimates of Cmax and AUC after single and multiple doses, supplemental analyses were conducted and are provided below. According to the study protocol, PK samples were to be collected over the first 7 administrations of study drug. Study drug was planned to be administered every 4 hours. However, as the study included pediatric post-operative patients from a wide age range, drug dosing and PK collection were often conducted at different times. Furthermore, up and down titration of study drug occurred for some patients. In order to provide meaningful Cmax and AUC values reflective of single and multiple doses, where all patients have received the same number of doses, single-dose and multiple-dose concentrations were predicted for each patient using the post-hoc PK parameters and where each patient was administered study drug every 4 hours for 7 doses, and PK (i.e., Cmax and AUC) was characterized over the first and last dosing interval. In these predictions, each patient received the actual dose received in the study, but without down or up titrations."

These simulated morphine Cmax and AUC values are presented by weight category in Table 8 below.

Table 8: Individual PK Parameters Following Administration of Morphine Tablets and Oral Solution to Pediatric Patients in Study MORP-OS+T-(2-17)-SPK-2 using 2016 PPK Model.

Weight Category	Recommended Dose	*n*	Single-dose (Geomean, Range)		Multiple-dose (Geomean, Range)	
			Cmax_pred (ng/mL)	AUC0-inf_pred[1] (ng*h/mL)	Cmax_pred (ng/mL)	AUCtau,ss_pred[2] (ng*h/mL)
10-12 kg	3 mg	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	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	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	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	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	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	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	*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]

Source: sequence 0101, module 1, question-answer-to-fda-email-20210303-0304.pdf, page 56 of 78

Based on this applicant recommends 0.15 to 0.3 mg/kg maximum 20 mg.

[*Reviewer comment: The table above with a flat dose level in each weight stratum is consistent with the approach the 0.3 mg/kg initial dose level was implemented in study SPK-2 (see section 4.3.2). However, the Applicant's proposed label language is to initiate at 0.15 to 0.3 mg/kg (and does not include the dosing table above).*

As the proposed dosing in the label is in mg/kg, and the PK simulations to support the dosing are presented in a table with flat dosing administered by weight strata, the reviewer conducted independent PK simulations to further assess the proposed dosing as a function of patient weight (see section 4.3.5).]

4.3.6 Reviewer 's Independent PK Simulations to Assess Dosing for Label

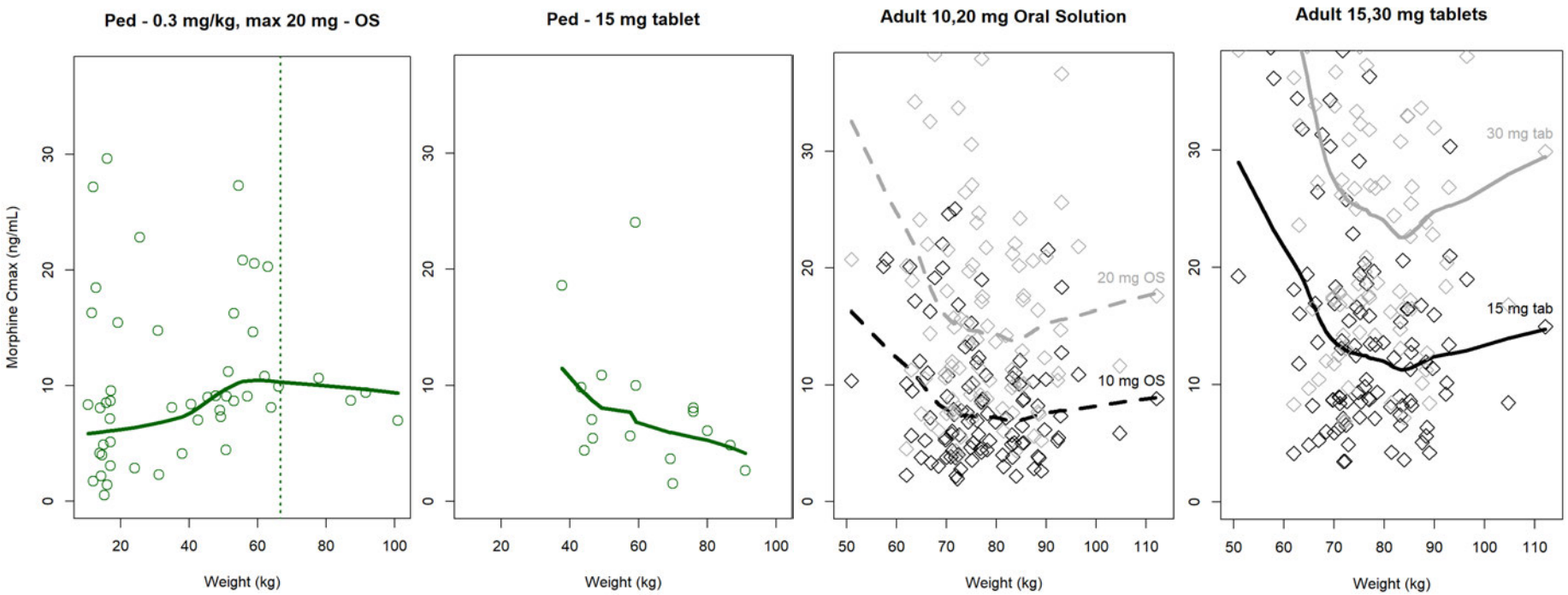
The reviewer conducted independent PK simulations to further assess the proposed initial dose for pediatric patients. The Applicant's PK simulations were presented in terms of a flat dose level administered by weight stratum. The reviewer's approach is to visualize the predicted PK value as a function of patient weight for the proposed dose regimen compared with the approved adult regimen.

The reviewer utilized the Applicant's individual PK parameter estimates for the n=66 pediatrics subjects in study SPK-2 obtained from the external validation exercise (see section 4.3.3). The reviewer utilized the individual adult PK parameter estimates from the 2016 PPK model for reference. The reviewer's simulations are presented with simulated PK versus body weight by dosage form and by patient population. This approach will provide an exact value of 0.3 mg/kg oral solution (maximum 20 mg) whereas the Applicant's approach of flat dose level within a weight stratum produces mg/kg values that differ from 0.3 mg/kg within each weight stratum.

Older pediatric subjects with higher body weight values in study SPK-2 received 15 mg morphine tablets rather than oral solution. These subjects that received tablets in study SPK-2 received 15 mg tablets in the reviewer's PK simulations.

The reviewer's PK simulations are presented in the figure below.

Figure 8: Simulated Morphine Cmax vs Weight By Dosage Form and By Patient Population (Reviewer's Independent Simulations).



The left panel represents pediatric subjects that received oral solution. The 2nd panel from the left represents pediatric subjects that received oral tablets. The far right panel represents adult subjects receiving tablets. The 2nd panel from the right represents adult subjects that received oral solution. The open circles represent predicted PK value for an individual pediatric subject at the proposed initiation dose. The open diamonds represent the predicted PK value for an individual adult subject at the labelled initiation dose levels for adults. The bold curves are the lowess (locally weighted smoothing) of the PK vs weight relationship. The vertical dotted line represents 66.67 kg, the weight at which the 0.3 mg/kg produces the maximum recommended dose level of 20 mg. Virtual subjects weighing > 66.67 kg were assigned to receive 20 mg, consistent with the proposed dosing (and thus, a mg/kg value that is < 0.3 mg/kg).

The reviewer's PK simulations presented in the figure above suggest that the proposed 0.3 mg/kg dose level as an initial dose are expected to produce Cmax consistent with the approved adult level of 10 mg oral solution. 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. The 15 mg tablet initial dose level was also administered to n=13 subjects and 30 mg (2 x 15 mg tablets) was administered n=3 subjects in out of the n=66 subjects with PK data in study SPK-2.

This medication is utilized Pro Re Nata (PRN; when needed, as soon as possible) and pediatric patients will be under the supervision of either medical staff or parents. Thus, the reviewer's simulations focus on informing the initial dose level, as subsequent administrations to pediatric patients will be driven by the pain level and patient tolerability.

While the 0.15 mg/kg dose level may not provide Cmax values consistent with approved adult dose levels, this reduced dose level may be helpful in scenarios where a lower dose morphine level is desirable (e.g. if pediatric patients are already on concomitant pain management medications).

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