SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. EN3319-304

AN OPEN-LABEL SINGLE-DOSE AND RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTIPLE-DOSE STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF OXYMORPHONE HCL FOR ACUTE MODERATE TO SEVERE POSTOPERATIVE PAIN IN PEDIATRIC SUBJECTS

Version 1.0

November 02, 2020

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This study was conducted at the request of the FDA as a class required Post Marketing Study in pediatric patients.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CF	Clear Fluids
CNS	Central Nervous System
CSR	Clinical study report
EKG	Electrocardiogram
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of Study
EOT	End of treatment
ET	Early termination
GGT	Gamma-glutamyl transferase
HCl	Hydrochloride
HEENT	Head, eyes, ears, nose, and throat
IDMC	Independent data monitoring committee
ITT	Intent-to-Treat
IV	Intravenous
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Nurse-controlled analgesia
NSAID	Nonsteroidal anti-inflammatory drug
PCA	Patient controlled analgesia
PREA	Pediatric Research Equity Act
PRN	Pro re nata (as needed, or when necessary)
PK	Pharmacokinetic
PP	Per Protocol population
PT	Preferred term
RBC	Red blood cell

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SOC	Standard of care
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This study has been prematurely terminated based on the recommendation of the Independent Data Review Committee (IDMC) on 12-July-2019. Upon reviewing the data, the IDMC indicated that further exposure of infants <2 months old to single doses of oxymorphone is not indicated or appropriate due to the risk of respiratory depression. This Statistical Analysis Plan (SAP) describes the safety analyses to be included in the abbreviated Clinical Study Report (CSR). All the specific information about the study is described in the EN3319-304 Clinical Study Protocol Amendment 5 dated 1 April 2019 (1).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to describe the efficacy of oxymorphone HCl in children aged below 2 years (0 to <2 years) for whom an opioid to treat acute moderate to severe postoperative pain of various etiologies may be an appropriate treatment option.

2.2. Secondary Objective

The secondary objectives of this study are:

- To characterize the safety and tolerability of oxymorphone HCl in children aged below 2 years (0 to <2 years) for whom an opioid to treat acute moderate to severe postoperative pain of various etiologies is an appropriate treatment option.
- To characterize the pharmacokinetics (PK) of oxymorphone HCl in children aged below 2 years (0 to <2 years) for whom an opioid to treat acute moderate to severe postoperative pain of various etiologies is an appropriate treatment option.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 3, post marketing study conducted to meet a Pediatric Research Equity Act (PREA) commitment. The study comprised an open-label, single-dose, dose selection phase and a randomized, double-blinded, active controlled multiple-dose phase to characterize the efficacy, safety, tolerability, and PK of oxymorphone HCl in pediatric subjects with acute moderate to severe postoperative pain for whom an opioid may be determined to be an appropriate treatment option. It is a multicenter study intended to be conducted at up to 25 sites. At the time the study was prematurely stopped, the study was conducted at 3 clinical sites.

The study was designed to be conducted in 2 phases: single-dose phase and multiple-dose phase. The single-dose phase was an open label dose selection phase intended to determine the dose (for each age group) in the multiple-dose phase (Figure 1) based on the recommendation of an IDMC. The multiple-dose phase included a double-blinded assessment of oxymorphone HCl vs. placebo.

Each study phase consisted of the following planned study periods:

- Screening period (within 5 days of surgery)

- Post-surgery evaluation
- Treatment period occurring after surgery
- End-of-treatment (EOT) assessment 24 hours after the last dose of study drug; and
- 2 follow-up contacts (at 3 ±1 and 14 ±2 days after the last dose of study drug).

All subjects were enrolled preoperatively up to 5 days before surgery with the expectation that they would require intravenous (IV) access after surgery and postoperative analgesia with an opioid.

It was intended to enroll subjects sequentially to each of the below mentioned four age groups with recruitment of older infants and toddlers preceding recruitment of the youngest age subjects:

- Group A: 6 months – <2 years (up to and inclusive of 729 days)
- Group B: 61 days – <6 months (up to and inclusive of 179 days)
- Group C: 31 days – 60 days
- Group D: 0 – 30 days

In the single-dose phase, it was planned that up to 3 cohorts of 5 subjects for each age group would receive oxymorphone HCl and in the multiple-dose phase a single cohort of 10 subjects were planned be enrolled to receive study drug or placebo in 1:1 allocation ratio for each age group. However, by the time Group B was to enroll subjects, the study was suspended (only 5 subjects were enrolled in Group B for cohort 1).

It was intended that the study would first enroll the subjects in oldest age group (Group A), and each subsequently younger age group (B, C, and D) would enter the study only after the preceding age group has completed enrollment and the data is reviewed by an IDMC. Each age group must complete their respective single-dose phase and IDMC review before proceeding to the multiple-dose phase.

3.1.1. Dose Selection at Single-Dose Phase

During the single-dose phase, the first cohort of 5 subjects from Group A entering the study were to receive 0.05 mg/kg oxymorphone HCl immediate-release oral liquid. The IDMC reviewed the data from the initial cohort for efficacy, safety, tolerability, and PK and made a recommendation for the dose for the second cohort of subjects from Group A. Each cohort of age groups progressed through the single-dose phase in the same manner until either 3 doses are assessed in the single-dose phase for each age group or as per the IDMC recommendation that an age group can proceed to the multiple-dose phase. The starting dose for the first cohort of subjects of Group B was determined based on IDMC recommendation following review of data from Group A.

Since it was intended to enroll subjects in Groups C and D to receive the IV formulation of oxymorphone HCl, the IDMC was also expected to review the PK modeling data aggregated from Groups A and B to determine the starting dose of Group C, and after its completion, the starting dose of Group D. However, no subjects were enrolled in Groups C and D.

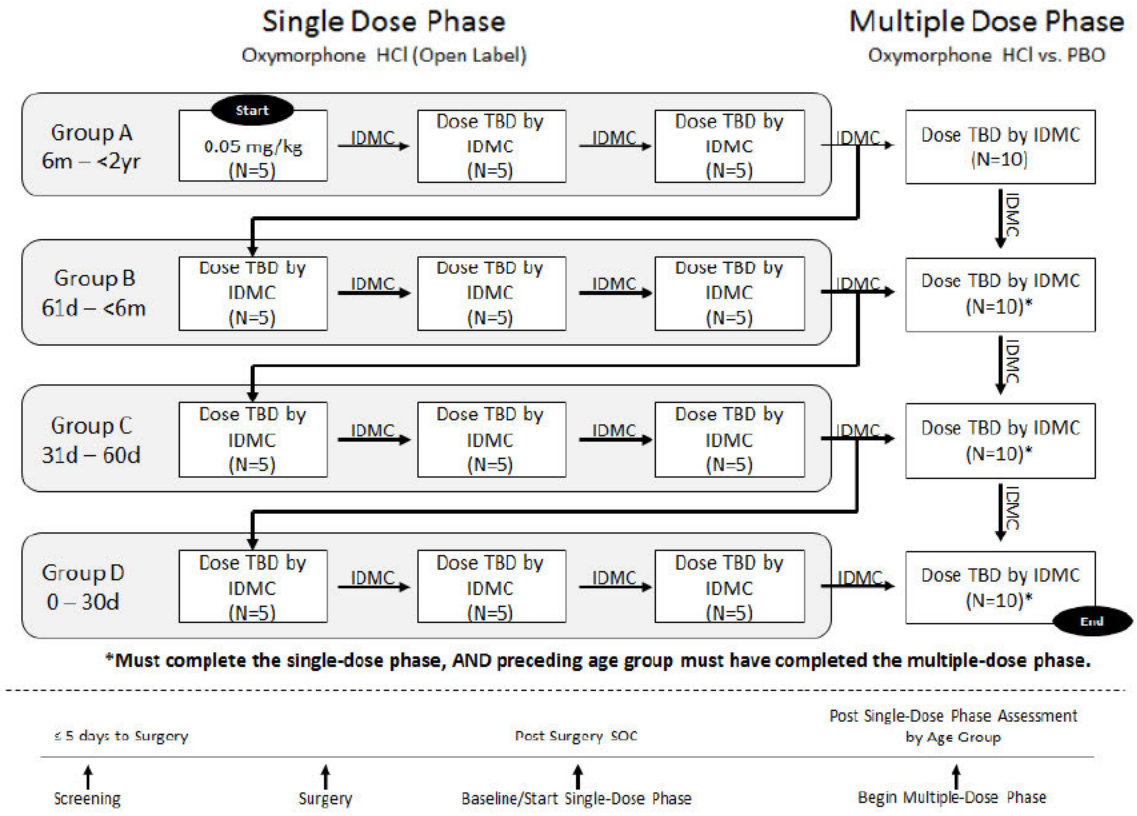
3.1.2. Dose Recommendation for Multiple-Dose Phase

It was intended that following the review of data related to the efficacy, safety, tolerability, and PK from the single-dose phase, the IDMC would provide a recommendation for a dose (for each age group) to be carried forth into the double-blind, placebo-controlled multiple-dose phase to assess efficacy of oxymorphone HCl versus placebo. However, by the time Group B was to enroll subjects in single-dose phase, the study was suspended (only 5 subjects were enrolled in Group B for cohort 1).

The multiple-dose phase was to include a double-blinded assessment of oxymorphone HCl versus placebo conducted in the same manner as the single-dose phase (i.e., the same progression of age groups, beginning with Group A, followed by Group B, etc.), but only a single dose level to be tested in each age group (Figure 1). New cohorts of 10 subjects per age group were to be randomized 1:1 to receive study drug as either oxymorphone HCl (N=5 per age group) at the dose established following IDMC review in the single-dose phase or placebo (N=5 per age group) every 4-6 hours PRN.

The multiple-dose phase used the similar age group stratification as used in the single-dose phase. Subjects were randomized to receive either oxymorphone HCl or placebo in a 1:1 ratio.

Figure 1: Study Design



d=Days; IDMC=Independent data monitoring committee; m=Months; PBO=Placebo; SOC=Standard of care; TBD=To be determined; yr=Years

The total duration of the study, excluding screening, for subjects in the open-label, dose-selection phase was approximately 15 days from the first dose of study drug to last follow-up. The total duration of the study, excluding screening, for subjects in the multiple-dose phase was up to 17 days from the first dose of study drug to last follow-up.

Refer to Table 1 and Table 2 below for details of the Schedule of Assessments/Procedures for the Single-Dose phase and Multiple-Dose phase, respectively.

Table 1: Schedule of Assessments/Procedures for the Single-dose Phase

	Pre-Treatment		Baseline/ Dosing [c]	Postdose (hours)											EOT Assessment	Follow-Ups (Phone)
	Screening (within 5 days of surgery)	Post-Surgery Evaluation [a]		0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0	24 hours post dose or ET	(3 [±1] and 14 [±2] days post last dose)
Time relative to dosing (hours)			0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0		
Informed consent	X															
Inclusion/exclusion criteria [a]	X	X														
Demographics	X															
Medical/surgical history [b]	X															
Physical examination	X														X	
12-lead EKG	X															
Study drug administration			X													
Blood sample for pharmacokinetics			X	X [n]			X		X		X			X	X	
Vital signs [d]	X	X	X	X	X	X	X		X		X		X	X	X	
Clinical laboratory tests [e]	X														X	
Continuous pulse oximetry		X	X	Monitored Throughout the Study												
Continuous telemetry		X	X	Monitored Throughout the Study												
Respiratory assessment [f]	X	X	X	X	X	X	X		X		X		X	X	X	
Neurological assessment [g]	X	X	X	X	X	X	X		X		X		X	X	X	
Adverse events [h]	X	Monitored Throughout the Study														X
Prior and concomitant medications [i]	X	Monitored Throughout the Study														X
Pain assessment [j]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Record surgical details [k]		X														
NCA rescue medication [l]			X													
Food consumption [m]			X													

Table 1: Schedule of Assessments/Procedures for the Single-dose Phase (continued)

Footnotes:

[a] Study eligibility was re-confirmed before the first dose of study drug was administered. All test results were reviewed by the Investigator or designee prior to dosing a subject.

[b] Subjects were generally healthy as documented in medical history, including a 12-lead electrocardiogram (EKG) as part of the screening assessment.

[c] See protocol section 8.1.3 and section 8.1.4 for Baseline Dosing Assessment Procedures and NCA Information. All baseline assessment procedures were completed prior to dosing the subject. After subjects in Groups A and B were postoperative and had shown signs of tolerating oral intake their SOC analgesic regimen were to be discontinued and they would enter the single-dose phase of the study. Subjects in Groups A and B were able to tolerate oral intake prior to receiving oxymorphone oral liquid. It was intended that after subjects in Groups C and D were post-operative, and had shown signs of awakening and arousal, their SOC analgesic regimen would be discontinued and they would enter either the single-dose phase of the study.

[d] Vital signs included heart rate, respiratory rate, blood pressure, and body temperature.

[e] Clinical laboratory (chemistry, hematology, and urinalysis) assessments were acceptable for study purposes provided they were taken prior to the first surgical incision and assessed by the Investigator prior to administration of the study drug.

[f] Respiratory assessment Included oxygen saturation.

[g] Neurological (sedation) assessments were completed using the Modified Ramsay Sedation Scale (Protocol Appendix A).

[h] Adverse events (AEs) were collected from the time of informed consent through 14 days after the last dose of study drug **(documented telephone follow-up is required)**.

[i] Concomitant medications were collected through 14 days after the last dose of study drug **(documented telephone follow-up is required)**.

[j] The FLACC were used for subjects in Groups A and B . The NIPS was planned to be used for subjects in Groups C and D.

[k] Surgical details includes type of procedure(s), date of procedure(s), surgical start/stop time, and anesthesia/analgesia start and stop time.

[l] Rescue medication were administered according to an NCA paradigm, with IV morphine sulfate immediately available.[3] The dose of NCA rescue medication was based on weight and age according to well-established standards.[4,5]

[m] Recording of food consumption from the period 1 hour prior to administration of study drug through EOT assessment; record all times that any food was consumed and what food was consumed (diet-as-tolerated [DAT], DAT-soft, full fluids [FF], clear fluids [CF], water, formula, breast milk)

[n] Blood samples for PK analysis were collected at 0.5 (for subjects with even subject numbers) or 1.0 hour (for subjects with odd subject numbers), and at 2.0, 3.0, 4.0 and 8.0 hours (protocol section 13.1.1). A window of ±10 minutes was allowed.

Abbreviations: BL=Baseline; EOT=End-of-treatment; ET=Early termination; EKG=Electrocardiogram; NCA=Nurse-controlled anesthesia

Table 2: Schedule of Assessments/Procedures for the Multiple-dose Phase

	Pre-Treatment		Doses 1-5 [c] (up to 18 hours post first dose)		EOT Assessment	Follow-Ups (phone)
	Screening (within 5 days of surgery)	Post-Surgery Evaluation [b]	Baseline [d]	Post Dose Assessments	(24 hours post last dose or ET)	(3 [±1] and 14 [±2] days post last dose)
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical/surgical history [e]	X					
Physical examination	X				X	
12-lead EKG	X					
Randomization [f]		X				
Study drug administration [a]			X			
Blood sample for pharmacokinetics [g]			X			
Vital signs [h]	X	X	X	See Footnote "i"	X	
Clinical laboratory tests [j]	X				X	
Continuous pulse oximetry		X	X	Monitored throughout the study		
Continuous telemetry		X	X	Monitored throughout the study		
Respiratory assessment [k]	X	X	X	See Footnote "i"	X	
Neurological assessment [l]	X	X	X	See Footnote "i"	X	
Adverse events [m]	X	Monitored Throughout the Study				X
Prior and concomitant medications [n]	X	Monitored Throughout the Study				X
Pain assessment [o]			X	See Footnote "o"		
Record surgical details [p]		X				
Food consumption [q]		Monitored Throughout the Study				
NCA rescue medication [r]			X			

Table 2: Schedule of Assessments/Procedures for the Multiple-dose Phase (Continued)

Footnotes:

[a] Prior to entering the multiple-dose phase, when subjects in Groups A and B were postoperative, and had shown signs of tolerating oral intake their SOC analgesic regimen were to be discontinued and they would be randomized and enter multiple-dose phase of the study.

It was intended that prior to entering the multiple-dose phase, when subjects in Groups C and D were post-operative, and had shown signs of awakening and arousal, their SOC analgesic regimen would be discontinued and they were to be randomized and enter the multiple-dose phase of the study. The FLACC were used for subjects in Groups A and B. The NIPS was planned to be used for subjects in Groups C and D. All subjects would then be closely monitored for pain and their pain score would be recorded at least hourly until their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time they were administered study drug (oxymorphone HCl immediate release oral liquid for Groups A and B; IV oxymorphone HCl for Groups C and D) or placebo. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. Morphine-NCA (protocol section 8.1.4) would be initiated coincident with but not earlier than study drug/placebo administration, and this time was designated as day 1 time zero.

[b] Study eligibility was re-confirmed before the first dose of study drug was administered. All test results were tot be reviewed by the Investigator or designee prior to dosing a subject.

[c] Subjects were dosed every 4 to 6 hours as needed. Following dose 1, subsequent doses should be administered no less than 4 hours apart, and at least 20 minutes have elapsed since the last bolus NCA rescue. The last dose of study drug would be administered no later than 18 hours post first dose.

[d] Back-to-back assessments were not needed between doses (e.g., final hourly assessments for a dose serve as baseline assessments for the next dose).

[e] Subject should be generally healthy as documented in medical history, including a 12-lead electrocardiogram (EKG) as part of the screening assessment.

[f] Once subjects had cleared to transition to oral pain medication, they were randomized to receive either oxymorphone HCl (oral or IV) or placebo.

[g] A pharmacokinetic (PK) sample was just before each dose. The date, time, and dose amount and date and time of sample collection was recorded.

[h] Vital signs included heart rate, respiratory rate, blood pressure, and body temperature.

[i] Post-dose vital signs, respiratory assessment, and neurological assessment were recorded at 0.5, 1, 2, 3, and 4 hours after administration of first dose of study drug; and at 0.5, 1, and 2 hours after administration of subsequent doses.

[j] Clinical laboratory (chemistry, hematology, and urinalysis) assessments were acceptable provided they were taken prior to the first surgical incision and assessed by the Investigator prior to administration of the study drug.

[k] Included oxygen saturation, heart rate, and respiratory rate.

[l] Neurological (sedation) assessments were completed using the Modified Ramsay Sedation Scale.

[m] Adverse events (AEs) were collected from the time of informed consent through 14 days after the last dose of study drug (documented telephone follow-up is required).

[n] Concomitant medications were collected through 14 days after the last dose of study drug (documented telephone follow-up is required).

[o] After the first dose of study drug, pain was assessed (using FLACC or NIPS, as age appropriate) every half hour throughout the study period until EOT.

[p] Surgical details included type of procedure(s), date of procedure(s), surgical start/stop time, and anesthesia/analgesia start and stop time.

[q] Recording of food consumption from the period 1 hour prior to administration of study drug through EOS assessment; record all times that any food was consumed and what food was consumed (diet-as-tolerated [DAT], DAT-soft, full fluids [FF], clear fluids [CF], water, formula, breast milk)

[r] Rescue medication was administered according to an NCA paradigm, with IV morphine sulfate immediately available.[6] The dose of NCA rescue medication was based on weight and age according to well-established standards.[7,8]

Abbreviations: BL=Baseline; EOT=End-of-treatment; ET=Early termination; EKG=Electrocardiogram; NCA=Nurse-controlled anesthesia

3.2. Eligibility Criteria for Subject Selection

The inclusion and exclusion criteria for subject selection can be found in Amendment 05 to Clinical Study Protocol EN3319-304, Section 9.

3.3. Study Drug Administration

Subjects in Groups A and B received oxymorphone HCl immediate-release liquid 1 mg/mL 0.05 mg/kg orally (or an oral liquid placebo matched in color and flavor for multiple-dose phase) with subsequent dose to be determined by IDMC. It was intended that the subjects in Groups C and D would receive oxymorphone HCl IV solution 1 mg/mL at doses to be determined by IDMC (or a matched placebo appropriate for parenteral administration). However, by the time Group B was to enroll subjects in single-dose phase, the study was suspended (only 5 subjects were enrolled in Group B for cohort 1).

The selection of dose has been described in the study design section and the timing of drug dosing will be as presented in Table 1 and Table 2 (Schedule of Events for single-dose and multiple-dose phases).

3.3.1. Determination of Sample Size

The sample size of the study was based on the assumptions of both efficacy and PK endpoints. The planned number of subjects for single-dose phase and multiple-dose phase are as follows:

- For the single-dose phase, 5 subjects from each age group (i.e. up to total of 60 subjects) were to receive oxymorphone depending on IDMC recommendations.
- For the multiple-dose phase, 10 subjects from each age group (i.e. total of 40 subjects) were to be randomized to receive either oxymorphone or placebo.

3.3.1.1. Efficacy

The efficacy sample size was determined based on primary analysis to compare cumulative morphine demand via NCA during the multiple-dose phase. To detect a difference in effect size of 0.9, 20 subjects for each group (active treatment group pooled across all age groups vs. placebo group pooled across all age groups) would have 80% power at 2-sided significance level of 0.05.

3.3.1.2. Pharmacokinetics

In earlier PK modeling it was indicated that the best fitting model was 2 compartmental and that the inter and intra-subject coefficient of variation (CV[%]) for clearance and volume of distribution were 54% and 20%, respectively. The sample size of the PK sample was determined based on the assumption that if each subject provides 3 data points in the ranges of absorption and terminal elimination phases, the total CV(%) (combination of the inter- and intra-subject CV[%]) is approximately 60%. Based on this assumption, a total of 34 subjects are needed to provide estimates of clearance and volume of distribution if their 95% confidence interval is within the range of 0.6 to 1.4 of the point estimates with 90% power.

3.3.2. Blinding and Randomization

3.3.2.1. Randomization

Subjects were to be stratified by 4 different age groups as outlined in Table 3 and Table 4. During the multiple-dose phase, subjects within each age group were randomized to receive either oxymorphone HCl or placebo in a 1:1 allocation ratio.

Table 3: Treatment Assignment – Single-Dose Phase

Age Group	Oxymorphone HCl (Max N)
6 months – <2 years (up to and inclusive of 729 days)	15
61 days – <6 months (up to and inclusive of 179 days)	15
31 days – 60 days	15
0 – 30 days	15
Total	60

Table 4: Treatment Assignment – Multiple-Dose Phase

Age Group	Oxymorphone HCl (N)	Placebo (N)
6 months – <2 years (up to and inclusive of 729 days)	5	5
61 days – <6 months (up to and inclusive of 179 days)	5	5
31 days – 60 days	5	5
0 – 30 days	5	5
Total	20	20

3.3.2.2. Blinding

The multiple-dose phase of this study was double-blinded. Subjects, parents, study staff, clinical staff, vendor staff with the exception of the packaging and labeling vendor, and the Sponsor (with the exception of the clinical supplies staff) and its designees were blinded to the study treatment being received by each subject.

3.4. Efficacy Assessments

The SAP for this abbreviated CSR includes safety assessments only. All efficacy endpoints and efficacy assessments planned in the protocol were removed. This change is included in the Change from Protocol Section of the SAP.

3.5. Medical and Surgical History

A medical and surgical history of the subject was collected during Screening. Medical history included relevant diagnoses including any surgical procedures with onset/resolutions dates.

3.6. Prior, Concomitant, and Follow-up Medications/Procedures

Any concomitant medication (including vitamin supplements, herbal remedies, and non-prescription medications) used while the subject was on study drug (up to 24 hours post first dose of study drug) was recorded. Concomitant medications were also collected through 14 days after the last dose of study drug.

Surgical medications were captured on the Surgical Medications page of the electronic Case Report Form (eCRF).

The concomitant/surgical medication name, dose (unit), start/end date and time, indication, frequency, and route of administration were recorded.

Surgical procedures were captured on the surgical procedure page of the eCRF and were to include type of procedure(s), date of procedure(s), and surgical start/stop time.

3.6.1. Prohibited Medications

The following medications were prohibited during the study:

- Preoperative opioids administered for a period of more than 72 hours in duration.
- Any investigational drugs other than oxymorphone HCl immediate-release oral liquid from 30 days prior to screening through End of Treatment (EOT).
- Oxycodone or oxymorphone within 48 hours prior to screening.
- Cough syrup containing an opioid from screening through EOT.
- MAOIs from screening through EOT.
- Products containing caffeine or xanthine.
- Non-opioid analgesics (acetaminophen and/or NSAIDs) during the Multiple-dose Phase.

3.7. Rescue Medication

All subjects were to receive rescue by morphine-NCA as needed. The dose of nurse-controlled analgesia (NCA) rescue medication was based on weight and age. NCA is an established form of postoperative analgesia, similar in nature to other demand-led analgesic regimens (e.g., patient-controlled analgesia [PCA]), but tailored for patients who are too young or unable to use PCA.

The morphine demand during the study was recorded including the start/end date and time, indication, dose (unit), frequency and route of administration.

3.8. Adverse Events

All adverse events (AEs) were collected by the investigator from the time of signing the informed consent/assent through 14 days after the last dose of study drug

3.8.1. Adverse Events Definitions

An AE was any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (e.g., chemistry, ECG, X-ray, etc.), or worsening of a pre-existing condition associated temporally with the use of the study drug whether or not considered related to the study medication. AEs include:

- Changes occurred in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occurred after the start of the study, which included any change in severity or frequency of pre-existing disease. Post-operative pain was captured as an AE after the EOT.
- All clinically relevant laboratory abnormalities or physical findings that occurred during the study.

3.8.2. Serious Adverse Events

Serious adverse events (SAEs) were those AEs that meet any of the following criteria:

- Resulted in death.
- Life-threatening event.
- Resulted in or prolongs an inpatient hospitalization.
- Resulted in permanent or substantial disability.
- Was a congenital anomaly or birth defect.
- Any important medical event that might have jeopardize the subject or might have required medical intervention to prevent one of the outcomes listed above.

3.9. Clinical Safety Laboratory Tests

Blood and urine samples were collected for testing the following clinical laboratory parameters at Pre-treatment and EOT (24 hours post dose) listed in Table 5.

Table 5: Clinical Laboratory Parameters

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell (RBC)	Potassium	Specific gravity
White blood cell (WBC)	Calcium	Nitrite
Platelets	CO_2	Blood[a]
WBC Differential	Inorganic phosphate	Leukocytes[a]
	Blood urea nitrogen	
	Creatinine	
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	

[a] Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

Any new clinically significant laboratory abnormality observed, were considered as an AE or SAE as appropriate.

3.10. Vital Signs

Vital sign measurements included systolic and diastolic blood pressure, respiratory rate, pulse, body temperature, and oxygen saturation. Length (height) and weight were recorded at screening only and body mass index (BMI) will be computed. Refer to Table 8 for BMI derivation.

For the single-dose phase, vital sign measurements were taken at Screening, post-surgery evaluation visit, baseline visit, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 24-hours post dose.

For the multiple-dose phase, vital sign measurements were taken at Screening, post-surgery evaluation visit, baseline visit, 0.5, 1.0, 2.0, 3.0 and 4.0 hours after administration of first dose of study drug; and at 0.5, 1.0 and 2.0 hours after administration of subsequent doses.

Clinically significant abnormalities (as per Investigator's criteria) in vital sign values were considered as an AE or SAE as appropriate.

3.11. Physical Examination

A complete physical examination (by body system) was conducted at Screening or pre-dose evaluation. A brief physical exam excluding height and weight was performed at the EOT assessments. The physical examination evaluation included an examination of abdomen, extremities, general appearance, genitourinary, heart, HEENT, lungs, lymphatic, musculoskeletal, neck, neurological, skin, thorax and other conditions of note. Physical examination findings were recorded as normal, abnormal or not done.

Clinically significant abnormalities (as per Investigator's or Sponsor's criteria) in physical examination findings were to be considered as an AE or SAE as appropriate.

3.12. Respiratory Function

All subjects were monitored for the appearance of respiratory symptoms through monitoring of oxygen saturation, heart rate, respiratory rate, apnea monitoring, and administration of an opioid antagonist (e.g. Naloxone).

Any appearance of respiratory symptoms were to be monitored not only at the time of scheduled assessments, but as needed throughout the study duration.

An AE or SAE was to be recorded, as appropriate, if any of the following occur:

- Oxygen saturation decreased to ≤90%
- Heart rate decreased to ≤50% of the expected norm for age
- Respiration rate decreased to ≤50% of the expected norm for age
- Any episodes of apnea
- Any administration of an opioid antagonist to treat respiratory depression

3.13. Neurological Function

All subjects were to be monitored for the appearance of central nervous system (CNS) symptoms by monitoring the level of sedation through the Modified Ramsay Sedation Scale. Neurological assessment (level of sedation) will be considered as an SAE if the score is >6 on the Modified Ramsay Sedation Scale. Table 6 describes the scores and the definitions of the Modified Ramsay Sedation Scale.

Table 6: Modified Ramsay Sedation Scale

Score	Definition
1	Awake and alert, minimal or no cognitive impairment
2	Awake but tranquil, purposeful responses to verbal commands at conversation level
3	Appears asleep, purposeful responses to verbal commands at conversation level
4	Appears asleep, purposeful responses to verbal commands but at louder than usual conversation level or requiring light glabellar tap
5	Asleep, sluggish purposeful responses only to loud verbal commands or strong glabellar tap
6	Asleep, sluggish purposeful responses only to painful stimuli
7	Asleep, reflex withdrawal to painful stimuli only (no purposeful responses)
8	Unresponsive to external stimuli, including pain

3.14. 12-lead Electrocardiogram

12-lead electrocardiogram (ECG) were collected as part of the screening assessments which included the overall interpretation of ECG as normal, abnormal – not clinically significant and abnormal – clinically significant along with the abnormality details.

3.15. Pharmacokinetic Assessments

The SAP for this abbreviated CSR includes safety assessments only. All PK assessments planned in the protocol were removed. This change is included in the Change from Protocol Section of the SAP.

4. STUDY PARAMETERS

4.1. Subject Disposition

Subjects were considered to have completed the study if they completed the 14-day follow-up telephone call. EOT procedures were completed per schedule of assessments for subjects who discontinued from the study for any reason, the reason and date for early discontinuation was also be recorded in the eCRF. In case discontinuation is due to subject withdrawal of consent, no EOT procedures were performed except the collection of AE information.

Screen failures were recorded in the eCRF.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics included the following parameters:

- Age
- Height (at Screening)
- Body weight (at Screening)
- BMI in kg/m^2 (at Screening)
- Gender
- Race
- Ethnicity

4.3. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock. Protocol deviations observed and recorded during clinical monitoring reports will be considered; deviations will not be determined programmatically.

The Endo study team will approve all final protocol deviation assignments and classify them as either major or minor during a protocol deviation review meeting held prior to the database lock.

4.4. Prior, Concomitant and Follow-up Medications

All medications will be coded using World Health Organization (WHO) Drug Dictionary Version March 2016, by active ingredient and anatomical therapeutic chemical (ATC) classification of ingredients.

A prior medication is defined as any medication taken within the 30 days prior to signing consent.

A concomitant medication is any medication starting on or after the informed consent is signed for this study and up to 24 hours post last dose or early termination (ET).

A follow-up medication is any medication starting after 24 hours post last dose through the 14-day follow-up period.

4.5. Safety Parameters

The safety parameters include AEs, clinical laboratory tests, vital sign measurements, and physical examination.

4.5.1. Adverse Events

AE verbatim terms as reported by the investigator will be mapped to System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

4.5.1.1. Treatment Emergent Adverse Events

TEAEs are defined as any AEs that occur or worsen (increase in severity) after treatment initiation through the 14-day follow-up period.

Refer to Section 6.3.1.1 to identify TEAE status when start date of an AE is unknown.

4.5.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs were be graded as "Mild", "Moderate" or "Severe". For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle. If the intensity of an AE changes, then the most severe intensity during the continuous episode will be recorded.

4.5.1.3. Relationship to Study Drug

The causal relationship with study drug was classified by the investigator and were reported as follows:

- Not related.
- Unlikely related.
- Possibly related.
- Probably related.

Related adverse events are AEs with the relationship described by the investigator as "probably related" or "possibly related". "Not related" or "Unlikely related" causality assessments are considered as not related.

"Probable" and "Possible" causality assessments will be considered as positive causality. "Not" and "Unlikely" causality assessments will be considered as negative causality.

Any missing relationship of an AE to study drug will be considered as related to study drug for the analyses, following worst case principle.

4.6. Other Safety Parameters

4.6.1. Respiratory and Neurological Function

All subjects were monitored for the appearance of respiratory and neurological symptoms.

Respiratory functions:

- Monitoring of oxygen saturation at the time of vital sign assessments
- Apnea monitoring
  - Were any episodes of apnea observed?
  - If apnea observed, was the episode considered to be an AE?

Neurological functions:

- Monitoring the level of sedation through Modified Ramsay Sedation Scale
  - Was sedation considered as an adverse event?
- Interpretation of Modified Ramsay Sedation Scale scores:
  - Score 2-3: Anxiolysis
  - Score 4-5: Moderate sedation
  - Score 6: Deep sedation
  - Score 7-8: General anesthesia

5. ANALYSIS POPULATIONS

This study was terminated early. Baseline assessments and safety assessments will be summarized using the Safety Population. Table 7 describes the analysis populations used to describe safety assessments in this study.

Table 7: Analysis Populations

Population	Definition	Displays
Single-Dose Safety Population	The Safety Population of the single-dose phase includes all subjects who receive at least 1 dose of study drug in the single-dose phase.	All safety analyses and demographic/baseline characterization for the single-dose phase will use this population.
Multiple-Dose Safety Population	The Safety Population of the multiple-dose phase includes all subjects who receive at least 1 dose of study drug or placebo in the multiple-dose phase. Subjects will be attributed to the treatment that they actually received regardless of their assigned randomized treatment.	All safety analyses and demographic/baseline characterization for the multiple-dose phase will use this population.
Overall Safety Population	Includes all the subjects in the Single-dose Safety Population and the Multiple-dose Safety Population	All the subject listings except disposition listings will use this population. Disposition will be based on all subjects enrolled.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables and data listings will be prepared using SAS version 9.4.

Continuous data will be summarized using descriptive statistics. Discrete data will be summarized using frequency counts and percentages. The denominator will be based on the number of evaluable subjects in the appropriate population.

For the purpose of display, the summary results will be rounded as follows:

- Minimum and maximum: same number of decimal places as the raw data.
- Mean and Median: one decimal place more than the raw data.
- Standard deviation (SD): Two decimal places more than the raw data.
- Percentages will be displayed with one decimal place precision.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Summary tables, subject listings, graphs and any supportive SAS output will include footnotes that will indicate:

- Date of data extraction.
- Date and time of output generation.
- SAS program name, including the path, which generated the output.

When calculating percentages, the denominator will be based on the number of subjects with non-missing values. If the denominator is expected to change over time, then the denominator used to calculate the percentage will be based on the number of subjects with non-missing values at each visit.

Summary tables and data listings without values will be presented with a note stating that "No Subjects Met Criteria".

Subject listings of all data from the eCRFs as well as any derived variables will be presented.

6.2. Derived Variables

Table 8 defines the derived variables for study parameters.

Table 8: Derived Variables and Definition

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Body Mass Index (BMI)	BMI will be computed using height measured at screening and body weight measured at respective visits as, BMI (kg/m^2) = Weight (kg) / Height $(m)^2$ and then rounded to 1 decimal place.
Relative Day	The day of the first dose of the study drug will be considered as relative Day 1.
Study Day	Study day will be computed as: Date of Assessment – Date of relative day 1
Baseline	Baseline is defined as the last assessment made prior to the first dose of study drug administration.
Change from Baseline	Change from baseline will be derived as: post-baseline visit/time point value – the baseline value
Last Date in Study	Last date in study is defined as: • The date of the 14-day follow-up if the subject completes the study. • The date of the early termination visit if the subject is terminated early from study at a non-scheduled visit. • The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up.
Duration (Hours) of Study Drug Exposure (Multiple-Dose phase)	Date/Time of Last Dose – Date/Time of First Dose
Duration of Morphine use (hours)	Date/Time of Last Dose Morphine – Date/Time of First Dose Morphine
Duration (Days) of AE	AE end date – AE start date + 1
AE Onset Day	AE start date – Date of first dose + 1

6.3. Handling of Missing Data

Missing baseline assessments will not be imputed. For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

There will be no imputation of missing safety data, however missing relationship between AE and study medication will be considered as related to study medication following worst case principle. For AEs with missing severity, the most severe assessment will be imputed for analyses.

6.3.1. Imputation of Partial Dates

6.3.1.1. TEAE Status for Completely Unknown Start Date

The following rules will apply in cases where start date of an AE is completely unknown:

- If the AE onset date is unknown and the end date/time is on or after first dose or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date/time is before first dose, then the AE will not be considered a TEAE.

- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst-case principle.

If the AE onset date is partly present and month/year is prior to the first dose, then the AE will not be considered a TEAE.

6.3.1.2. Concomitant Status of Medication for Completely Unknown Start Date

The following rules will apply in cases where start date of concomitant medication is completely unknown:

- If the medication onset date is unknown and the end date/time is after the screening date but on or before 24 hours post first dose or the medication is ongoing, then the medication will be considered as concomitant.
- If the medication onset date is unknown and the end date/time is before the screening date, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication will be considered as concomitant. This approach is the most conservative following the worst-case principle.

If the medication onset date is partly present and month/year is prior to the first dose, then the medication will be considered as concomitant.

6.4. Treatment Groups

The data for the single-dose phase and the multiple-dose phase will be summarized separately.

The data for the single-dose phase will be summarized by age group and dose group. The multiple-dose phase will be summarized by age group and treatment group.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The subject disposition will be summarized separately for the single-dose phase and the multiple-dose phase.

The number and percentage of subjects screened, enrolled, completed, and withdrawn from the study, as well as reason of withdrawal from the study will be summarized.

A subject listing of disposition data will be provided. Reasons for screen failure will be listed. In addition, a subject listing by inclusion/exclusion criteria not met will be presented.

7.2. Protocol Deviations

The major and minor protocol deviation categories will be summarized separately for the single-dose phase and the multiple-dose phase. In addition, an overall summary of the protocol deviations for single-dose phase and multiple dose phase will be provided.

A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized separately by the single-dose phase and by the multiple-dose phase.

Age (days), height (cm), body weight (kg), and BMI (kg/m^2) will be summarized as continuous variables using appropriate descriptive statistics.

Gender, race, and ethnicity will be summarized as categorical variables using frequency and percentages.

All demographic and baseline characteristics will be presented in a subject listing.

7.4. Medical and Surgical History

Medical and surgical history will be coded using MedDRA Version 19.0. Medical and surgical history by subject will be listed.

7.5. Prior, Concomitant and Follow-up Medications

Prior, concomitant, and follow-up medication use will be summarized separately by the single-dose phase and by the multiple-dose phase.

Prior, concomitant, and follow-up medications will be summarized using frequency and percentages by active ingredient within each ATC classification, with ATC classification and active ingredients ordered alphabetically. Multiple uses of the same medication by a subject will be counted only once.

A subject listing of medications indicating prior, concomitant, and follow-up classification will be presented. Additionally, the surgical procedures and surgical medications will be listed separately.

7.6. Efficacy Analysis

Only safety analyses are being conducted for this abbreviated CSR, hence no efficacy analyses will be conducted.

7.7. Rescue Medication

Rescue medication includes the total dose of morphine used and the duration of morphine (hours) use during the study, which will be summarized descriptively and will be presented separately for the single-dose and multiple-dose phases.

7.8. Safety Analyses

7.8.1. Study Drug Exposure

The total dose administered, total volume administered and duration of exposure (hours) will be summarized for subjects in the multiple-dose phase. The total volume administered during single-dose phase will also be summarized.

The study drug exposure details including the date/time of dose administration, route of administration, dose level and volume administered and whether food was consumed within 2 hours prior to or 1 hour after study drug administration will be presented in a subject listing.

7.8.2. Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified.

An overall summary of AE will be presented and will include the following:

- Total number of TEAEs reported
- Total number of TEAEs reported by severity
- Subjects with at least one treatment related TEAE
- Subjects with at least one severe TEAE
- Subjects with at least one Serious Adverse Events
- Subjects with at least one TEAE leading to drug interruption/withdrawals
- Subjects with at least one TEAE leading to deaths

TEAEs will be summarized by system organ class and PT. A subject will only be counted once per system organ class and PT.

For TEAEs summarized by severity (i.e., mild, moderate, severe), if a subject has multiple events occurring in the same system organ class or same PT, then the event with the maximum severity (i.e., severe) will be counted.

For the study drug related TEAEs, if a subject has multiple events occurring in the same system organ class or same PT, the event with the highest association (i.e., related) to study drug will be considered for analyses.

TEAEs will be presented in decreasing order of the incidence at system organ class level and within each system organ class, in decreasing order of the incidence at the PT level.

The following summary tables will be presented by system organ class and PT separately for the single-dose phase and the multiple-dose phase.

- All TEAEs.
- Serious TEAEs.
- TEAEs by severity.
- All study drug related TEAEs.
- TEAEs leading to study drug interruption/withdrawal.

The following listings will be presented by subject:

- All TEAEs.
- Serious TEAEs.
- AEs resulting in study drug withdrawal/interruption.
- AEs resulting in death.

7.8.3. Clinical Laboratory

Hematology and biochemistry parameter values will be summarized separately for the single-dose and the multiple-dose phase using descriptive statistics for observed and change from baseline values at the EOT/ET visit.

Additionally, shift tables will be provided. The shift in laboratory results at EOT/ET (i.e., low, normal, high) from baseline classification will be summarized using frequency and percentages.

Hematology, biochemistry, and urinalysis parameter values will be listed by subject.

7.8.4. Height, Body Weight and BMI

Baseline height, weight, and BMI will be summarized and listed.

7.8.5. Vital Signs

Vital signs values (i.e., systolic and diastolic blood pressure, pulse, respiratory rate, body temperature and oxygen saturation (%)) will be summarized separately by the single-dose phase and by the multiple-dose phase using descriptive statistics. The observed values and change from baseline at all post-baseline assessment visits and at the EOT/ET visit will be presented. Vital sign values will be listed by subject.

7.8.6. Physical Examination

Physical examination results (by body system) at baseline and EOT/ET visits will be presented separately for the single-dose phase and the multiple-dose phase using frequency and percentages.

A subject listing will be presented for the physical examination results (by body system).

7.8.7. 12-lead ECG

A subject listing of 12-lead ECG results will be provided.

7.9. Other Safety Parameters

7.9.1. Respiratory and Neurological Function

The respiratory and neurological function assessments will be summarized separately for the single-dose phase and the multiple-dose phase.

The following will be summarized using frequency and percentages:

- Were any episodes of apnea observed?
- If apnea observed, was the episode considered to be an adverse event?
- Was sedation noted?
- If sedation noted, was sedation considered as an adverse event?

Modified Ramsay Sedation Scale scores will be summarized using descriptive statistics for observed and change from baseline at all post-baseline assessment visits and at the EOT/ET visit. Additionally, the level of sedation will be summarized using frequency and percentages.

A subject listing of respiratory and neurological functions will be presented. Oxygen saturation and Modified Ramsay Sedation Scale scores along with level of sedation will also be listed.

7.10. Pharmacokinetic Analysis

Only safety analyses are being conducted for this abbreviated CSR, hence no PK analyses will be conducted.

8. CHANGE FROM PROTOCOL

This SAP is based on Amendment 05 to Clinical Study Protocol, 01 April 2019. Since the study was terminated early and the abbreviated CSR will only include the safety analyses. The efficacy and PK analyses described in the protocol will not be conducted.

9. REVISION HISTORY

This is the first version of the SAP. Non-editorial changes made to any of the modules of this SAP will be recorded as necessary as revision history.

10. REFERENCES

1. Clinical Study Protocol: An Open-Label Single-Dose and Randomized, Double-Blind, Placebo-Controlled Multiple-Dose to evaluate Efficacy, Safety, Tolerability and Pharmacokinetics of Oxymorphone HCl for acute moderate to severe postoperative pain in Pediatric Subjects.

11. TABLES, LISTINGS, AND GRAPH SHELLS

The layouts of the summary tables, subject listings, and graphs are presented in SAP Module 2.

These layouts incorporate all the appropriate table titles, table numbers, and footnotes.