# OXYMORPHONE HCl IMMEDIATE-RELEASE ORAL LIQUID

# EN3319-302

# AN OPEN-LABEL, NON-RANDOMIZED, MULTICENTER, ASCENDING DOSE BY AGE, SINGLE- AND MULTIPLE-DOSE EVALUATION OF THE EFFECTIVENESS, SAFETY, AND TOLERABILITY OF OXYMORPHONE HCl IMMEDIATE-RELEASE ORAL LIQUID FOR ACUTE POSTOPERATIVE PAIN IN PEDIATRIC SUBJECTS

**Date:**

Original Protocol: June 18, 2010

Amendment 1: April 19, 2011

Amendment 2: April 26, 2012

Amendment 3: July 19, 2012

Amendment 4: May 2, 2013

Amendment 5: August 21, 2013

**Sponsor:**

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355
USA
Telephone: 484-216-0000

# SUMMARY OF CHANGES

**NOTE: Protocol Amendment 4 was not implemented at clinical sites, so the Summary of Changes below reflects changes between Amendment 3 and Amendment 5.**

| Protocol Section(s) | Summary of Change |
|---|---|
| Table 1 | Updated study contact personnel and contact information. |
| Section 2 | Updated study period<br>***Changed from**:* February 2013<br>***Changed to**:* December 2013 |
| Throughout | Table 4 is altered to reflect assessments around each dose (instead of hours post-1st dose). Table 5 and Table 6 and all associated references to these tables were removed due to the changes in Table 4.<br>Revised text throughout protocol to reflect new assessment scheduling of PK blood draws, vital signs, pain assessments, respiratory and neurological assessments. |
| Section 2 (Pharmacokinetic Analysis) | ***Removed**:* Plasma concentrations below the limit of quantification (BLQ) will be set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non BLQ concentrations will be set to missing. For the computation of pharmacokinetic variables, the BLQ concentrations prior to the first measurable concentration will be set to zero and other BLQ concentrations will be set to missing. |
| Section 5 | Updated Opana ER description<br>***Removed**:* EN3202 |
| Section 2<br>Table 3 (footnote f)<br>Table 4 (footnote g)<br>Section 7.1.1<br>Section 8.1<br>Section 12.5<br>Appendix E | ***Clarification regarding clinical labs – blood labs must be drawn prior to first incision and assessed prior to first administration of study drug.*** |
| Table 4 | Added footnote o:<br>Maximum treatment time is 48hrs. The number of ATC doses administered will vary with to Q4-6h dosing interval<br>Added footnote p:<br>Time "0" indicates pre-dose, or "baseline" for the indicated dose. |
| Section 2<br>Section 8.1 | Updated Inclusion Criteria #2 to include BMI<br>***Changed from***: Subjects must be at least 10 kg.<br>***Changed to***: Subjects must be at least 10 kg and BMI ≤30. |
| Section 9.7 | Updated Treatment Compliance<br>***Changed from**:* Any suspicion of diversion will be carefully investigated according the instructions in the Sponsor's Drug Diversion Plan and must be reported as an SAE<br>***Changed to**:* Any suspicion of diversion will be carefully investigated by the Sponsor, as outlined in the Clinical Supplies Guidance Document and the Monitoring Plan, and may be required to be reported as an SAE. |
| Section 10.2 | Changed study drug packaging details |

**NOTE: Protocol Amendment 4 was not implemented at clinical sites, so the Summary of Changes below reflects changes between Amendment 3 and Amendment 5.**

| Protocol Section(s) | Summary of Change |
|---|---|
| Section 10.4 | ***Changed from***: 20mL clear bottles<br>***Changed to:*** 30mL amber bottles |
| Section 12.1.4 | Updated FAX number for reporting SAEs<br>***Changed from*** [redacted] |
| Table 7 | (Formerly named Table 9 – renamed Table 7)<br>***Removed:*** C12 – Trough plasma concentration at the end of the 12-hour dosage interval<br>***Changed from***: CL/F – Apparent oral clearance, calculated as Dose/$AUC_{0\text{-}inf}$<br>***Changed to:*** CL/F – Apparent oral clearance, calculated as Dose/$AUC_{0\text{-}inf}$ for single dose or Dose/AUC(0-τ) for steady-state |
| Appendix E | Updated number of blood samples collected in Multiple-Dose Phase<br>***Changed from:*** 16<br>***Changed to:*** 15 (max)<br>Updated Total Amount (mL) Collected Per Subject for Multiple-Dose Phase<br>***Changed from:*** 20.0 mL<br>***Changed to:*** 18.75 mL<br>Updated Grand Total for Multiple-Dose Phase<br>***Changed from:*** 25.0 mL<br>***Changed to:*** 23.75 mL |

# PROCEDURES IN CASE OF EMERGENCY

**Table 1: Emergency Contact Information**

| Role in Study | Name | Address and Telephone Number(s) |
|---|---|---|
| Clinical Study Leader | [redacted] | Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted] |
| Clinical Trial Manager | [redacted] | Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted] |
| Responsible Physician | [redacted] | Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted] |
| Drug Safety Physician | [redacted] | Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted] |
| 24-Hour Emergency Contact | [redacted]<br><br>Secondary Contact:<br>[redacted] | Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted]<br>Endo Pharmaceuticals Inc.<br>1400 Atwater Drive<br>Malvern, PA 19355<br>[redacted] |

# 2. SYNOPSIS

**Name of Sponsor/Company**: Endo Pharmaceuticals Inc.

**Name of Investigational Product**: EN3319 Oxymorphone HCl Immediate-Release Oral Liquid

**Name of Active Ingredient**: Oxymorphone HCl

**Title of Study**: An Open-Label, Non-randomized, Multicenter, Ascending Dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety, and Tolerability of Oxymorphone HCl Immediate-Release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects

**Study Center(s)**: 20 sites

**Principal Investigator**: N/A
**Investigators**: N/A

| **Studied Period (Years)**: | | **Phase of Development**: III |
|---|---|---|
| Date first subject enrolled: | December 2010 | |
| Estimated date last subject completed: | December 2013 | |

**Objectives**:

***Primary:***

- The primary objective of both the Single-Dose and Multiple-Dose Phase is to characterize the effectiveness, safety, and tolerability of oxymorphone hydrochloride (HCl) immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies.

***Secondary:***

- The secondary objectives are: 1) to characterize the pharmacokinetic profile of oxymorphone HCl immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies; and 2) to establish the appropriate dosing recommendations for oxymorphone HCl immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies.

**Methodology**:

***Study Design***: This open-label, non-randomized, ascending-dose by age, single- and multiple-dose phase, multicenter study is designed to characterize the effectiveness, safety, tolerability, and pharmacokinetics of a single-dose and multiple-dose postoperative treatment paradigm utilizing oxymorphone HCl immediate-release oral liquid in pediatric subjects aged 2 to ≤12 years with postoperative pain requiring an opioid.

***Single-Dose Phase***:

During the Single-Dose Phase, 2 separate age groups of subjects will be given a single dose of oxymorphone HCl immediate-release oral liquid. Within each age group, there will be up to 3 treatment cohorts (6 subjects per cohort approximately evenly distributed across each of the cohorts) comprised of different doses of oxymorphone HCl immediate-release oral liquid. The age groups of subjects will be:

A. 6 years – ≤12 years
B. 2 years – <6 years

Within each age group, there will be up to 3 treatment cohorts of 6 subjects each:

1. 0.05 mg/kg oxymorphone HCl immediate-release oral liquid
2. 0.10 mg/kg oxymorphone HCl immediate-release oral liquid
3. 0.15 mg/kg OR 0.20 mg/kg oxymorphone HCl immediate-release oral liquid, based on recommendation of the Independent Data Monitoring Committee (IDMC)

Age groups A and B will be studied in parallel; up to 3 treatment cohorts of the Single-Dose Phase will be completed, after which enrollment will begin for the Multiple-Dose Phase of the study.
In the Single-Dose Phase, the first treatment cohort of 6 subjects from each age group will be given a

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| single dose of oxymorphone HCl immediate-release oral liquid 0.05 mg/kg following postoperative parenteral analgesia according to each institution's standard of care (SOC). Administration of the study drug will occur at the time when (according to each institution's SOC) oral analgesics are to commence in the subject's postoperative analgesic regimen. Following completion of the first treatment cohort of 6 subjects within each age group, data will be assessed by an external IDMC and, with an acceptable safety review and IDMC recommendation, a second treatment cohort of 6 subjects in each age group will be dosed with oxymorphone HCl immediate-release oral liquid 0.1 mg/kg. If the second treatment cohort within each age group demonstrates acceptable safety and tolerability, then, upon recommendation of the IDMC, a third treatment cohort of 6 subjects in each age group will be administered oxymorphone HCl immediate-release oral liquid 0.15 mg/kg or 0.20 mg/kg (based on recommendation from the IDMC; the IDMC may at this point recommend a different dose of oxymorphone HCl immediate-release oral liquid [not to exceed 0.30 mg/kg] or to proceed directly into the Multiple-Dose Phase).<br><br>In the Single-Dose Phase, as each treatment cohort of subjects within each age group is completed, the effectiveness, safety, and tolerability will be assessed by the IDMC before enrolling subjects into the next-higher treatment cohort. The IDMC will also provide recommendation on whether the subsequent treatment cohorts are needed in the Single-Dose Phase (up to 3 treatment cohorts in total may be tested in the Single-Dose Phase).<br><br>If needed, non-oxycodone, non-oxymorphone rescue analgesia will be available according to SOC at each institution.<br><br>Blood from a patent line (see section 12.4.1) will be collected to assess pharmacokinetics, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (eg, naloxone-based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.<br><br>The effect of food on oxymorphone HCl immediate-release oral liquid pharmacokinetics in children has not been studied; the impact of feeding on the pharmacokinetics and safety of OPANA® in children will be assessed as data permit. No food restrictions will be imposed in this study around the time of dosing.<br><br>***Multiple-Dose Phase***:<br><br>At the end of the Single-Dose Phase for each age group, the IDMC will make recommendations for up to 3 dose levels to be used in the Multiple-Dose Phase. The Multiple-Dose Phase will proceed using the same age group stratification used in the Single-Dose Phase:<br><br>A. 6 years – ≤12 years<br>B. 2 years – <6 years<br><br>Age groups A and B will be studied in parallel. Following postoperative parenteral analgesia, when oral dosing is to commence according to each institution's SOC, dosing will begin at the lowest dose selected by the IDMC based on results from the Single-Dose Phase for each age group. Subjects will be dosed every 4 to 6 hours (no sooner than every 4 hours and no later than every 6 hours) for up to 48 hours. Subjects may receive non-oxycodone, non-oxymorphone rescue medication and discontinue from the study in the event that the study drug does not provide adequate pain relief. |

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In the Multiple-Dose Phase, the first treatment cohort of 6 subjects from each age group will be given multiple doses of oxymorphone HCl immediate-release oral liquid at an initial dose recommended by the IDMC following postoperative parenteral analgesia according to each institution's SOC. The IDMC will use data from each age group's Single-Dose Phase to recommend the dose(s) to be used in each respective age group's Multiple-Dose Phase. Following completion of the first treatment cohort of 6 subjects within each age group, the effectiveness, safety, and tolerability will be assessed by an external IDMC. Following their review, the IDMC may recommend that a second treatment cohort of 6 subjects in each age group be dosed with oxymorphone HCl immediate-release oral liquid at the second dose (recommended by the IDMC). Following review of the effectiveness, safety, and tolerability of the second treatment cohort within each age group, the IDMC may recommend that a third treatment cohort of 6 subjects in each age group commence (at the third dose recommended by the IDMC; the IDMC may at this point recommend to end the Multiple-Dose Phase of the study).

If needed, non-oxycodone, non-oxymorphone rescue analgesia will be available according to SOC at each institution.

Blood from a patent line will be collected to assess pharmacokinetics, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (eg, naloxone-based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.

The effect of food on oxymorphone HCl immediate-release oral liquid pharmacokinetics in children has not been studied; the impact of feeding on the pharmacokinetics and safety of OPANA in children will be assessed as data permit. No food restrictions will be imposed in this study around the time of dosing.

***Assessment of Analgesic Effectiveness***: Effectiveness of analgesia will be assessed by an age-appropriate pain assessment instrument. For subjects aged 6 to ≤12 years, assessment of current pain intensity will be obtained using the Faces Pain Scale – Revised (FPS-R). For subjects aged 2 to <6 years, assessment of current pain intensity will be obtained using the Face, Legs, Activity, Cry, and Consolability (FLACC) behavioral measurement.

**Number of Subjects (Planned)**: Up to 72 (the exact number will be determined by IDMC based on the expected number of treatment cohorts)

| Age Group | Study Phase | N |
|---|---|---|
| 6 years – ≤12 years | Single-Dose Phase | Up to 18 |
| 6 years – ≤12 years | Multiple-Dose Phase | Up to 18 |
| 2 years – <6 years | Single-Dose Phase | Up to 18 |
| 2 years – <6 years | Multiple-Dose Phase | Up to 18 |
| Total | | Up to 72 |

**Diagnosis and Inclusion/Exclusion Criteria**: Acute postoperative pain requiring a strong oral opioid analgesic for moderate-to-severe pain.

***Inclusion Criteria***:

1. Males or females between 2 to ≤12 years of age. Females of child-bearing potential must be practicing abstinence or using a medically acceptable form of contraception (eg, intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all peri- and post-pubertal females will be considered to be of child-bearing potential unless they are biologically sterile or surgically sterile for more than 1 year.
2. Subjects must be at least 10 kg and BMI ≤30.

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3. Scheduled to have a surgery for which oral opioid analgesia will be needed to manage post-operative pain for at least 24 hours (Single-Dose Phase) or 48 hours (Multiple-Dose Phase) following intraoperative and/or postoperative parenteral analgesia
4. Be hospital inpatients, expected to be hospitalized for at least 24 hours (Single-Dose Phase) and 48 hours (Multiple-Dose Phase) following the initial administration of oxymorphone immediate-release
5. Lab samples, either drawn intraoperatively (prior to surgical incision) or from within 21 days preoperatively, for clinical chemistry and hematology laboratory analytes (the results must have been reviewed by the Investigator prior to study drug administration for study eligibility)
6. Able to provide pain assessment evaluations using an age-appropriate instrument provided in the protocol
7. On an intravenous analgesic regimen utilizing a short-acting opioid analgesic following surgery AND anticipated to be switched to an oral opioid as part of the analgesic regimen (according to institution SOC)
8. Demonstrated the ability to tolerate clear fluids following surgery according to the SOC at each institution
9. Informed of the nature of the study and written informed consent has been obtained from the legally responsible parent(s)/legal guardian(s)
10. Provided assent in accordance with Institutional Review Board (IRB) requirements
11. Line in place for blood sampling

***Exclusion Criteria****:*

1. Known allergies or sensitivities to oxymorphone or other opioid analgesics
2. Known sensitivity to any component of the study drug
3. Life expectancy <4 weeks
4. Positive pregnancy test at screening (females of reproductive age only)
5. Pregnant and/or lactating
6. Cyanotic heart disease
7. Respiratory, hepatic, renal, neurological, psychological disease, or any other clinically significant condition that would, in the Investigator's opinion, preclude participation in the study
8. Preoperative opioids administered for a period of more than 72 hours in duration
9. Abdominal trauma that would interfere with absorption of study drug
10. Increased intracranial pressure
11. Respiratory condition requiring intubation
12. History of uncontrolled seizures that are not being managed with anti-convulsants
13. Significant prior history of substance abuse or alcohol abuse
14. Received any investigational drug within 30 days prior to the first dose of study drug, or are scheduled to receive an investigational drug other than oxymorphone HCl immediate-release oral liquid during the course of the study
15. Received a monoamine oxidase inhibitor (MAOI) within 14 days prior to the start of study drug
16. Received oxycodone or oxymorphone within 48 hours prior to study start
17. Investigator anticipates that the subject and/or parent(s)/legal guardian(s) would be unable to comply with the protocol
18. Subject (and/or parent[s]/legal guardian[s]) is(are) unable to communicate effectively with study personnel at an age-appropriate level

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| **Investigational Product, Dosage and Mode of Administration**: Single-Dose Phase; EN3319 Oxymorphone HCl Immediate-Release Oral Liquid 1 mg/mL dosed at 0.05 mg/kg, 0.10 mg/kg, and 0.15 or 0.20 mg/kg (or a different dose [not to exceed 0.30 mg/kg] as determined by the IDMC) by mouth. Multiple-Dose Phase; up to 3 dose levels of EN3319 Oxymorphone HCl Immediate-Release Oral Liquid 1 mg/mL based on the recommendation of the IDMC. |
| **Duration of Study**:<br>Screening Phase – up to 21 days<br>Single-Dose Phase – 1 day<br>Multiple-Dose Phase – 2 days<br>Follow-up telephone call – 14 days |
| **Reference Therapy, Dosage and Mode of Administration**: Not applicable |
| **Criteria for Evaluation**:<br>***Effectiveness***: For subjects aged 6 to ≤12 years, assessment of current pain intensity will be obtained using the FPS-R for 12 hours (Single-Dose Phase) or 48-hours (Multiple-Dose Phase) following dose administration, or until rescue medication is used in accordance with the Schedule of Study Assessments/Procedures (see Table 3 and Table 4). For subjects aged 2 to <6 years, assessment of current pain intensity will be obtained using the FLACC behavioral measurement for up to 12 hours (Single-Dose Phase) or up to 48-hours (Multiple-Dose Phase) following dose administration, or until rescue medication is administered in accordance with the Schedule of Study Assessments/Procedures (see Table 3 and Table 4).<br>***Pharmacokinetics***: Single-Dose Phase: determination of $C_{max}$, $T_{max}$, $C_{12}$, $AUC_{0-t}$, $AUC_{0-24}$, $AUC_{0-\infty}$, $\lambda_n$, $t_{1/2}$, CL/F (clearance) and V/F (volume of distribution); Multiple-Dose Phase: determination of $C_{max}$, $T_{max}$, $AUC_{0-t}$, $\lambda_n$, $t_{1/2}$, CL/F, and V/F.<br>***Safety and Tolerability***: Safety will be assessed using adverse events (AEs), assessments of respiratory and neurological function, vital signs, urine drug screen, and clinical laboratory tests. Assessment of safety and tolerability will also include a pharmacokinetic assessment. Blood samples for pharmacokinetic assessments of oxymorphone HCl immediate-release oral liquid will be obtained over a 24-hour period (Single-Dose Phase) or over a 48-hour period (Multiple-Dose Phase) following oxymorphone HCl immediate-release oral liquid administration. |
| **Statistical Methods**:<br>***Sample Size Consideration:*** The sample size of 6 subjects in each age group (A and B), treatment cohort, and study phase was selected to describe the effectiveness, safety, tolerability, and pharmacokinetic properties of the study drug in children aged 2 to ≤12 years. With up to 3 treatment cohorts and 6 subjects per treatment cohort, up to 36 subjects will be enrolled in each study phase. Assuming the %CVs for clearance and volume of distribution are both as high as 72% for pediatric subjects, then with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% confidence interval (CI) for both clearance and volume of distribution is (0.71*X, 1.40*X), where X represents the geometric mean of either clearance or volume of distribution, respectively. In other words, with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% CIs are within 60% and 140% of the point estimates for the geometric mean estimates of both clearance and volume of distribution for oxymorphone in all age groups. |

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| ***Analysis Populations:*** The safety population will include all subjects who take at least 1 dose of study drug. All safety analyses will be performed using this population. The effectiveness population will include all subjects who take at least 1 dose of study drug and who have completed at least 1 post dose pain intensity assessment. All effectiveness analyses will be performed using this population. All subjects who receive study drug as planned and have sufficient plasma concentration data to facilitate the calculation of pharmacokinetic variables will be evaluable for pharmacokinetic analysis. Final subject evaluability will be determined prior to locking the database.<br><br>All statistical analyses will be performed using the current version of SAS® (SAS Institute, Cary, NC). All CIs will be 2-sided.<br><br>***Subject Disposition:*** The number of subjects in each analysis population will be presented. The numbers and percentages of subjects who complete or discontinue from the study will be summarized by age group, treatment cohort, and study phase for all enrolled subjects. For subjects who discontinue from the study, the reason for discontinuation will be tabulated.<br><br>***Demographics and Baseline Characteristics:*** Demographic and baseline characteristics including age, sex, race, height, weight, and body mass index (BMI) will be summarized by age group, treatment cohort, and study phase using appropriate descriptive statistics.<br><br>***Prior and Concomitant Medications:*** Medications administered prior to and concomitantly with study treatment will be tabulated for the safety population. These medications will be coded using the World Health Organization (WHO) drug dictionary.<br><br>***Effectiveness Analysis:*** The pain intensity difference (PID) at each post dose time point will be calculated as the pain intensity score at baseline minus the current pain intensity score at each post dose time point. Summary statistics of the pain intensity scores at each time point and PID at each post dose time point will be presented by pain assessment instrument, age group, treatment cohort, and study phase. For each subject, the PID over time will be transformed into a summary measure by calculating area under curve of PID ($AUC_E$) using the trapezoidal formula, adjusted for study duration. All time points before the first rescue medication will be used to calculate $AUC_E$. $AUC_E$ will be analyzed by a heterogeneous analysis of variance (ANOVA) model with fixed effects for age group, treatment cohort, and the interaction of age group by treatment cohort for each study phase. The potential heterogeneity between the age-specific measurements will be assessed using a dummy variable for the difference in the statistical model. Least squared means of $AUC_E$ for each combination of age groups and treatment cohorts and the corresponding 2-sided 95% CIs will be calculated based on the model.<br><br>Numbers and percentages of subjects who need rescue medication will be calculated by age group, treatment cohort, and study phase.<br><br>***Safety and Tolerability Analysis:*** Assessment of safety and tolerability will be based on the incidence of AEs, AEs resulting in discontinuation, and serious adverse events (SAEs). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will be provided showing the number and percentage of subjects who experience at least 1 AE. These summaries will be presented by system organ class and preferred term. The occurrence of AEs will also be tabulated by severity. SAEs and AEs resulting in discontinuation will be summarized separately.<br><br>Assessment of safety and tolerability will also be based on pharmacokinetic analysis (described below), clinical laboratory results, vital sign measurements, respiratory and neurological assessments, and other safety variables, which will be summarized by age group, treatment cohort, and study phase for each time point using appropriate descriptive statistics. |

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| ***Pharmacokinetic Analysis:*** Pharmacokinetic variables (Single-Dose Phase: $C_{max,}$ $T_{max}$, $C_{12}$, $AUC_{0-t}$, $AUC_{0-24}$, $AUC_{0-\infty}$, $\lambda_n$, $t_{1/2}$, CL/F, and V/F; Multiple-Dose Phase: $C_{max,}$ $T_{max}$, $AUC_{0-t}$, $\lambda_n$, $t_{1/2}$, CL/F, and V/F) will be estimated from the plasma concentration data using standard non-compartmental methods. Actual sample times, rather than scheduled times, will be used in the computation of pharmacokinetic parameters. The definitions and methods of determination for each pharmacokinetic variable are summarized in Table 7.<br><br>Pharmacokinetic variables (CL/F, V/F, $\lambda_n$, and $t_{1/2}$, and dose normalized $C_{max}$, $C_{12}$, $AUC_{0-24,}$ $AUC_{0-t}$, $AUC_{0-\infty}$) will be summarized by age group using N, mean, standard deviation (SD), geometric mean, CV, minimum, median, and maximum following dosing in the Single-Dose Phase and the first and third doses in the Multiple-Dose Phase. In addition, a 2-sided 95% CI will be constructed for both CL/F and V/F. $T_{max}$ will be summarized by age group using median, minimum, and maximum. |

# 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 2: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| $AUC_{0-\infty}$ | Area under the concentration versus time curve from time 0 to infinite |
| $AUC_{0-24}$ | Area under the concentration versus time curve from time 0 to 24 hours (end of dosing interval) |
| $AUC_{0-t}$ | Area under the concentration versus time curve from time 0 to the last measured concentration ($C_t$) in the dosing interval, calculated by linear trapezoidal rule |
| $AUC_E$ | Area under the curve of PID versus time from time 0 to the time of measured pain intensity before the rescue medication/last measured time point divided by the duration of time |
| BTP | Breakthrough pain |
| BLQ | Below limit of quantification |
| BMI | Body mass index |
| Baseline | Baseline will occur at the time when postoperative oral dosing with an opioid analgesic commences according to each institution's standard of care (SOC). |
| $C_{12}$ | Trough plasma concentration at the end of the 12-hour dosage interval |
| CF | Clear fluids |
| CI | Confidence interval |
| Cl/F | Apparent oral clearance |
| $C_{max}$ | Maximum plasma concentration |
| CNS | Central nervous system |
| $CO_2$ | Carbon dioxide |
| CRF | Case report form |
| CV | Coefficient of variation |
| DAT | Diet-as-tolerated |
| DEA | Drug Enforcement Administration |
| eCRF | Electronic case report form |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| EOS | End-of-study |
| ER | Extended-release |
| ET | Early termination |
| F | Oral bioavailability |
| FDA | Food and Drug Administration |

**Table 2: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| FF | Full fluids |
| FLACC | Face, Legs, Activity, Cry, Consolability scale |
| FPS-R | Faces Pain Scale - Revised |
| GCP | Good Clinical Practice |
| HCl | Hydrochloride |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IR | Immediate-release |
| IRB | Institutional Review Board |
| IVRS | Interactive voice response system |
| $K_2$EDTA | Dipotassium ethylenediaminetetraacetic acid |
| LC-MS/MS | Liquid chromatography dual mass spectrometry |
| LDH | Lactic dehydrogenase |
| MAOI | Monoamine oxidase inhibitor |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAIDs | Nonsteroidal anti-inflammatory drugs |
| $O_2$ | Oxygen |
| OTC | Over-the-counter |
| PCA | Patient controlled analgesia |
| PDF | Portable document format |
| Ped-IMMPACT | Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials |
| PET | Polyethylene terephthalate |
| PID | Pain intensity difference calculated by the pain intensity score at baseline minus the current pain intensity score |
| PI-NRS | Numerical Rating Scale |
| PK | Pharmacokinetic |
| PVRM | Pharmacovigilance and risk management |
| q4-6h | Every 4 to 6 hours |
| SAE | Serious adverse event |
| SAS® | Statistical Analysis System |
| SD | Standard deviation |
| SOC | Standard of care |
| $T_{½}$ | Terminal half-life |
| TEAE | Treatment-emergent adverse event |

**Table 2: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| $T_{max}$ | Time at which $C_{max}$ was observed |
| VAS | Visual Analog Scale |
| V/F | Apparent volume of distribution |
| WHO | World Health Organization |
| $\lambda_n$ | Terminal rate constant |

# 5. INTRODUCTION

[redacted]

## 5.1. Study Rationale

Postoperative pain following many pediatric surgeries is expected to be moderate to severe and often requires opioids for mitigation. The safe and effective use of opioid analgesics in a pediatric population is well documented.(5-11) In addition, many operative procedures result in pain that is predictable and limited in duration. According to current clinical practice, children are usually started on oral post-operative pain medication within hours following surgery. In this pediatric study, subjects will be selected where the need for opioid analgesia postoperatively is medically indicated.

The liquid formulation of oxymorphone IR was created to allow weight-based dosing (mg/kg) and to provide a dosing option for children unable to swallow tablets.

Over 2000 adult subjects (≥18 years old) have received oxymorphone in clinical studies to date; some of these subjects have been dosed for up to 2 years. This study is designed to provide effectiveness, safety, and tolerability data on an oral liquid formulation in children experiencing post-operative pain.

## 5.2. Study Design Rationale

This is an open-label, non-randomized, multicenter, ascending dose by age, single- and multiple-dose phase study to evaluate the effectiveness, safety, and tolerability of oral liquid oxymorphone for post-operative pain in pediatric subjects. The oxymorphone HCl immediate-release oral liquid dose was chosen based on an established equivalent morphine dose (0.3 mg/kg by mouth every 3 to 4 hours) in children being treated for acute pain.(12)

The study subjects will be stratified into 2 age groups; the study will enroll using parallel enrollment with these age groups (spanning ages 2 to ≤12 years). These age groups will be studied in parallel because they have mature pathways for metabolism of opioids.(13)

In both the Single- and Multiple-Dose Phases, as each treatment cohort of subjects within each age group is completed, the effectiveness, safety, and tolerability will be assessed by the Independent Data Monitoring Committee (IDMC) before enrolling subjects into the next-higher treatment cohort. Upon completion of each treatment cohort (of each age group) during the Single-Dose Phase, the IDMC will provide recommendation on whether additional cohorts are needed in the Single-Dose Phase (up to 3 treatment cohorts in total may be tested in the

Single-Dose Phase for each age group). As each age group completes the Single-Dose Phase, the IDMC will assess the data based on the effectiveness, safety, and tolerability of the study drug and will provide recommendations for the doses to be used in the age group's Multiple-Dose Phase. Up to 3 treatment cohorts (ie, doses) of subjects may be tested in the Multiple-Dose Phase for each age group.

## 5.3. Dose Rationale

This study is designed to characterize the effectiveness, safety, tolerability, and pharmacokinetics of single-dose and multiple-dose postoperative treatment utilizing oxymorphone HCl immediate-release oral liquid in children aged 2 to≤12 years with postoperative pain requiring an opioid. The equianalgesic ratio of oral oxycodone to oral oxymorphone has been determined to be approximately 2 to 1,(14) conferring an equianalgesic ratio of oral morphine to oral oxymorphone of approximately 3 to 1. The recommended starting dose of oral morphine for a child/adult <50 kg is 0.3 mg/kg.(8) Thus, from previous findings that have established equianalgesic ratios, the predicted equianalgesic dose of liquid oxymorphone that should provide equivalent analgesia to 0.3 mg/kg of oral morphine would be 0.1 mg/kg. Because the safety and effectiveness of oxymorphone have not been fully assessed in a pediatric population, a starting dose of 0.05 mg/kg oxymorphone HCl immediate-release oral liquid was chosen for the current study, which represents approximately half of the predicted equianalgesic starting dose of oral morphine.

In the current study, Single-Dose Phase, oxymorphone HCl immediate-release oral liquid may be studied at the 0.05-, 0.10-, and either 0.15- or 0.20-mg/kg dose (determined by IDMC recommendation following review of data from the 0.10-mg/kg cohort; the IDMC may at this point recommend a different dose of oxymorphone HCl immediate-release oral liquid [not to exceed 0.30 mg/kg] or to proceed directly into the Multiple-Dose Phase). In the Multiple-Dose Phase, oxymorphone HCl immediate-release oral liquid may be studied at up to 3 dose levels that will be determined by the IDMC following review of data from the Single-Dose Phase of the study; the IDMC may recommend to end the study after completion of 2 dose levels in the Multiple-Dose Phase based on review of the data from the first 2 studied doses of oxymorphone HCl immediate-release oral liquid.

For this study, oxymorphone will be available in liquid form (immediate release) at a concentration of 1 mg/mL. An opioid antagonist (eg, naloxone based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.

# 6. OBJECTIVES

## 6.1. Primary Objective

The primary objective of the Single-Dose and Multiple-Dose Phase is to characterize the effectiveness, safety, and tolerability of oxymorphone HCl immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies.

## 6.2. Secondary Objectives

The secondary objectives are: 1) to characterize the pharmacokinetic profile of oxymorphone HCl immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies; and 2) to establish the appropriate dosing recommendations for oxymorphone HCl immediate-release oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies.

# 7. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This open-label, non-randomized, ascending-dose by age, single- and multiple-dose phase, multicenter study will be performed at approximately 20 multidisciplinary clinical centers. The study is designed to characterize the effectiveness, safety, tolerability, and pharmacokinetics of single-dose and multiple-dose postoperative treatment utilizing oxymorphone HCl immediate-release oral liquid in 2 to ≤12 year old subjects with postoperative pain requiring an opioid. The study subjects will be stratified into 2 age groups based on the developmental ability of the subjects to use age-specific pain assessment tools (see section 11.1):

A. 6 years to ≤12 years
B. 2 years to <6 years

All vital signs, respiratory assessments, and neurological assessments will be monitored and recorded by the Investigator, or designee, at the pre-specified timepoints in Table 3 and Table 4 (and upon early termination [ET]). An opioid antagonist (eg, naloxone based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.

An external IDMC will be used in this study to assess all individual and aggregate effectiveness, safety, and tolerability data prior to dose escalation within each age group and study phase. In both the Single- and Multiple-Dose Phases, as each treatment cohort of subjects in both age groups is completed, the effectiveness, safety, and tolerability will be assessed by the IDMC before enrolling subjects into the next-higher treatment cohort.

The effect of food on oxymorphone HCl immediate-release oral liquid (OPANA) pharmacokinetics in children has not been studied; the impact of feeding on the pharmacokinetics and safety of OPANA in children will be assessed as data permit. No food restrictions will be imposed in this study around the time of dosing.

**Single-Dose Phase**

During the Single-Dose Phase, 2 age groups of subjects will be given a single dose of oxymorphone HCl immediate-release oral liquid. Within each age group, there will be up to 3 treatment cohorts (6 subjects per cohort, approximately evenly distributed across each of the cohorts) comprised of different doses of oxymorphone HCl immediate-release oral liquid. The age groups of subjects will be:

A. 6 years to ≤12 years
B. 2 years to <6 years

Within each age group, there will be up to 3 treatment cohorts of subjects:

1. 0.05 mg/kg oxymorphone HCl immediate-release oral liquid
2. 0.10 mg/kg oxymorphone HCl immediate-release oral liquid
3. 0.15 mg/kg OR 0.20 mg/kg oxymorphone HCl immediate-release oral liquid, based on recommendation of the IDMC

Age groups A and B will be studied in parallel; up to 3 treatment cohorts of the Single-Dose Phase will be completed, after which enrollment will begin for the Multiple-Dose Phase of the study.

In the Single-Dose Phase, the first treatment cohort of 6 subjects from each age group will be given a single dose of oxymorphone HCl immediate-release oral liquid 0.05 mg/kg following postoperative parenteral analgesia according to each institution's standard of care (SOC). Administration of the study drug will occur at the time when (according to each institution's SOC) oral analgesics are to commence as part of the subject's postoperative analgesic regimen. Following completion of the first treatment cohort (0.05 mg/kg) of 6 subjects within each age group, data will be assessed by an external IDMC and, with an acceptable safety review and IDMC recommendation, a second treatment cohort of 6 subjects in each age group may be dosed with oxymorphone HCl immediate-release oral liquid 0.1 mg/kg. If the second treatment cohort within each age group demonstrates acceptable safety and tolerability, then, upon recommendation of the IDMC, a third treatment cohort of 6 subjects in each age group may be administered oxymorphone HCl immediate-release oral liquid 0.15 mg/kg or 0.20 mg/kg (based on recommendation from the IDMC; the IDMC may at this point recommend a different dose of oxymorphone HCl immediate-release oral liquid (not to exceed 0.30 mg/kg) or to proceed directly into the Multiple-Dose Phase).

In the Single-Dose Phase, as each treatment cohort of subjects within each age group is completed, the effectiveness, safety, and tolerability will be assessed by the IDMC before enrolling subjects into the next-higher treatment cohort. The IDMC will also provide recommendation on whether the subsequent treatment cohorts are needed in the Single-Dose Phase (up to 3 treatment cohorts in total may be tested in the Single-Dose Phase). If needed, non-oxycodone, non-oxymorphone rescue analgesia will be available according to SOC at each institution. Blood from a patent line (see section 12.4.1) will be collected to assess pharmacokinetics, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (eg, naloxone-based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.

**Multiple-Dose Phase**

At the end of the Single-Dose Phase for each age group, the IDMC will make recommendations for up to 3 dose levels to be used in the Multiple-Dose Phase. The Multiple-Dose Phase will proceed using the same age group stratification used in the Single-Dose Phase:

A. 6 years to ≤12 years
B. 2 years to <6 years

Age groups A and B will be studied in parallel. Following postoperative parenteral analgesia, when oral dosing is to commence according to each institution's SOC, dosing will begin at the lowest dose selected by the IDMC based on results from the Single-Dose Phase for each age group. Subjects will be dosed every 4 to 6 hours (no sooner than every 4 hours and no later than every 6 hours) for up to 48 hours. Subjects may receive non-oxycodone, non-oxymorphone rescue medication and discontinue from the study in the event that the study drug does not provide adequate pain relief.

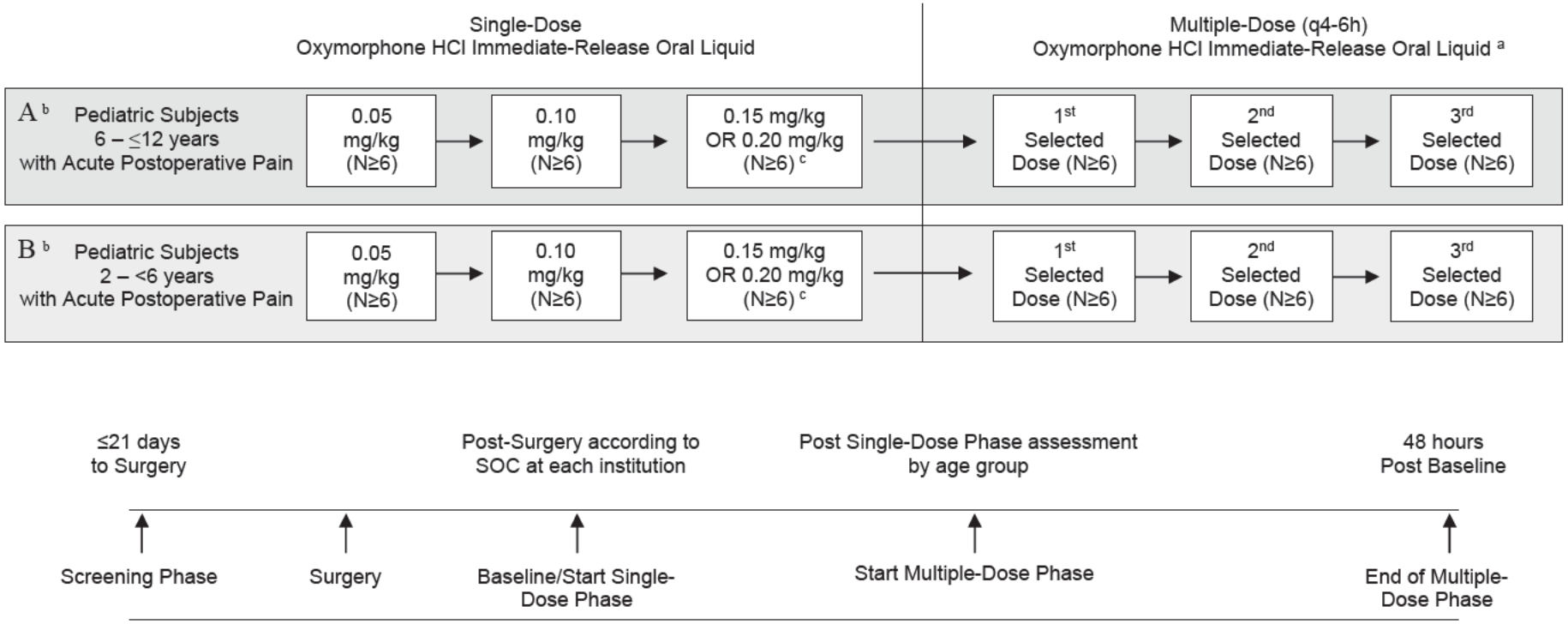
In the Multiple-Dose Phase, the first treatment cohort of 6 subjects from each age group will be given multiple doses of oxymorphone HCl immediate-release oral liquid at an initial dose recommended by the IDMC following postoperative parenteral analgesia according to each institution's SOC. The IDMC will use data from each age group's Single-Dose Phase to recommend the dose(s) to be used in each respective age group's Multiple-Dose Phase. Following completion of the first treatment cohort of 6 subjects within each group, the effectiveness, safety, and tolerability will be assessed by an external IDMC. Following their review, the IDMC may recommend that a second treatment cohort of 6 subjects in each group be dosed with oxymorphone HCl immediate-release oral liquid at the second dose (recommended by the IDMC). Following review of the effectiveness, safety, and tolerability of the second treatment cohort within each age group, the IDMC may recommend that a third treatment cohort of 6 subjects in each age group commence (at the third dose recommended by the IDMC; the IDMC may at this point recommend to end the Multiple-Dose Phase of the study).

If needed, non-oxycodone, non-oxymorphone rescue analgesia will be available according to the SOC at each institution.

Blood from a patent line will be collected to assess pharmacokinetics, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (eg, naloxone based) will be readily available for immediate intravenous administration at the discretion of the Investigator; subjects requiring naloxone rescue will be discontinued from the study.

The study design for EN3319-302 is illustrated in Figure 1.

**Figure 1: Study Design for EN3319-302**




**FOOTNOTES:**

[a] Up to 3 ascending dose levels for the Multiple-Dose Phase will be selected from the results of the Single-Dose Phase by the IDMC

[b] Each subject will only be enrolled into one of the treatment cohorts in either the Single-Dose Phase or the Multiple-Dose Phase; a subject will not progress from one treatment cohort to the next treatment cohort.

[c] Dose will be selected based on IDMC recommendation and review of the results of the 0.10 mg/kg cohort (if a dose other than 0.15 mg/kg or 0.20 mg/kg is selected by the IDMC, the dose must not exceed 0.30 mg/kg); the IDMC may also recommend to proceed directly into the Multiple-Dose Phase

IR=Immediate Release; q4-6=Every 4 to 6 hours; SOC=Standard of Care

NOTE: Within each age group, dose assignment will begin at lowest single dose and will proceed to the next dose after completion of all subjects. During the Single-Dose Phase, if rescue is needed, all study procedures (including PK) will continue except collection of pain scores. PK will only be discontinued if rescue is via oxycodone or oxymorphone. Within each age group, the Multiple-Dose Phase may proceed after IDMC assessment of the Single-Dose Phase data and selection by the IDMC of the treatment cohort doses that will be used in the Multiple-Dose Phase.

## 7.1. Study Assessments and Procedures

A schedule of study assessments and procedures is provided in Table 3 (Single-Dose Phase) and Table 4 (Multiple-Dose Phase). The timepoints for the Single-Dose and Multiple-Dose Phase were designed to capture assessments/procedures/blood draws based on comprehensive blood sampling for pharmacokinetic analysis.

Subjects will be enrolled in either the 24-hour Single-Dose Phase or the 48-hour Multiple-Dose Phase, depending on the status of the study. Each subject will only be enrolled into one treatment cohort and will not progress from that treatment cohort into the next, higher dose level treatment cohort in this study. End-of-study (EOS) evaluations will commence immediately after completion of a subject's respective study phase (Single- or Multiple-Dose) or upon early discontinuation from the study; each subject will be required to complete all EOS evaluations and procedures unless consent/assent has/have been withdrawn. In this case, only adverse event (AE) information will be collected. A detailed account of the conduct of the study is provided after the schedule of study procedures.

**Table 3: Schedule of Assessments/Procedures - Single-Dose Phase**

| Assessment | Visit 1 | Visit 2 (Hospital) | | | | | | | | | | | | Teleconference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Treatment | | | After Dose (h) | | | | | | | | | EOS Evaluation | Follow-Up |
| | Screening (within 21d of surgery) | (Pre-op or Intra-op) [a] | BL | 0.25 | 0.5 | 1 | 1.5 | 2 | 4 | 6 | 8 | 12 | (24h post 1st dose or ET) | (14d post EOS/ET) |
| Informed Consent by parent(s)/guardian(s) | X | | | | | | | | | | | | | |
| Assent by minor, if IRB-required | X | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Medical/Surgical History | X or | X | | | | | | | | | | | | |
| Physical Examination | X or | X | | | | | | | | | | | X | |
| Assess Entry Criteria | X | | X | | | | | | | | | | | |
| Train/retrain on completion of pain assessments [b] | X | | X | | | | | | | | | | | |
| Assess cognitive ability to complete pain assessments [c] | X | | | | | | | | | | | | | |
| Urine Drug Screen | X | | | | | | | | | | | | | |
| Pregnancy test (serum/urine) [d] | X | | X | | | | | | | | | | | |
| Study Drug Administration | | | X | | | | | | | | | | | |
| Blood sample for PK assessment | | | X [e] | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Clinical laboratory tests [f] | X or | X | | | | | | | | | | | X | |
| Adverse Events/Serious Adverse Events [g] | X | Monitored Throughout Study [h] | | | | | | | | | | | | |
| Respiratory assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Neurology assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Prior and Concomitant Medications [i] | X | Monitored Throughout Study [h] | | | | | | | | | | | | |
| Pain Assessment (age appropriate) [j] | | | X | X | X | X | X | X | X | X | X | X | X | |
| Record Surgical Details [k] | | X | | | | | | | | | | | | |
| Record food consumption [l] | | X | Monitored Throughout Study | | | | | | | | | | | |
| Rescue medication [m] | | | As Needed Throughout Study | | | | | | | | | | | |
| Convert subject to discharge opioid of Investigator's choice | | | | | | | | | | | | | X | |
| Schedule 14-day follow-up call with site | | | | | | | | | | | | | X | |
| Study Completion | | | | | | | | | | | | | | X |

**FOOTNOTES:**

Abbreviations: BL=Baseline; EOS=End-of-Study; ET=Early Termination; IRB=Institutional Review Board; PK=Pharmacokinetic; Pre-Op=Preoperative; Intra-op=Intraoperative

[a] Tests results must be available for assessment by the Investigator, or designee, prior to dosing a subject.

[b] Investigator, or designee, will train/retrain subjects, parent(s)/legal guardian(s) on the proper use and completion of the pain assessments.

[c] Investigator, or designee, will assess if the subject has the cognitive ability to correctly complete the required pain assessments.

[d] Pregnancy test (for females of child-bearing potential only) must be completed and the result assessed prior to administration of study drug. Serum βhCG at screening; urine pregnancy test before study drug administration, except if screening occurs in hospital.

[e] Blood sample drawn before dosing study drug.

[f] Clinical labs drawn as part of the SOC will be acceptable for study purposes. Intraoperative labs are acceptable provided they are drawn prior to first surgical incision and assessed by the Investigator prior to administration of the first dose of study drug.

[g] Captured following execution of informed consent/assent.

[h] Collected by the Investigator for up to 14 days after the last dose of study drug **(documented telephone follow-up required)**.

[i] See Appendix B and section 9.3 for concomitant medication reporting.

[j] A pain assessment will also be completed at the time of rescue immediately prior to rescue medication administration. **No pain assessments will be completed beyond rescue**.

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

[l] Record all times that any food was consumed and what food was consumed (Diet-as-tolerated [DAT], DAT-soft, Full Fluids, Clear Fluids, water) by the subject from 1h prior to dosing through to EOS at 24h post 1st dose/ET

[m] Non-oxycodone, non-oxymorphone-containing, opioid-based PCA rescue medication will be allowed for as long as the PCA device remains in place per institutional SOC. Oral rescue medications will also be allowed during the study, but must not contain oxycodone or oxymorphone.

**Table 4: Schedule of Assessments/Procedures - Multiple-Dose Phase**

| Assessment | Visit 1 | Visit 2 (Hospital) | | | | | | | | | | | | | | | | | Telecon-ference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Treatment | | Hours After Each Dose | | | | | | | | | | | | | | | EOS Evaluation | Follow-Up |
| | | | Dose 1 | | | | | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | | | | | Doses 8-12 [o] | |
| | Screening (within 21d of surgery) | (Pre-op or Intra-op) [a] | (BL) 0 | 0.5 | 1 | 1.5 | 2 | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0.5 | 1 | 1.5 | 2 | 0 [p] | 48h post 1st dose or ET | 14d post EOS/ET |
| Informed Consent by parent(s)/guardian(s) | X | | | | | | | | | | | | | | | | | | | |
| Assent by minor, if IRB-required | X | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | |
| Medical/Surgical History | X or X | | | | | | | | | | | | | | | | | | | |
| Physical Examination | X or X | | | | | | | | | | | | | | | | | | X | |
| Assess Entry Criteria | X | | X | | | | | | | | | | | | | | | | | |
| Train/retrain on completion of pain assessments [b] | X | | X | | | | | | | | | | | | | | | | | |
| Assess cognitive ability to complete pain assessments [c] | X | | | | | | | | | | | | | | | | | | | |
| Urine Drug Screen | X | | | | | | | | | | | | | | | | | | | |
| Pregnancy test (serum/urine) [d] | X | | X | | | | | | | | | | | | | | | | | |
| Study Drug Administration (first dose) | | | X | | | | | | | | | | | | | | | | | |
| Study Drug Administration (eg, dosing every 4-6h) [e] | | | | | | | | X | X | X | X | X | X | | | | | X | | |
| Blood sample for PK assessment [e, f] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | |
| Clinical Laboratory tests [g] | X or X | | | | | | | | | | | | | | | | | | X | |
| Adverse Events/Serious Adverse Events [h] | X | Monitored Throughout Study [i] | | | | | | | | | | | | | | | | | | |
| Respiratory Assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | |
| Neurology Assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | |
| Prior and Concomitant Medications [j] | X | Monitored Throughout Study [i] | | | | | | | | | | | | | | | | | | |
| Pain Assessment (age appropriate) [k] | | | X | X | X | X | X | X | X | X | X | X | X | | | | | X | X | |
| Record Surgical Details [l] | | X | | | | | | | | | | | | | | | | | | |

| Assessment | Visit 1 | Visit 2 (Hospital) | | | | | | | | | | | | | | | | | Telecon-ference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Treatment | | Hours After Each Dose | | | | | | | | | | | | | | | EOS Evaluation | Follow-Up |
| | | | Dose 1 | | | | | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | | | | | Doses 8-12 [o] | |
| | Screening (within 21d of surgery) | (Pre-op or Intra-op) [a] | (BL) 0 | 0.5 | 1 | 1.5 | 2 | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0 [p] | 0.5 | 1 | 1.5 | 2 | 0 [p] | 48h post 1st dose or ET | 14d post EOS/ET |
| Record food consumption [m] | | X | Monitored Throughout Study | | | | | | | | | | | | | | | | | |
| Rescue medication [n] | | | As Needed Throughout Study | | | | | | | | | | | | | | | | | |
| Convert subject to discharge opioid of Investigator's choice | | | | | | | | | | | | | | | | | | | X | |
| Schedule 14day follow-up call with site | | | | | | | | | | | | | | | | | | | X | |
| Study Completion | | | | | | | | | | | | | | | | | | | | X |

**FOOTNOTES:**

Abbreviations: BL=Baseline; EOS=End-of-Study; ET=Early Termination; IRB=Institutional Review Board; PK=Pharmacokinetic; Pre-Op=Preoperative; Intra-op=Intraoperative

[a] Tests results must be available for assessment by the Investigator, or designee, prior to dosing a subject.

[b] Investigator, or designee, will train/retrain subjects, parent(s)/legal guardian(s) on the proper use and completion of the pain assessments.

[c] Investigator, or designee, will assess if the subject has the cognitive ability to correctly complete the required pain assessments.

[d] Pregnancy test (for females of child-bearing potential only) must be completed and the result assessed prior to administration of study drug. Serum βhCG at screening; urine pregnancy test before study drug administration, except if screening occurs in hospital.

[e] Dosing times (see section 12.4.1) will vary depending upon the dosing interval.

[f] Blood sample drawn before dosing study drug. Maximum number of blood samples for PK is 15 (Appendix E).

[g] Clinical labs drawn as part of the SOC will be acceptable for study purposes. Intraoperative labs are acceptable provided they are drawn prior to first surgical incision and assessed by the Investigator prior to administration of the first dose of study drug.

[h] Captured following execution of informed consent/assent.

[i] Collected by the Investigator for up to 14 days after the last dose of study drug **(documented telephone follow-up required)**.

[j] See Appendix B and section 9.3 for concomitant medication reporting.

[k] A pain assessment will also be completed at the time of rescue immediately prior to rescue medication administration. **No pain assessments will be completed beyond rescue**.

[l] Must include type of procedure(s), date of procedure(s), surgical start/stop time, and anesthesia/analgesia start and stop time.

[m] Record all times that any food was consumed and what food was consumed (Diet-as-tolerated [DAT], DAT-soft, Full Fluids, Clear Fluids, water) by the subject from 1h prior to dosing through to EOS at 48h post 1st dose/ET.

[n] Non-oxycodone, non-oxymorphone-containing, opioid-based PCA rescue medication will be allowed for as long as the PCA device remains in place per institutional SOC. Oral rescue medications will also be allowed during the study, but must not contain oxycodone or oxymorphone.

[o] Maximum treatment time is 48hrs. The number of ATC doses administered will vary with the Q4-6h dosing interval.

[p] Time "0" indicates pre-dose, or "baseline" for the indicated dose.

### 7.1.1. Screening Phase and Pre-Treatment Assessments and Procedures

The Investigator, or designee, will identify a potential candidate for the EN3319-302 study. The Investigator, or designee, will obtain informed consent (and assent, according to the child's age as required by the Institutional Review Board [IRB]/Institutional Ethics Committee [IEC]) and will screen the subject at any time within 21 days of surgery. After the informed consent/assent has/have been signed, and a unique subject number has been assigned, Screening assessments/procedures will be completed (see Table 3 and Table 4). Informed consent and assent from minors will be obtained prior to initiation of any study-related procedures. Blood samples for clinical laboratory tests may be collected at any time within 21 days prior to surgery. Clinical labs drawn as part of the SOC (including the pre-operative and intraoperative period) will be acceptable for study purposes provided they are taken prior to first surgical incision and assessed by the Investigator prior to the first dose of study drug. Details on selection of subjects will be based on their anticipated need for oral opioids for management of pain following surgery. The Investigator will explain the study to the subject (where age-appropriate) and to the subject's parent(s)/legal guardian(s). All Screening Phase assessments and procedures will be completed according to protocol preferably on the same day as outlined in Table 3 (Single-Dose Phase) and Table 4 (Multiple-Dose Phase). Each subject will also be assessed for his/her cognitive ability by the Investigator, or designee, to complete pain assessments and procedures as per protocol; documentation of the outcome will be recorded.

Screening visit activities will include:

- Obtaining written informed consent from parent(s)/legal guardian(s) and assent by minor (if required by the IRB/IEC)
- Recording demography: gender, age, and race
- Recording medical/surgical history: all previously existing and current medical conditions including any past surgical procedures. This assessment may be deferred until the preoperative or intraoperative time point.
- Performing physical examination: a comprehensive physical examination, including height and weight, to assess the subject's overall health and physical status. Record only abnormalities observed during the examination. This assessment may be deferred until the preoperative or intraoperative time point.
- Obtaining urine drug screen (see section 12.5.2).
- Assessing entry criteria: inclusion/exclusion criteria will be assessed during the Screening Phase and confirmed prior to beginning Baseline assessments/procedures.
- Assessing cognitive ability of the subjects to complete pain assessments.
- Training subjects and parent(s)/legal guardian(s) on the proper use and completion of the pain assessments.
- Obtaining clinical laboratory tests: may be deferred until the preoperative or intraoperative time point provided the labs are drawn prior to the first surgical incision. Intraoperative drawn labs that are used for study evaluability must be assessed by the Investigator prior to administration of the first dose of study drug.

- Obtaining serum pregnancy test: female subjects of child-bearing potential will be given a pregnancy test.
- Measuring vital signs: temperature, heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (systolic and diastolic blood pressure, mmHg).
- Collecting AEs/serious AEs (SAEs): all AEs/SAEs that occur during the Screening Phase and thereafter that started after Informed Consent/Assent, as applicable, has/have been signed.
- Completing a respiratory assessment: see section 12.2 for the tests to be included in this assessment.
- Completing a neurology assessment: see section 12.3 and Appendix A for the test to be included in this assessment.
- Recording prior and concomitant medications: medications taken within 30 days prior to signing consent/assent, as applicable, as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (see Appendix B). Over-the-counter (OTC) acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) may be used only to manage fever or headache.

Blood samples for clinical laboratory tests must be collected at either the Screening Visit or during the preoperative or intraoperative period (prior to first surgical incision). Chemistry panels may include analysis of the analytes listed in section 12.5.3.

Hematology panels may include analysis of the analytes listed in section 12.5.4.

All appropriate restrictions on concomitant medication usage during the preoperative period should be followed per section 9.3.

### 7.1.2. Surgical Period (Preoperative or Intraoperative) Assessments and Procedures

Each subject will undergo surgery. Details of the surgical procedure(s) will be recorded on the appropriate source document and entered into the electronic case report form (eCRF) including the exact type of procedure(s) performed, the date and time of the surgery (start/stop time), and the time anesthesia/analgesia began and ended. The details of preoperative, intraoperative, and postoperative medications will be recorded (refer to Appendix B) .

Preoperative or intraoperative study procedures will include:

- Measuring vital signs: temperature, heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (systolic and diastolic blood pressure, mmHg).
- Completing a respiratory assessment: see section 12.2 for the tests to be included in this assessment.
- Completing a neurological assessment: see section 12.3 and Appendix A for the test to be included in this assessment.
- Recording of surgical details

- Recording of food consumption: from 1 hour prior to administration of study drug; record all times that any food was consumed and what food was consumed (diet-as-tolerated [DAT], DAT-soft, full fluids [FFs], clear fluids [CFs], water).

If not already obtained at Screening, preoperative or intraoperative study procedures may include:

- Recording medical/surgical history
- Performing physical examination, including height and weight
- Obtaining clinical laboratory tests

Blood samples for clinical laboratory tests taken during the intraoperative period as part of the SOC may be used for study purposes provided they are collected prior to first surgical incision and assessed by the Investigator prior to the administration of the first dose of study drug.

- Chemistry panels may include analysis of the analytes listed in section 12.5.3.
- Hematology panels may include analysis of the analytes listed in section 12.5.4.

All appropriate restrictions on concomitant medication usage during the postoperative period should be followed per section 9.3.

### 7.1.3. Baseline Assessments and Procedures

Subjects who meet all inclusion/exclusion criteria will be enrolled into the study and assigned to receive a dose of oxymorphone HCl immediate-release oral liquid (study drug) based on order of enrollment.

Administration of the study drug will occur at the time postoperative parenteral analgesia is discontinued and oral dosing with opioid analgesics commences according to each institution's SOC. The subject's baseline level of pain will be assessed using an age-appropriate pain assessment instrument (Appendix C, Faces Pain Scale-Revised [FPS-R]) or Appendix D, the Face, Legs, Activity, Cry, Consolability scale [FLACC]).

The investigational staff will record the time, date, and dose of the study drug that the subject is administered in the source document and in the eCRF.

Baseline assessments and procedures will include the following:

- Assessing entry criteria: inclusion/exclusion criteria will be confirmed prior to beginning Baseline assessments/procedures.
- Retraining on completion of pain assessments: at Visit 2 before starting Baseline assessments and procedures.
- Obtaining urine pregnancy test: female subjects of child-bearing potential will be given a pregnancy test.
- Measuring vital signs: temperature, heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (systolic and diastolic blood pressure, mmHg).

- Completing a respiratory assessment: see section 12.2 for the tests to be included in this assessment.
- Completing a neurological assessment: see section 12.3 and Appendix A for the test to be included in this assessment.
- Assessing current pain intensity (immediately prior to administration of study drug): each subject will provide a Baseline level of pain intensity using an age-appropriate pain assessment instrument (FPS-R for ages 6 to ≤12; FLACC for ages 2 to <6 [see Appendix C and Appendix D, respectively]) prior to first dosing of study drug administration as well as just before each dose of study drug during the Multiple-Dose Phase; pain intensity scores will also be assessed just before taking the first rescue medication dose.
- Collecting a blood sample for pharmacokinetic assessment: draw prior to drug administration.
- Dosing the subject with study drug
  - The exact time when study drug was taken must be recorded. Any dose of study drug should not be administered for at least 2 hours following any opioid-based rescue medication.
  - For subjects receiving parenteral opioid analgesia: study drug will be administered when parenteral analgesia is discontinued and oral dosing with an opioid analgesic commences according to each institution's SOC.
  - Note: Laxative and antiemetic regimens may be used; all subjects will be allowed use of a laxative and antiemetic throughout the study. All study drug taken by the subjects (including rescue medication) will be recorded in the eCRF.
- Updating and recording all concomitant medications: medications taken within 30 days prior to signing consent/assent, as applicable, as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (see Appendix B). OTC acetaminophen or NSAIDs may be used only to manage fever or headache.
- Collecting AEs/SAEs: all AEs/SAEs that occur during the Screening Phase and thereafter that started after Informed Consent/Assent, as applicable, has/have been signed.

### 7.1.4. Single-Dose Phase Assessments and Procedures

The following assessments and procedures will be performed during the Single-Dose Phase (see Table 3) after the baseline assessments have been completed and the subject is dosed. Every effort should be made to collect blood samples at the assigned time intervals relative to the time of administration of study drug:

- Assess and record current pain intensity at 15 and 30 minutes and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours (or upon ET) after administration of study drug or until the subject requires rescue medication. Assessments must be made by the Investigator, or designee. Pain will be assessed at time of rescue, but no pain assessments will be completed beyond administration of rescue medication.
- Measurement of vital signs at 15 and 30 minutes and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours (or upon ET) after administration of study drug.
- Assess respiratory (see section 12.2) and neurological function (see section 12.3 and Appendix A) at 15 and 30 minutes and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours (or upon ET) after administration of study drug. Assessments must be made by the Investigator, or designee.
- Collection of blood samples for pharmacokinetic assessments at 15 and 30 minutes and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours (or upon ET) after administration of study drug.
- Record food consumption: capture the date and time of each consumption of food as well as what was consumed eg, DAT, DAT-soft, FFs, CFs, water from 1 hour prior to first dose of study drug administration through EOS/ET.
- Record rescue medication: provide rescue medication on an as needed basis for breakthrough pain (BTP). Rescue medication may include opioid-based patient controlled analgesia (PCA) rescue (but must NOT contain oxycodone or oxymorphone) for as long as the PCA device remains in place per SOC. Oral rescue medications will also be allowed during the study, but also must NOT contain oxycodone or oxymorphone.
- Monitor and document AEs/SAEs throughout the study.
- Update and record concomitant medications (including rescue medications).

Subjects will complete the Single-Dose Phase when they complete the EOS assessments and procedures at 24 hours (or upon ET) following initial study drug administration.

### 7.1.5. Multiple-Dose Phase Assessments and Procedures

The following assessments and procedures will be performed during the Multiple-Dose Phase (see Table 4) after the baseline assessments have been completed and the subject is dosed. Every effort should be made to collect blood samples at the assigned time intervals relative to the time of administration of study drug:

- Assess and record current pain intensity at 0.5, 1, 1.5, and 2 hrs post-Dose 1, and immediately prior to all remaining Doses administered up through 48 hrs after administration of the initial dose of study drug or until ET or the subject requires rescue medication. Assessments must be made by the Investigator, or designee. Pain will be assessed at time of rescue, but no pain assessments will be completed beyond administration of rescue medication.
- Measurement of vital signs at 0.5, 1, 1.5, and 2 hrs post-Dose 1, and immediately prior to all remaining Doses administered up through 48hrs (or upon ET) after initial administration of study drug.
- Assess respiratory (see section 12.2) and neurological function (see section 12.3 and Appendix A) at 0.5, 1, 1.5, and 2 hrs post-Dose 1, and immediately prior to all remaining Doses administered up through 48hrs (or upon ET) after initial administration of study drug. Assessments must be made by the Investigator, or designee.
- Collection of blood samples for pharmacokinetic assessments at 0.5, 1, 1.5, and 2 hrs post-Dose 1, immediately prior to Doses 2, 3, 4, 5, 6, 7, and at 0.5, 1, 1.5, and 2 hrs post Dose 7..
- Record food consumption: capture the date and time of each consumption of food as well as what was consumed eg, DAT, DAT-soft, CFs, FFs, water from 1 hour prior to first dose of study drug administration through EOS/ET.
- Record rescue medication: provide rescue medication on an as needed basis for BTP. Rescue medication may include opioid-based PCA rescue (but must NOT contain oxycodone or oxymorphone) for as long as the PCA device remains in place per SOC. Oral rescue medications will also be allowed during the study, but also must NOT contain oxycodone or oxymorphone.
- Monitor and document AEs/SAEs throughout the study.
- Update and record concomitant medications (including rescue medications).

Subjects will complete the Multiple-Dose Phase when they complete the EOS assessments and procedures at 48 hours (or upon ET) following initial study drug administration.

### 7.1.6. End-of-Study/Early Termination Assessments and Procedures

At the completion of the single- or multiple-dose phases, EOS/ET assessments and procedures will occur at 24 or 48 hours after initial study drug administration or upon early discontinuation. Each subject will be required to complete all EOS/ET assessments and procedures unless consent/assent, as applicable, has/have been withdrawn. End-of-study assessments will include:

- Collecting AEs/SAEs: all AEs/SAEs that occur during the Screening Phase and thereafter that started after Informed Consent/Assent, as applicable, has/have been signed.
- Performing physical examination: a comprehensive physical examination, excluding height and weight, to assess the subject's overall health and physical status. Record only abnormalities observed during the examination.
- Measuring vital signs: temperature, heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (systolic and diastolic blood pressure, mmHg.
- Collecting a blood sample for pharmacokinetic assessments
- Collecting a blood sample for clinical laboratory tests: clinical laboratory tests as part of SOC will be acceptable.
  - Chemistry panels may include analysis of the analytes listed in section 12.5.3.
  - Hematology panels may include analysis of the analytes listed in section 12.5.4.
- Assessing respiratory and neurological function (see sections 12.2 and 12.3 and Appendix A). Assessments must be made by the Investigator, or designee.
- Updating and recording concomitant medications (including rescue medications).
- Assessing and recording current pain intensity (prior to giving rescue or further analgesics according to SOC) using an age-appropriate pain assessment instrument (FPS-R for ages 6 to ≤12; FLACC for ages 2 to <6 [see Appendix C and Appendix D, respectively]).
- Converting subjects to a discharge marketed opioid, if required.
- Scheduling the 14-day follow-up telephone call: assessment to include ongoing or new AEs, SAEs, and associated concomitant medications.

### 7.1.7. Follow-Up Telephone Call

A documented follow-up telephone call will be required 14 days after the last dose of study drug. Site staff will collect information regarding new AEs (including SAEs) or resolution of ongoing AEs/SAEs, including concomitant medications being used to treat any SAE or ongoing AE and any new analgesic medications started after Visit 2 (EOS/ET).

The date of discharge from the study will be recorded by the Investigator on the Completion/Discontinuation source document and eCRF page and will be the official EOS/ET for each subject. Study participation will end with the completion of the 14-day follow-up telephone call.

### 7.1.8. Throughout the Study - Adverse Events and Serious Adverse Events

- Any AE will be treated by the Investigator according to standard institution medical practices and guidelines.
- All AEs will be followed-up by the Investigator through 14 days after the last dose of study drug or until resolution, whichever comes first. SAEs will be followed until resolution, stabilization or until follow-up is no longer possible. The 14-day follow-up will occur by telephone and will be documented in the source record. Results of all follow-up blood analyses and medical, pharmacological, and non-pharmacological interventions must be documented by the Investigator in the source documents and on the appropriate pages of the eCRF.

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## 8.1. Subject Inclusion Criteria

1. Males or females between 2 to ≤12 years of age. Females of child-bearing potential must be practicing abstinence or using a medically acceptable form of contraception (eg, intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all peri- and post-pubertal females will be considered to be of child-bearing potential unless they are biologically sterile or surgically sterile for more than 1 year
2. Subjects must be at least 10 kg and BMI ≤30.
3. Scheduled to have a surgery for which oral opioid analgesia will be needed to manage post-operative pain for at least 24 hours (Single-Dose Phase) or 48 hours (Multiple-Dose Phase) following intraoperative and/or postoperative parenteral analgesia
4. Be hospital inpatients, expected to be hospitalized for at least 24 hours (Single-Dose Phase) and 48 hours (Multiple-Dose Phase) following the initial administration of oxymorphone immediate-release
5. Lab samples, either drawn intraoperatively (prior to surgical incision) or from within 21 days preoperatively, for clinical chemistry and hematology laboratory analytes (the results must have been reviewed by the Investigator prior to study drug administration for study eligibility)
6. Able to provide pain assessment evaluations using an age-appropriate instrument provided in the protocol
7. On an intravenous analgesic regimen utilizing a short-acting opioid analgesic following surgery AND anticipated to be switched to an oral opioid as part of the analgesic regimen (according to institution SOC)
8. Demonstrated the ability to tolerate clear fluids following surgery according to the SOC at each institution
9. Informed of the nature of the study and written informed consent has been obtained from the legally responsible parent(s)/legal guardian(s)
10. Provided assent in accordance with IRB requirements
11. Line in place for blood sampling

## 8.2. Subject Exclusion Criteria

1. Known allergies or sensitivities to oxymorphone or other opioid analgesics
2. Known sensitivity to any component of the study drug
3. Life expectancy <4 weeks
4. Positive pregnancy test at screening (females of reproductive age only)

5. Pregnant and/or lactating
6. Cyanotic heart disease
7. Respiratory, hepatic, renal, neurological, psychological disease, or any other clinically significant condition that would, in the Investigator's opinion, preclude participation in the study
8. Preoperative opioids administered for a period of more than 72 hours in duration
9. Abdominal trauma that would interfere with absorption of study drug
10. Increased intracranial pressure
11. Respiratory condition requiring intubation
12. History of uncontrolled seizures that are not being managed with anti-convulsants
13. Significant prior history of substance abuse or alcohol abuse
14. Received any investigational medication within 30 days prior to the first dose of study drug, or are scheduled to receive an investigational drug other than oxymorphone HCl immediate-release oral liquid during the course of the study
15. Received a monoamine oxidase inhibitor (MAOI) within 14 days prior to the start of study drug
16. Received oxycodone or oxymorphone within 48 hours prior to study start
17. Investigator anticipates that the subject and/or parent(s)/legal guardian(s) would be unable to comply with the protocol
18. Subject (and/or parent[s]/legal guardian[s]) is(are) unable to communicate effectively with study personnel at an age-appropriate level

## 8.3. Subject Withdrawal Criteria

Subjects may be discontinued from the study for the following reasons, but not limited to, if deemed appropriate, by the Sponsor or Investigator:

- Subject enters the study in violation of the protocol
- Protocol deviation during the conduct of the study
- Subject (or subject's parent/legal guardian as age appropriate) withdraws consent (reason[s] for the study withdrawal must be specified)
- If, in the Investigator's opinion, it is not in the subject's best interest to continue (reason[s] for study withdrawal must be specified)
- Lack of analgesic effect
- Adverse event
- Pregnancy
- Use of an opioid antagonist (eg, naloxone)

- Other reasons (reason must be specified, for example, the subject moved, Investigator decision, Sponsor decision to terminate trial)

When a subject is "lost to follow-up" (ie, fails to return for study visits), a reasonable effort, comprised of no less than 3 documented phone calls on separate occasions and a certified mail letter, should be made to contact the subject's parent(s)/legal guardian(s) to determine a reason for the failure to return. If, following these actions, the subject fails to be contacted or fails to return to the clinic, the subject should be identified as "lost to follow-up" in the eCRF.

The date a subject discontinues and the reason for discontinuation will be documented in the source and entered into the eCRF. If a subject discontinues from the study (regardless of the cause), all EOS/ET assessments and procedures should be completed. If, however, a subject withdraws consent, no EOS/ET assessments or procedures will be required except for the collection of AE information. This information should be recorded in the source document and entered into the eCRF.

# 9. TREATMENT OF SUBJECTS

## 9.1. Description of Study Drug

EN3319, oxymorphone HCl immediate-release oral liquid 1 mg/mL will be supplied by Endo Pharmaceuticals Inc.

Labeling and storage information are provided in sections 10.2 and 10.3, respectively. Drug accountability is described in section 10.6.

## 9.2. Method of Assigning Subjects to Treatment Groups

This is an open-label, multicenter, ascending-dose by age, Single- and Multiple-Dose Phase study that doesn't require randomization. Subjects will be stratified by age into 2 groups, and each group will have up to 3 treatment cohorts of study drug. Enrollment will continue up to 72 evaluable subjects, approximately evenly distributed across each of the 2 age groups (as feasible) and within each treatment cohort, are enrolled. Sites will call the interactive voice response system (IVRS) for assignment of treatment phase and dose for all subjects. The age groups of subjects are:

A. 6 years to ≤12 years
B. 2 years to <6 years

Up to 3 treatment cohorts include:

1. 0.05 mg/kg oxymorphone HCl immediate-release oral liquid
2. 0.10 mg/kg oxymorphone HCl immediate-release oral liquid
3. 0.15 mg/kg OR 0.20 mg/kg oxymorphone HCl immediate-release oral liquid, based on recommendation of the IDMC; the IDMC may recommend a different dose of study drug (not to exceed 0.30 mg/kg) or that this treatment cohort is not necessary

### 9.2.1. Single-Dose Phase

The treatment assignment for the Single-Dose Phase is summarized in Table 5.

**Table 5: Treatment Assignment - Single-Dose Phase**

| | Treatment Cohort | | | |
|---|---|---|---|---|
| **Age Group** | **0.05 mg/kg** | **0.10 mg/kg** | **0.15 mg/kg (or 0.20 mg/kg) [a]** | **Total** |
| A. 6 years to ≤12 years | 6 | 6 | 6 | 18 |
| B. 2 years to <6 years | 6 | 6 | 6 | 18 |
| **Total** | | | | **36** |

[a] As determined by IDMC

### 9.2.2. Multiple-Dose Phase

At the end of the Single-Dose Phase for each age group, the IDMC will make recommendations for up to 3 doses that will be used in the Multiple-Dose Phase. The Multiple-Dose Phase will proceed using the same age group stratification used in the Single-Dose Phase:

A. 6 years – ≤12 years
B. 2 years – <6 years

Within each age group, up to 3 treatment cohorts will be studied with the doses determined by the IDMC.

The treatment assignment for the Multiple-Dose Phase is summarized in Table 6.

**Table 6: Treatment Assignment - Multiple-Dose Phase**

| Age Group | Treatment Cohort | | | Total |
|---|---|---|---|---|
| | Dose 1 [a] | Dose 2 [a] | Dose 3 [a] | |
| A. 6 years to ≤12 years | 6 | 6 | 6 | 18 |
| B. 2 years to <6 years | 6 | 6 | 6 | 18 |
| **Total** | | | | **36** |

[a] Doses and number of cohorts will be determined by IDMC (up to 3 cohorts may be included)

## 9.3. Concomitant Medications

Following execution of the informed consent, any concomitant medication (including vitamin supplements, herbal remedies, and nonprescription medications) used while the subject is on study drug (up to 24/48 hours post first dose of study drug depending on study phase) will be recorded. Surgical medications will be captured on the Surgical Medications page. Medications as noted in Appendix B will be entered into the eCRF. The medication name, dose, date, time, and indication for use will be recorded. The Medical Monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies are administered. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study drug may be given at the discretion of the Investigator. Medications known to have analgesic effects or to influence the subject's perception of pain must be avoided during the study except as provided for in the protocol. The following restrictions will apply:

- During the Single-Dose Phase, no analgesics other than the study drug will be permitted during the 12-hour assessment period (except rescue); analgesia according to SOC at each institution will be permitted after the 12-hour assessment period (or after rescue) with the exception of oxycodone or oxymorphone, and any products containing oxycodone or oxymorphone, which are prohibited throughout the 24-hour pharmacokinetic assessment period.

- During the Multiple-Dose Phase, no analgesics other than the study drug will be permitted during the 48-hour assessment period (except rescue); analgesia according to SOC at each institution will be permitted after rescue, with the exception of oxycodone or oxymorphone, and any products containing oxycodone or oxymorphone, which are prohibited throughout the 48-hour pharmacokinetic assessment period.
- OTC acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) may be administered for fever or headache only.
- Central nervous system (CNS) depressants, muscle relaxants, and antihistamines, which have been given regularly (unchanged dose [±10%] and dosing frequency) during the pre- and/or post-operative period, and will be given at the same dose and dosing frequency during the study period, will be permitted; otherwise these medications will be prohibited from 4 hours prior to stopping postoperative opioid pain medication until the completion of study observations.
- Diphenhydramine can be given for nausea/vomiting, pruritus, or as a sleep aid.
- Antidepressant therapy (excluding MAOIs) will remain stable (unchanged dose [±10%] and dosing regimen) throughout the study.

Constipation is the most common opioid AE. Laxatives should be used at the Investigator's, or designee's, discretion during treatment with study drug and recorded as a concomitant medication.

Nausea and vomiting are common opioid-induced AEs. It is expected that some of the subjects will need to be administered an antiemetic. Any antiemetic used during treatment with study drug should be recorded as a concomitant medication.

The use of investigational drugs other than oxymorphone is prohibited.

## 9.4. Prohibited Medications

- Preoperative opioids administered for a period of more than 72 hours in duration
- Any investigational drugs other than oxymorphone HCl immediate-release oral liquid
- Oxycodone or oxymorphone within 48 hours prior to study start
- Cough syrup containing an opioid
- MAOIs

## 9.5. Rescue Medication

Subjects entering the study with non-oxycodone- or non-oxymorphone-containing, opioid-based PCA rescue medication will be allowed to continue to utilize their PCA rescue for as long as the device remains in place per institutional SOC. Oral rescue medication will also be allowed during the study, but also must NOT contain oxycodone or oxymorphone. Following completion of the study, subjects will be prescribed a rescue medication at the discretion of the Investigator, or designee, for BTP.

## 9.6. Precautions and Warnings

The Investigator/study staff should be familiar with the Investigator's Brochure and the OPANA Prescribing Information prior to starting this study. If significant toxicity is seen, dosing in that individual must be stopped and the Sponsor informed immediately.

Adverse experiences should be treated in accordance with standard medical practice. During the course of the study, the Sponsor and the Investigator will review the overall safety and tolerability of all study treatments. The IDMC will also review all safety data as outlined in the protocol.

AEs in the oxymorphone clinical program are presented in the Investigator's Brochure and in the OPANA Prescribing Information. Oxymorphone, like all strong opioids, has the potential to cause significant adverse experiences, including: constipation, respiratory depression, increased intracranial pressure, postural hypotension, histamine release and bronchospasm, depression of the CNS, and spasm of the sphincter of Oddi.

Due to the potential for additive CNS and respiratory depression, all opioid analgesics should be used with caution in subjects who are concurrently receiving other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, or alcohol.

Any dose of oxymorphone HCl immediate-release oral liquid should not be taken for at least 2 hours following any opioid-based rescue dose.

## 9.7. Treatment Compliance

Discrepancies between the number of doses taken as recorded in the eCRF and the amount of returned drug will be recorded in the drug accountability log. Qualified study personnel will perform a qualitative review for compliance by reviewing the eCRF against returned study drug and discussing any variations from the protocol defined dosing schedule with study personnel. Compliance and accountability will be recorded on the Drug Accountability Forms that will be provided to each clinical site. Any suspicion of diversion should be carefully investigated by the Sponsor, as outlined in the Clinical Supplies Guidance Document and the Monitoring Plan, and may be required to be reported as an SAE.

## 9.8. Randomization and Blinding

This is an open-label, multicenter study that does not require randomization. No blinding will be performed.

# 10. STUDY DRUG MATERIALS AND MANAGEMENT

## 10.1. Study Drug

The study drug EN3319 is oxymorphone HCl prepared as an oral IR solution. EN3319 is light sensitive.

## 10.2. Study Drug Packaging and Labeling

EN3319, oxymorphone HCl immediate-release oral liquid 1 mg/mL will be provided in 30 mL bottles. Each bottle will be labeled with a single 2-panel label. Panel 1 of the labels will include at a minimum the following information (as appropriate): protocol number, study drug name, strength, dosage form, Class II designation, quantity, lot number, an area to write in the subject number, directions for use, appropriate storage instructions, Sponsor's identification and address, and appropriate cautionary statements. Panel 2, which will be detached at time of dispensation to be placed in the source documents, will contain protocol number, study drug name, strength, dosage form, quantity, and lot number.

## 10.3. Study Drug Storage

Medication will be stored in a locked facility with restricted access. This may be a locked cabinet or room for which the number of keys is limited and in compliance with standards of the Drug Enforcement Administration (DEA) for Schedule II narcotics. Chain of custody of the investigational product will be followed in accordance with the individual site's standard procedures, which will be documented by the site and provided to the sponsor. Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. In addition, oxymorphone HCl immediate-release oral liquid is light sensitive and, therefore, must be stored in its original cardboard carton.

## 10.4. Study Drug Preparation

The study drug will be provided in 30 mL amber polyethylene terephthalate (PET) bottles packaged in a cardboard carton. Due to light sensitivity, the study drug bottles must be maintained within the original cardboard carton other than during time of preparation in the pharmacy. The study drug should be dispensed with an oral syringe (1 mL, 5 mL, or 10 mL) appropriate for the prescribed dose. Refer to the Clinical Supplies Guidance Document within the Pharmacy Binder for specific instructions for determining and dispensing the appropriate dose. The concentration of the study drug (oxymorphone HCl immediate-release oral liquid) is 1 mg/mL. Any study drug drawn into a syringe should remain protected from light in an envelope or sleeve immediately following preparation until just prior to administration. Any study drug drawn into a syringe for administration must be dispensed within 48 hours or returned to pharmacy.

## 10.5. Administration

The study drug will be administered orally based on body weight using dosing syringes provided by the Sponsor. There is no restriction on food consumption around the time of dosing; a child may opt to take the study drug with water.

**The study drug must NOT be taken less than 2 hours after a rescue dose has been administered.**

## 10.6. Study Drug Accountability

The Principal Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for and that dispensed study drug is recorded both in the eCRF and in the appropriate study drug accountability log. Each bottle of study drug will be allocated for use for a single patient. The pharmacy will handle accountability at the bottle level and Investigator staff will need to account for the number of syringes received from the pharmacy and the number of syringes administered to the subject. The Investigator, or designee, will verify drug accountability with study personnel (see section 9.7 for details on treatment compliance).

The Principal Investigator will not supply the study drug to any person except those named as sub-investigators, other designated staff, and subjects in this study and will not dispense the study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

Chain of custody of the study drug will be followed in accordance with the individual site's standard procedures, which will be documented by the site.

## 10.7. Study Drug Handling and Disposal

The Principal Investigator will retain and store all bottles until inventoried by the Sponsor or Sponsor's representative. The Principal Investigator will return all unused study drug in the original bottles, including empty and partially empty bottles, and with appropriate documentation as specified by the Sponsor per the Clinical Supplies Guidance Document, to the Sponsor's return vendor.

# 11. ASSESSMENT OF EFFECTIVENESS

## 11.1. Pain Intensity

Subjects in the 6 to ≤12 year old group (Group A) will receive training on completing the self-report pain assessments; completion of the training will be documented in the source record. Each subject (ages 6 to ≤12 years) will assess his/her pain intensity at the designated times during the study (see Table 3 and Table 4) using the FPS-R. The Investigator, or designee will conduct the pain assessments at the designated times during the study (see Table 3 and Table 4) for subjects in age group 2 to <6 years (Group B) using the FLACC; all pain scores in age group B will be recorded by the Investigator, or designee.

Current pain intensity will be collected at the following times during the study:

- Single-Dose Phase: Immediately prior to dosing; 15 minutes, 30 minutes, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post dose (or upon ET) or just prior to administration of rescue medication. Upon rescue, any remaining scheduled pain assessments will be discontinued.
- Multiple-Dose Phase: Immediately prior to first dosing; 0.5, 1, 1.5, and 2 hrs post-Dose 1, and immediately prior to all remaining Doses administered up through 48hrs after administration of the initial dose of study drug or until ET or just prior to administration of rescue medication. Upon rescue, any remaining scheduled pain assessments will be discontinued.

Selection of pain scales in children is complex because there is no single instrument suitable for all ages. While the use of a visual analog scale (VAS) is commonly employed in adults for the assessment of pain, the use of a VAS in young children is complicated by communication barriers. The selection of data collection instruments in this study is based on those with the widest acceptability and best evidence of psychometric properties regarding the appropriateness in the target population. The Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (Ped-IMMPACT) recommended core outcome domains (including pain intensity) to be considered in clinical trials for acute and recurrent/chronic pain, which included the FPS-R and the Numerical Rating Scale (PI-NRS).(15)

### 11.1.1. Faces Pain Scale - Revised (FPS-R)

The FPS-R (see Appendix C) is a validated, self-report measure used to assess pain intensity in children.(16) The revision from the original Faces Pain Scale incorporates several key changes, including adaptation to a common metric (0 to 10), and the removal of the "smiling face" and "tears" anchors to avoid the confounding of affect and pain intensity, and other complicating effects of these anchors.(17) The FPS-R consists of 6 faces, visually representing increasing changes in pain intensity bounded on the left by "no pain" and on the right by "very much pain," as seen in Appendix C. The FPS-R has demonstrated test-retest reliability, content validity, responsiveness and feasibility.(18) Compared to several other measures, the FPS-R appears to be the most psychometrically sound measure in school-age children. It is recommended for self-report of acute pain intensity in clinical trials in children and adolescents, 4 to 12 years of age and will be used in subjects aged 6 to ≤12 years in the current study.(15)

### 11.1.2. Face, Legs, Activity, Cry, Consolability (FLACC)

The Ped-IMMPACT consensus concluded that self-reported measures of pain intensity, alone, are not sufficiently valid for children <3 years of age.(15) There is wide variability in young children's ability to use self-report measures especially between the ages of 3 and 7 years of age, so it would be reasonable to use a behavioral observational measure as an outcome measure in this age group.(18) The FLACC scale (see Appendix D) is a well-established observational behavioral measure that is based on a 5-item scale that raters use to score each of 5 categories of pain response, namely, (F) Face; (L) Legs; (A) Activity; (C) Cry; and (C) Consolability, which are scored from 0 to 2 (see Appendix D).(19) There are extensive reliability and validity data on the FLACC, including pre-verbal children.(19,20) The FLACC uses items similar to other well-established instruments, but with a more easily understood 0 to 10 scale.(21) It has a low users' burden and excellent inter-rater reliability. The FLACC has demonstrated moderate concurrent validity with FACES and good concurrent validity with VAS. The Ped-IMMPACT consensus recommended the FLACC as an observational measure of acute pain intensity in children 1 year and above.(15) Moreover, a Task Force approved by the American Society for Pain Management and Nursing Board of Directors recommended the use of the FLACC in subjects aged 2 months to 7 years for post anesthesia care, in the intensive care unit, in acute care settings, for surgical pain, and for acute pain.(19-23) In the current study, the FLACC will be used in all subjects aged 2 to <6 years for pain assessment, encompassing all subjects in age group B.

### 11.1.3. Summary

In summary, subject reported outcome tools that will be used in this study are:

1. FPS-R for subjects 6 years to ≤12 years
2. FLACC for subjects 2 to <6 years

# 12. ASSESSMENT OF SAFETY

## 12.1. Adverse Events (AEs)

Any subject who experiences an AE (defined in section 12.1.2) after entering the study (following execution of informed consent/assent) will have the condition recorded as an AE and will require follow-up until all AEs are resolved, or through 14 days after the last dose of study drug if the AE remains unresolved. If available at the time of follow-up, a probable diagnosis should be obtained, and a relationship to study treatment will be determined.

### 12.1.1. Monitoring

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related including any new signs, symptoms, injury or illness, and increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to signing informed consent/assent will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study drug; relationship will be classified as not related, unlikely related, possibly related, or probably related (see section 12.1.2 for definitions). Any lab result obtained as part of SOC will be reviewed by the Investigator; any clinically meaningful lab value abnormality will be recorded as an AE at the discretion of the Investigator.

All AEs will be collected by the Investigator through 14 days after the last dose of study drug; this includes any AEs that are ongoing at the completion/termination of the study, and any AEs that start after the last dose of study drug, but before the 14-day post-study period.

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study or within 14 days following cessation of the study treatment or premature discontinuation from the study whether or not related to the investigational product, must be reported via facsimile or telephone within 24 hours of first being advised of the SAE. Follow-up information collected for any initial report of an SAE must be reported to the Sponsor within 24 hours of receipt by the Investigator. In the event discussion is necessary regarding treatment of the subject, the Investigator should call the Medical Monitor. SAEs will be followed until resolution, stabilization or until follow-up is no longer possible.

### 12.1.2. Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, electrocardiogram [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 drug.

A treatment-emergent adverse event (TEAE) is any condition that was not present prior to treatment with study drug, but appeared following treatment, was present at treatment initiation, but worsened during treatment, or was present at treatment initiation, but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including observed or volunteered problems, complaints, signs or symptoms, must be captured in source documents and entered into the AE page of the eCRF, regardless of whether associated with the use of study drug. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). To avoid colloquial expressions, the AE should be recorded in standard medical terminology.

The Investigator will evaluate each AE for duration, intensity, and relationship to (association with) study drug, record the action taken, and any treatment given. Recurrent symptoms of a chronic pre-existing condition are not considered AEs unless they occur in a worse or unexpected pattern during study drug administration.

**Intensity of AEs**

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

**Mild AEs** are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.

**Moderate AEs** introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

**Severe AEs** interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of the AE changes more frequently than once daily, the maximum intensity for the event is recorded. If the intensity category changes after a number of days, then these sub-events or changes are recorded separately (ie, having distinct onset and stop dates).

**Relationship to Study Drug**

The degree of "relatedness" of the AE to the study drug may be described using the following scale:

**Not related** indicates that the AE is definitely not related to the study drug.

**Unlikely related** indicates that there are other, more likely causes and study drug is not suspected as a cause.

**Possibly related** indicates that a direct cause and effect relationship between study drug and the AE has not been demonstrated but there is a reasonable possibility that the event was caused by the study drug.

**Probably related** indicates that there probably is a direct cause and effect relationship between the AE and the study drug.

It is the Sponsor's policy to consider "Probable" and "Possible" causality assessments as positive causality. It is the Sponsor's policy to consider "Not" and "Unlikely" causality assessments as negative causality.

**Serious Adverse Events (SAEs)**

An SAE is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE unless it is due to a worsening of a condition that existed prior to treatment)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study drug regardless of time to diagnosis)
- Is considered an important medical event

Life-threatening events are defined as events that place the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

In the event of an SAE that is ongoing at EOS, any concomitant medications given for that AE will be recorded until:

- The SAE resolves
- The SAE resolves to a point beyond which, in the opinion of the Investigator, no further resolution is possible
- The subject dies
- The subject is lost to follow-up

### 12.1.3. Recording Adverse Events

AEs will be recorded in source documents and entered into the eCRF and must indicate clearly the event being assessed.

### 12.1.4. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study or within 30 days following cessation of the study treatment or premature discontinuation from the study whether or not related to the investigational product, must be reported via facsimile or telephone within 24 hours of first being advised of the SAE. Follow-up information collected for any initial report of an SAE must be reported to the sponsor within 24 hours of receipt by the Investigator. In the event discussion is necessary regarding treatment of the subject, the Investigator should call the Medical Monitor.

**All SAEs should be submitted to Endo Pharmaceuticals,** [redacted]

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to the FDA. If so, the Sponsor (or the Sponsor's representative) will report the event to the FDA. The Investigator will transmit a written report of the circumstances and outcome to the Sponsor as soon as he/she is made aware of the circumstances. The Investigator will report all SAEs to the IRB.

### 12.1.5. Overdose/Misuse/Abuse

#### 12.1.5.1. Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Study drug compliance (see section 9.7) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study drug eCRF.

All AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 12.1.4, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

#### 12.1.5.2. Misuse/Abuse

Adverse events associated with misuse or abuse will be appropriately reported as AEs or SAEs, and monitored per section 12.

### 12.1.6. Pregnancy

Any uncomplicated pregnancy that occurs during this clinical study will be **reported for tracking purposes only**. All pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred within 14 days or 5 half-lives (whichever is longer) after exposure to study drug need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. Pregnancies that occur in the partner of a treated subject (ie, female partner of male subject) also need to be reported. The Investigator should report all pregnancies within 24 hours using the Initial

Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 12.1.4. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should immediately notify the Investigator of any pregnancies.

A subject who becomes pregnant must be withdrawn from the study. Should a subject discontinue treatment due to pregnancy, alternative treatment (if available) should be arranged according to standard of care, as determined by the Investigator.

### 12.1.7. AEs/SAEs Experienced by Non-Subjects Exposed to Study Drug

Non-subjects exposed to study drug are persons who are not enrolled study participants, but have been exposed to study drug, including instances of diversion of study drug. All such AEs/SAEs occurring in association with such exposure will be recorded on the Endo Pharmaceuticals Inc. Clinical Trial Report Form for SAEs/AEs of special interest. All events occurring in non-subjects exposed to study drug will be processed within the same SAE reporting timelines as described in section 12.1.4.

## 12.2. Assessments of Respiratory Function

In children, a rare, but well known, side effect of all opioids is respiratory depression. In this study, all subjects will be monitored for the appearance of the following respiratory symptoms not only at the time of scheduled assessments, but as needed throughout the study duration through the aid of respiratory monitoring equipment:

- Oxygen saturation and heart rate will be monitored using a pulse oximeter. Oxygen saturation and heart rate will be recorded at the time of vital sign assessment. If oxygen saturation decreases to ≤90%, the event will be recorded as an AE at the discretion of the Investigator. If the heart rate decreases to ≤50% of the expected norm for age, the event will be recorded as an AE at the discretion of the Investigator. NB. Bradycardia for age may be indicative of hypoxia in children; tachycardia for age may be indicative of inadequate analgesia in children.
- If the respiration rate decreases to ≤50% of the expected norm for age, the event will be recorded as an AE of respiratory depression at the discretion of the Investigator.

- Apnea monitoring may be conducted using direct observation and counting, impedance pneumography, or capnography, based on practice at the respective institution. Apnea may be defined as a cessation of respiration for a period of ≥15 seconds. Episodes of apnea will be recorded as an AE at the discretion of the Investigator (or an SAE per respective definition in the safety section of the protocol [see section 12.1.2]).
- Any administration of an opioid antagonist (eg, naloxone) to treat respiratory depression will be recorded as an SAE per definition in section 12.1.2.

## 12.3. Assessments of Neurological Function

Because opioid drugs may produce adverse effects on the CNS, subjects will be monitored for the appearance of CNS symptoms not only at the time of scheduled vital sign assessments, but as needed throughout the study duration. Level of sedation will be assessed according to SOC at each Institution. Examples include the Ramsay Sedation Scale and the University of Michigan Sedation Scale (see Appendix A). If sedation is determined to be clinically significant, it should be recorded as an AE.

## 12.4. Pharmacokinetic Assessments

### 12.4.1. Blood Sample Collections

Blood collection may be performed using an existing line (arterial or venous noted on eCRF) at the start of the study (the use of EMLA® at the insertion site is permitted). If access for blood sampling is lost, a new line will only be established as part of the clinical management of the subject; otherwise, the subject's participation in the study will be early terminated. Procedures for blood draws should follow institutional SOC. All catheter lines should be appropriately flushed per institutional SOC prior to each blood draws. The discard volume must be restricted to 0.5 mL for tubing with a dead space of ≤0.5 mL and up to 1.0 mL for tubing with a dead space >0.5 mL. Calculation and evaluation of the following pharmacokinetic variables will be performed for all subjects participating in study: (Single-Dose Phase: $C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-24}$, $AUC_{0-\infty}$, $\lambda_n$, $t_{1/2}$, CL/F [clearance], and V/F [volume of distribution]; Multiple-Dose Phase: $C_{max}$, $T_{max}$, $AUC_{0-t}$, $\lambda_n$, $t_{1/2}$, and CL/F; see Table 7 for definitions). Blood samples (0.5 mL) will be obtained and placed into 2.0-mL dipotassium ethylenediaminetetraacetic acid ($K_2$EDTA) tubes at each blood collection time point for both phases (see Table 3 and Table 4). The samples will be obtained at the following times:

- Single-Dose Phase: Serial blood will be collected at time 0 (Baseline), at 15 and 30 minutes, and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post dose.
- Multiple-Dose Phase: Serial blood will be collected at: 0 (Baseline), at 0.5, 1, 1.5, and 2 hrs post-Dose 1, immediately prior to Doses 2, 3, 4, 5, 6, 7, and at 0.5, 1, 1.5, and 2 hrs post Dose 7.

**Table 7: Pharmacokinetic Variables**

| Variable | Definition |
|---|---|
| $C_{max}$ | Maximum plasma concentration; the highest concentration observed during a dosage interval |
| $T_{max}$ | The time at which $C_{max}$ was observed |
| $AUC_{0-t}$ | Area under the concentration versus time curve from time 0 to the last measured concentration ($C_t$) in the dosing interval, calculated by linear trapezoidal rule |
| $AUC_{0-\infty}$ | Area under the concentration versus time curve from time 0 to infinity, calculated as $AUC_{0-t} + C_t/\lambda_n$ |
| $AUC_{0-24}$ | Area under the concentration versus time curve from time 0 to 24 hours (end of dosing interval) |
| $\lambda_n$ | Terminal rate constant, calculated as the negative slope of the ln-linear portion of the terminal plasma concentration-time curve |
| $t_{½}$ | Terminal half-life, calculated as $\lambda_n/(\ln 2)$ |
| CL/F | Apparent oral clearance, calculated as Dose/$AUC_{0-inf}$ for single dose or Dose/AUC(0-τ) for steady-state |
| V/F | Apparent volume of distribution, calculated as Dose/($AUC_{0-inf}$ * $\lambda_n$) |

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at 1,500 × g. The plasma fraction will be withdrawn by pipette and placed into a polypropylene freezing tube in 1 aliquot for subjects with body weights 3 to 6 kg and in 2 approximately equal aliquots for subjects with body weights greater than 6 kg. All sample collection and freezing tubes will be clearly labeled in a manner that identifies the subject and the collection time. Labels will be fixed to the freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be placed into a freezer at –70°C or below within 1 hour after collection. The additional blood draws for the purposes of pharmacokinetic assessment in this study do not pose more than a minor risk to the subjects.

Total blood volume that will be collected for research purposes, including any discard volume, will be based on the age and weight criteria in section 12.4.2.

### 12.4.2. Blood Volumes

The total blood volume that will be collected for the study purposes will be limited to 3% (rounded to the nearest mL) of the total blood volume of the study subject based on Investigator feedback and values reviewed in Aladangady et al. and Howie).(24,25) This volume limitation includes discard volume, which should be limited to between 0.5mL to 1.0 mL depending upon the dead space of the blood collection tubing (see Appendix E footnotes). The blood volume of the study population is estimated to be 75 to 80 mL/kg.(25) The minimum age limit for participation in the study will be 2 years, which according to recent Center for Disease Control pediatric growth charts, has a minimum weight of approximately 10 kg (approximate lowest fifth

percentile weight for females).(26) Refer to Appendix E for required sample volumes for pharmacokinetic analyses.

### 12.4.3. Sample Storage and Shipment

All plasma samples will be stored frozen (at –70°C or below) until they are shipped to the analytical facility. Prior to shipping, the samples will be packed into thermal insulated containers and packed in sufficient dry ice to assure they remain frozen, and are protected from breakage during shipment. Samples will be shipped by overnight via priority courier. The samples will be divided into 2 shipments for subject with 2 aliquots, each containing 1 aliquot of plasma for each time point. The samples will be sent in 1 shipment for subjects with 1 aliquot (ie, 1 aliquot of plasma for each time point). After receipt of verification that the first shipment was received by the analytical facility, the second shipment (plasma) will be processed, if applicable.

Samples will be shipped in batches by age group and treatment cohort, for example, when the 0.05 mg/kg treatment cohort of 6 to ≤12 year olds has completed the Single-Dose Phase of the study, samples from all 6 subjects will be shipped from all sites (actual samples in 2 aliquots) and analyzed as a batch. For weeks containing a holiday, sites will contact the Sponsor for shipping instructions. The shipping address and contact information will be provided in a separate document.

### 12.4.4. Analytical Methodology

A validated microvolume liquid chromatography dual mass spectrometry (LC-MS/MS) analytical method will be used for the determination of the concentrations of oxymorphone and 6-OH-oxymorphone in the plasma samples. The microvolume assay will require 50 µL of plasma per sample. Details of the method validation and sample analysis will be included with the bioanalytical report (in the final clinical study report).

## 12.5. Clinical Laboratory Tests

Blood samples will be collected from subjects prior to dosing (baseline) and post dosing. Blood samples for baseline clinical laboratory tests may be collected at any time within 21 days prior to surgery. See sections 12.5.3 and 12.5.4 for the list of analytes to be included. Clinical labs drawn as part of the SOC (including the pre-operative and intraoperative period) will be acceptable for study purposes provided they are taken prior to first surgical incision and assessed by the Investigator prior to the first dose of study drug administration. Blood samples after dosing will be taken at 24 and 48 hours (or upon ET) post first dose in the Single- and Multiple-Dose Phases, respectively, and evaluated by the Investigator for clinical significance. Where possible, results from clinical laboratory tests performed as part of the SOC will be used for study purposes. A separate blood draw for the clinical laboratory test portion of this protocol will occur only if the clinical laboratory tests as part of the SOC will not be available to coincide with approximately the time scheduled by protocol or if clinical laboratory testing is not a part of SOC. All baseline test results must be available for review by the Investigator prior to first administration of study drug. Clinical laboratory test analytes listed in sections 12.5.3 and 12.5.4 will be entered into the eCRF.

### 12.5.1. Pregnancy Tests

Serum/urine pregnancy test ([serum] βhCG at Screening; subsequently, [urine] βhCG or per institution's SOC) will be completed as per Table 3 and Table 4.

### 12.5.2. Urine Drug Screen

Qualitative urine drug screen panel will include the following minimum set of analytes:

- Opioids, oxycodone, benzodiazepines, marijuana, cocaine, amphetamine, tricyclic antidepressants, and barbiturates

### 12.5.3. Chemistry

Chemistry panels may include analysis of the following analytes:

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- bilirubin (total)
- blood urea nitrogen
- calcium
- creatinine
- glucose
- lactic dehydrogenase (LDH)
- inorganic phosphorus
- sodium
- potassium
- chloride
- total Carbon dioxide ($CO_2$)
- total protein
- albumin

### 12.5.4. Hematology

Hematology panels may include analysis of:

- hemoglobin
- hematocrit
- red blood cell count
- white blood cell count with differential
- platelet count

## 12.6. Vital Signs

Vital signs (respiratory rate, body temperature, heart rate, and blood pressure) will be taken at the screening visit, pre- or intraoperatively, at baseline, and at each specified time point during the Single- and Multiple-Dose Phases (see Table 3 and Table 4). Blood pressure should always be taken in the same arm and when the subject has been supine for 5 minutes.

## 12.7. Physical Examination

A physical examination, including height and weight, will be conducted at Screening; a physical examination, excluding height and weight, will be conducted at the EOS/ET evaluation or early termination.

# 13. STATISTICS

## 13.1. Sample Size Consideration

The sample size of 6 subjects in each age group (A and B), treatment cohort, and study phase was selected to describe the safety, effectiveness and pharmacokinetic properties of the study drug in children aged 2 to ≤12 years. With up to 3 treatment cohorts and 6 subjects per treatment cohort, up to 18 subjects will be enrolled in each study phase. Assuming the %CVs for clearance and volume of distribution are both as high as 72% for pediatric subjects, then with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% confidence interval (CI) for both clearance and volume of distribution is (0.71*X, 1.40*X), where X represents the geometric mean of either clearance or volume of distribution, respectively. In other words, with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% CIs are within 60% and 140% of the point estimates for the geometric mean estimates of both clearance and volume of distribution for oxymorphone in all age groups.

## 13.2. Analysis Populations

The safety population will include all subjects who take at least 1 dose of study drug. All safety analyses will be performed using this population. The effectiveness population will include all subjects who take at least 1 dose of study drug and who have completed at least 1 post dose pain intensity assessment. All effectiveness analyses will be performed using this population. All subjects who receive study drug as planned and have sufficient plasma concentration data to facilitate the calculation of pharmacokinetic variables will be evaluable for pharmacokinetic analysis. Final subject evaluability will be determined prior to locking the database.

## 13.3. Statistical Methods

All statistical analyses will be performed using the current version of SAS® (SAS Institute, Cary, NC). All CIs will be 2-sided.

### 13.3.1. Subject Disposition

The number of subjects in each analysis population will be presented. The numbers and percentages of subjects who complete and discontinue from the study will be summarized by age group treatment cohort and study phase for all enrolled subjects. For subjects who discontinue from the study, the reason for discontinuation will be tabulated.

### 13.3.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics including age, sex, race, height, weight, and body mass index (BMI) will be summarized by age group, treatment cohort, and study phase using appropriate descriptive statistics.

### 13.3.3. Prior and Concomitant Medications

Medications administered prior to and concomitantly with study treatment will be tabulated for the safety population. These medications will be coded using the World Health Organization (WHO) drug dictionary.

## 13.4. Effectiveness Analysis

The pain intensity difference (PID) at each post dose time point will be calculated as the pain intensity score at baseline minus the current pain intensity score at each post dose time point. Summary statistics of the pain intensity scores at each time point and PID at each post dose time point will be presented by pain assessment instrument, age group, treatment cohort, and study phase. For each subject, the PID over time will be transformed into a summary measure by calculating area under curve of PID ($AUC_E$) using the trapezoidal formula, adjusted for study duration. All time points before the first rescue medication will be used to calculate $AUC_E$. $AUC_E$ will be analyzed by a heterogeneous analysis of variance (ANOVA) model with fixed effects for age group, treatment cohort, and the interaction of age group by treatment cohort for each study phase. The potential heterogeneity between the age-specific measurements will be assessed using a dummy variable for the difference in the statistical model. Least squared means of $AUC_E$ for each combination of age groups and treatment cohorts and the corresponding 2-sided 95% CIs will be calculated based on the model.

Numbers and percentages of subjects who need rescue medication will be calculated by age group, treatment cohort, and study phase.

## 13.5. Safety and Tolerability Analysis

Assessment of safety and tolerability will be based on the incidence of AEs, AEs resulting in discontinuation, and SAEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will be provided showing the number and percentage of subjects who experience at least 1 AE. These summaries will be presented by system organ class and preferred term. The occurrence of AEs will also be tabulated by severity. SAEs and AEs resulting in discontinuation will be summarized separately.

Assessment of safety and tolerability will also be based on pharmacokinetic analysis (described in section 13.6) clinical laboratory results, vital sign measurements, respiratory and neurological assessments, and other safety variables, which will be summarized by age group, treatment cohort, and study phase for each time point using appropriate descriptive statistics.

## 13.6. Pharmacokinetic Analysis

Pharmacokinetic variables (Single-Dose Phase: $C_{max,}$ $T_{max}$, $C_{12}$, $AUC_{0-t}$, $AUC_{0-24}$, $AUC_{0-\infty}$, $\lambda_n$, $t_{1/2}$, CL/F, and V/F; Multiple-Dose Phase: $C_{max,}$ $T_{max}$, $AUC_{0-t}$, $\lambda_n$, $t_{1/2}$, CL/F, and V/F) will be estimated from the plasma concentration data using standard non-compartmental methods. Actual sample times, rather than scheduled times, will be used in the computation of pharmacokinetic parameters. Plasma concentrations below limit of quantification (BLQ) will be set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations will be set to missing. For the computation of pharmacokinetic variables, the BLQ concentrations prior to the first measurable concentration

will be set to zero and other BLQ concentrations will be set to missing. The definitions and methods of determination for each pharmacokinetic variable are summarized in Table 7.

Pharmacokinetic variables (CL/F, V/F, $\lambda_n$, and $t_{1/2}$, and dose normalized $C_{max}$, $C_{12}$, $AUC_{0-24}$, $AUC_{0-t}$, $AUC_{0-\infty}$) will be summarized by age group using N, mean, standard deviation (SD), geometric mean, CV, minimum, median, and maximum following dosing in the Single-Dose Phase and the first and third doses in the Multiple-Dose Phase. In addition, a 2-sided 95% CI will be constructed for both CL/F and V/F. $T_{max}$ will be summarized by age group using median, minimum, and maximum.

## 13.7. Handling of Missing Data

All observed demographic, effectiveness and safety data will be used in the analyses. No data imputation will be performed other than for the pharmacokinetic plasma concentrations described in section 13.6.

## 13.8. Protocol Deviations

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments. Prior to data base lock, an evaluation of subjects with protocol deviations will be performed to assess the appropriateness of their inclusion in the analysis.

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 14.1. Study Monitoring

The study will be initiated by the monitor, or designee, during an on-site visit after all required documents have been processed. Qualified clinical monitors will perform on-site monitoring visits as frequently as is deemed necessary.

During the site visit, the monitor will compare the data entered into the eCRF with the source documents. The first visit after initiation will usually be made as soon as possible after enrollment has been started. At these visits, the monitor will compare the data entered onto the eCRFs with source documents. Source documents include but are not limited to original documents, data and records such as hospital/ medical records, clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc.). At a minimum, all data required to be collected by the protocol shall be recorded in source documents first and then entered into the eCRF (unless otherwise specified). The monitor will review and verify: the diagnosis, medical history, inclusion/exclusion criteria, physical exams and vital signs, efficacy evaluations; AEs and SAEs; concomitant medications and procedures; and the use of study drug. Specific items required as source documents will be reviewed with the Investigator prior to the study.

In addition, the monitor will verify that standards of Good Clinical Practice (GCP) were followed. This includes, but is not limited to: completion of regulatory documents (eg, FDA Form 1572, financial disclosure, IRB/ IEC approvals, submitting safety/progress reports, etc.) ensuring Informed Consent was adequately performed and documented, that study drug dispensation and accountability was handled properly, SAEs were reported to the Sponsor and IRB/IEC in a timely manner, that the protocol was followed and that the rights and welfare of subjects were protected.

Findings from the review of case report forms (CRFs)/eCRFs, source documents, and study conduct will be discussed with the Investigator. The dates of the monitoring visits will be recorded by the monitor in a sign-in log to be kept at the site. The Sponsor expects that, during monitoring visits, the study coordinator and Investigator will be available, the source documentation will be available, and a suitable environment will be provided for review of study related documents.

## 14.2. Audits and Inspections

The Sponsor, or designee, FDA and any other regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with Federal regulations. The Investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection. An audit may also be conducted by a representative of the Sponsor.

## 14.3. Institutional Review Board (IRB)

The Principal Investigator must have written and dated approval/favorable opinion from the IRB for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The Principal Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The Principal Investigator will provide the IRB with reports, updates, and other information (eg, Safety Updates, Amendments) as required by regulations.

Protocol amendments will not be implemented by the Investigator without prior written approval by the Sponsor and IRB, unless required to remove an immediate hazard from a subject. In such case, the protocol deviation will be immediately reported to both Sponsor and IRB by the Principal Investigator.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of study-related data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative.

Data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor, or designee. Data will be processed and analyzed following procedures defined by the Sponsor, or designee.

The study may be audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), GCP E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be issued by the Sponsor, or designee, listing all audit activities performed during the clinical study.

# 16. ETHICS

## 16.1. Ethics Review

It is the Investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate IRB/IEC. The IRB/IEC must also review and approve the site's informed consent form (ICF) and any other written information provided to the subject, prior to the enrollment of subjects and any advertisement that will be used for subject recruitment. The Investigator or designee must forward to the Sponsor copies of the IRB/IEC approval and the approved informed consent materials, which the Sponsor must receive prior to the start of the study.

## 16.2. Ethical Conduct of the Study

This study will be conducted in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the Sponsor representatives and/or regulatory authority representatives at any time. In accordance with any applicable local regulations, the Sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiating the study in that country or jurisdiction.

### 16.2.1. Investigator Obligations

The Investigator should have adequate time to conduct the trial properly and should have an adequate number of qualified staff to assist with the conduct the trial. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

The Investigator and/or a qualified sub-investigator shall be responsible for the subject's medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator, or designee, will report all AEs as required by the protocol (section 12.1). The Investigator, or designee, will inform study subjects of new information regarding the study drug as it becomes available.

## 16.3. Written Informed Consent

### 16.3.1. General

Each qualified subject's parent(s)/legal guardian(s) must voluntarily sign and date the informed consent (and other locally required documents) after the nature of the study has been fully explained. The consent form must be signed prior to performance of any study-related activity. The parent(s)/legal guardian(s) will be given a copy of the signed/dated consent/assent form and the consent/assent process shall be documented in the source documents. The consent form that is used must be approved by both the reviewing IRB and by the Sponsor. An assent from minors must be obtained in accordance with IRB requirements. The consent form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorized representatives of the

Sponsor, a regulatory authority or an IRB/IEC may require direct access to source data relevant to the study, including the subjects' medical history.

### 16.3.2. Assent for Pediatric Subjects

Where indicated by local law, IRB determination, or institutional practice, study participants should assent to enroll in the study prior to any study procedures being conducted. In some cases, pediatric subjects will be legally unable to provide informed consent/assent. Therefore, pediatric subjects participating in this study will be dependent on a parent(s)/legal guardian(s) to assume responsibility for their participation. Pediatric subjects participating in this study must be informed to the fullest extent possible about the study in language and terms they are able to understand. Participants of appropriate intellectual maturity should personally sign and date a written assent form. In all cases, participants should be made aware of their rights to decline participation or to withdraw from the study at any time. Although a participant's request to withdraw from the study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent(s) or legal guardian(s), the welfare of the pediatric subject would be jeopardized by his or her failing to participate in the study. In such a situation, continued parental or legal guardian(s) consent will be sufficient to allow continued participation in the study. Emancipated or mature minors (as defined by local laws) may be capable of giving autonomous consent.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Data Collection

During each subject's clinic visit, the Investigator, sub-investigator(s) or study coordinator participating in the study will record progress notes to document all data required by the protocol.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in the progress notes as described above. For transmission to the Sponsor, de-identified information from the study progress notes and other source documents will be promptly entered into the eCRFs.

Any changes to information in the study progress notes, or other source documents must be initialed and dated on the date the change is made by a clinician authorized to make the change. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician. All data discrepancies that are generated by system edit checks or by manual review of data will be handled via the query generation and resolution aspect of the electronic data capture (EDC) system.

## 17.2. Study Documentation

Throughout the conduct of this study, all required data will be entered into the eCRFs supplied by Endo, or its designee, for each subject. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Endo in the eCRFs and in all required reports, and as such will be asked to sign and date the appropriate eCRF page(s), as verifying and taking responsibility for the data collected. This also applies to entries for those subjects who fail to complete the study (even during an enrollment screening period if an eCRF was initiated). If a subject withdraws from the study, the reason must be noted on the eCRF.

Data entered into the eCRFs should be consistent with source documents. Any change or correction to an eCRF will be captured in the EDC system audit trail.

Upon study completion, archival eCRFs in portable document format (PDF) will be created from the EDC system for record retention at the sites and Endo will archive these PDFs under secure conditions for the defined periods.

## 17.3. Inspection of Records

Periodically the Sponsor or Sponsor representative will review the Investigator study file and the study data to verify compliance with applicable regulations and the protocol, and to verify the accuracy of the data.

## 17.4. Study Files and Record Retention

The Investigator must maintain adequate and accurate records as specified in Essential Documents for the Conduct of a Clinical Trial (E6, Section 8 of the ICH Guideline for GCP) to enable the conduct of the study to be fully documented and the study data to subsequently verified. These documents should be classified into 2 separate categories: (1) Investigator's study file and (2) subject clinical source documents.

Essential documents should be retained until at least 2 years after notification by the Sponsor that investigations have been discontinued or 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. These documents should be retained for a longer period; however if required by the applicable regulatory requirements or by an agreement with Endo. In addition, the Investigator shall arrange for the retention of the subject identification codes for at least 15 years after completion or discontinuation of the study. Endo will notify investigators in writing when these documents no longer need to be retained. The Investigator must notify Endo prior to destroying any clinical study records.

## 17.5. Regulatory Documentation

Documents that must be provided to the Sponsor prior to study initiation are as follows:

- Signed (original and dated) FDA Form 1572 plus an current curriculum vitae for each individual named on the form
- Financial Disclosure for each individual listed on the 1572
- Signed (original) and dated Investigator Agreement
- Assurance of an IRB/IEC, which complies with requirements set forth in Title 21 Part 56 of the Code of Federal Regulations, will be responsible for the approval of the clinical study. The required documentation will consist of name and address of the IRB/IEC and a current list of IRB/IEC members, including the title, gender, occupation, and any institutional affiliation of each member. A general assurance number from the Department of Health and Human Services may be substituted for this list.
- Written notification (copy) to the Investigator from the IRB/IEC approving the protocol. The written notification is to be signed by the chairman or authorized designee and must identify the protocol. In cases where an IRB member has a known conflict of interest, abstention of that individual from voting should be documented
- IRB/IEC approved instrument of informed consent (copy) and any other adjunctive materials to be used in the study, including IRB approval of these items.

# 18. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

# 19. INVESTIGATOR AGREEMENT

Each Investigator will sign an Investigator Agreement (see Appendix F) for this protocol. The Investigator's signature will affirm that the Investigator has read the protocol and agrees that the protocol and related Clinical Trial Agreement contain the details necessary to carry out the study. In addition, the Investigator's signature will affirm that the Investigator will conduct the study according to the protocol.

# 20. STUDY REPORTS AND PUBLICATIONS

Endo is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements. Publication policy is discussed in the Investigator's Clinical Trial Agreement.

# 21. REFERENCES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# APPENDIX A. SEDATION SCALES

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# APPENDIX B. GUIDELINES FOR CAPTURE OF PRIOR AND CONCOMITANT MEDICATIONS

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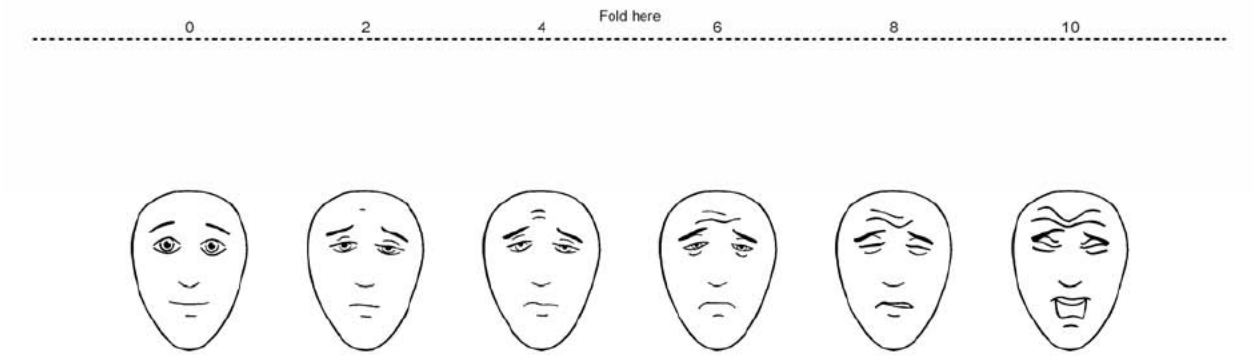


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Hicks CL, von Baeyer CL, Spafford PA, Van Korlaar I, Goodenough B. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;93(2):173-183.

## APPENDIX D. [redacted]

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## APPENDIX F. INVESTIGATOR AGREEMENT

[redacted]

Signature of Investigator Date

Typed or Printed Name of Investigator