This study was initiated at the request of the FDA as a class required Post-marketing Study in Pediatric Patients.

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355 USA

OXYMORPHONE HCl

EN3319-304

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

IND 58,602

Date:

Original Protocol: September 17, 2013

Amendment 1: March 26, 2014

Amendment 2: October 5, 2015

Amendment 3: February 22, 2016

Amendment 4: May 13, 2016

Amendment 5: 01 April 2019

[redacted]

SUMMARY OF CHANGES

EN3319-304 protocol amendments and amended informed consent forms (as necessary) have been reviewed and approved by the governing Institutional Review Boards (IRBs) before implementation of the amendment at each study center.

Amendment 5 was incorporated into the protocol on 01-April-2019. The major reasons for this amendment were to: 1) clarify that the FLACC instrument is used to assess pain in subjects in Groups A and B and the NIPS instrument will be used to assess pain in subjects in Groups C and D and 2) to clarify when analgesics may be used during the single- and multiple- dose phases of the study and during follow-up, and 3) to clarify that loss of an arterial or venous line will not result in termination of study participation. 4) to clarify that tolerance of oral liquids prior to study drug administration is only required for Groups A and B, and 5) to clarify that End of Treatment assessments in the multiple-dose phase are to be conducted 24 hours after the last study drug administration. Additional text is noted in bold. Deletions are noted in strikethrough.

Table 1: Summary of Changes

Section	Original Text (Reason for Change)	Revised Text
Table 2, Sponsor Contact Information	[redacted] **Reason for Change:** Administrative change	[redacted]
Synopsis Investigational Product, Dosage, and Mode of Administration	**Original Text:** EN3319 oxymorphone HCl immediate-release oral liquid 1 mg/mL dosed at 0.05 mg/kg by mouth, with subsequent doses to be determined by IDMC. Oxymorphone HCl IV solution 1 mg/mL at doses to be determined by IDMC. **Reason for Change:** Added study groups for further clarity.	EN3319 oxymorphone HCl immediate-release oral liquid **(Groups A and B)** 1 mg/mL dosed at 0.05 mg/kg by mouth, with subsequent doses to be determined by IDMC. Oxymorphone HCl IV solution **(Groups C and D)** 1 mg/mL at doses to be determined by IDMC.

Section	Original Text (Reason for Change)	Revised Text
Section 3, Tables 3 and 4 Schedule of Assessments, EOT Assessments	**Original Text:** 24 hours post first dose or ET (Tables 3 and 4) **Reason for Change**: Table 3: Deletion of "first" since there is only 1 dose in the single dose phase Table 4: Deletion of first since EOT assessments must be conducted 24 hours after the last dose	Table 3: 24 hours post ~~first~~ dose or ET Table 4: 24 hours post ~~first~~ last dose or ET
Section 3, Tables 3 and 4 Schedule of Assessments – Follow-ups Phone	**Original Text: Follow-ups Phone**- Post-dose assessments- 3 and 14 days post last dose **Reason for Change:** Added window to match protocol text	(3 **[±1]** and 14 **[±2]** days post last dose)
Section 3, Schedule of Assessments, Table 4, footnote c" Section 8.1.6, Multiple-dose Phase, and Section 8.3, Study Drug Administration	**Original Text:** Subjects will be dosed every 4 to 6 hours or as needed **Reason for Change:** Removed "or" as needed and corrected to every 4 to 6 hours as needed.	Subjects will be dosed every 4 to 6 hours ~~or~~ as needed
Section 3, Table 3 Schedule of Assessments Footnote "n", Section 8.1.5, Single Dose Phase, Section 8.4.1, Single dose Phase, Section 14.1.2, Pharmacokinetics; Synopsis, Multiple-dose Phase	**Original Text:** Blood samples for PK analysis should be collected at 0.5 (for subjects with even subject numbers) or 1.0 hour (for subjects with odd subject numbers), and at 2.0, 3.0, 4.0 and 8.0 hours (section 12.1.1). **Reason for Change:** Added window.	Blood samples for PK analysis should be collected at 0.5 (for subjects with even subject numbers) or 1.0 hour (for subjects with odd subject numbers), and at 2.0, 3.0, 4.0 and 8.0 hours (section **13**.1.1). **A window of ±10 minutes is allowed.**

Section	Original Text (Reason for Change)	Revised Text
Schedule of Assessments, Table 3 footnote "j", Section 8.1.5 Single-dose Phase, Section 8.1.6 Multiple-dose Phase; Synopsis, Single and Multiple-dose Phase	**Original Text:** The FLACC will be used for subjects between the ages of 6 months and 2 years. The NIPS will be used for patients 0 to <6 months. **Reason for Change:** Clarify that the FLACC will be used for Groups A and B and the NIPS will be used for Groups C and D.	The FLACC will be used for subjects in **Groups A and Group B. The NIPS will be used for subjects in Groups C and D.**
Section 6.1 Background	**Original Text:** ….In addition, oxymorphone HCl is currently available in the United States in an injectable formulation. … Subjects aged 0 to 60 days will be administered the approved, commercially available oxymorphone HCl injectable formulation (oxymorphone HCl injection). **Reason for Change:** Oxymorphone IR solution is no longer commercially available.	~~In addition, oxymorphone HCl is currently available in the United States in an injectable formulation.~~ Subjects aged 0 to 60 days will be administered ~~the approved, commercially available~~ oxymorphone HCl injectable formulation (oxymorphone HCl injection).
Section 6.4.1 Study Design Rationale, Section 8.4 Discussion of Study Design Including the Choice of Control Groups, Section 8.4.1 Single-Dose Phase, Section 8.4.2 Multiple Dose Phase, Synopsis, Study Design	**Original Text:** The study subjects will be stratified into 4 age groups: A. 6 months (180 days) -< 2 years B. 61 days -<6 months **Reason for Change**: Clarify the cut-off date for enrollment on a day-level to reflect what is programmed by the Interactive Response Technology (IRT) provider	The study subjects will be stratified into 4 age groups: A. 6 months (180 days) -< 2 years **(up to and inclusive of 729 days),** B. 61 days -<6 months **(up to and inclusive of 179 days)**

Section	Original Text (Reason for Change)	Revised Text
Section 8.1 Study Design, Synopsis, Study Design	**Original Text:** The study will consist of a screening period; a predose evaluation; a treatment phase (single dose open label phase and placebo-controlled, double-blinded, multiple-dose phase, each occurring after surgery) to evaluate efficacy, safety, tolerability, and PK; an end-of-treatment (EOT) assessment 24 hours after the last dose of study drug; and 2 follow-up contacts (at 3 +/-2 and 14 +/-2 days after the last dose of study drug). Subjects will also receive a follow-up contact from a member of the study staff 3 +/-2 and 14 +/-2 days after the last dose of study drug. **Duration of Study** Follow-up telephone contact – 3 +/-2 and 14 +/-2 days after the last dose of study drug **Reason for Change:** Correct a typo; Change time frame for follow-up to 3±1 instead of 3 ±2	The study will consist of a screening period; a predose evaluation; a treatment phase (single dose open label phase and placebo-controlled, double-blinded, multiple-dose phase, each occurring after surgery) to evaluate efficacy, safety, tolerability, and PK; an end-of-treatment (EOT) assessment 24 hours after the last dose of study drug; and 2 follow- up contacts (at 3 ±/~~-2~~ 1 and 14 ±2 days after the last dose of study drug). Subjects will also receive a follow-up contact from a member of the study staff 3 ±~~-2~~ 1 and 14 ±2 days after the last dose of study drug. **Duration of Study** Follow-up telephone contact 3 ±1 and 14± 2 days after the last dose of study drug
Section 8.1 Study Design, Synopsis, Study Design	**Original text:** The total duration of the study, excluding screening, for subjects in the open-label, dose-selection phase will be approximately 15 days from the first dose of study drug to last follow-up. The total duration of the study, excluding screening, for subjects in the multiple-dose phase will be up to 16 days from the first dose of study drug to last follow-up **Reason for Change:** Modify duration of the study to 17 days to account for the change in monitoring to 24 hours after the last dose instead of 24 hours after the initial dose.	The total duration of the study, excluding screening, for subjects in the open-label, dose-selection phase will be approximately 15 days from the first dose of study drug to last follow-up. The total duration of the study, excluding screening, for subjects in the multiple-dose phase will be up to 1~~6~~7 days from the first dose of study drug to last follow-up.

Section	Original Text (Reason for Change)	Revised Text
Section 8.1.2 Post-Surgery Evaluation; Section 3, Schedule of Assessments, Table 3, footnote "c"; Synopsis, Study Design	**Reason for Change:** Added text. Clarify eligibility requirements for subjects in Groups A through D	• **After subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will enter either the single-dose or multiple-dose phase of the study (depending on study progression). Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.** • **After subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they will enter either the single-dose or multiple-dose phase of the study (depending on study progression).**
Section 8.1.1 Screening Phase	**Original Text:** Blood samples for baseline clinical laboratory tests as may be collected at any time within 5 days prior to surgery. **Reason for Change:** Clarify that all laboratory tests detailed are required during the Screening Phase.	Blood samples for baseline clinical laboratory tests **as detailed in Table 9** may be collected at any time within 5 days prior to surgery.
Section 8.1.3, Baseline Dosing Assessments (Day 1, Time 0)	**Original Text:** Updating and recording all concomitant medications: medications taken within 30 days prior to signing consent as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (Appendix B). For groups C and D, over-the-counter (OTC) acetaminophen or SOC may be used only to manage fever. **Reason for Change:** Clarify that non-opioid analgesics are permitted for all age groups to treat breakthrough pain and that acetaminophen or SOC are permitted to treat fever in all age groups. Clarify the time frame for administration.	Updating and recording all concomitant medications: medications taken within 30 days prior to signing consent as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (Appendix B). ~~For Groups C and D, over-the-counter (OTC) acetaminophen or SOC may be used only to manage fever.~~ **For single-dose cohorts, non-opioid analgesics (acetaminophen and/or non-steroidal anti-inflammatory drugs [NSAIDS] per SOC may be used to treat breakthrough pain not earlier than 6 hours following administration of study drug.** • **Across all age groups, acetaminophen or SOC may be administered for subjects who develop fever during the study period.**

Section	Original Text (Reason for Change)	Revised Text
Section 8.1.3, Baseline Assessments (Day 1, Time 0)	**Original Text:** When subjects are tolerating oral intake, their analgesic regimen will be discontinued and they will be closely monitored for pain (pain scores will be recorded at least hourly until time of dosing). Subjects will be administered study drug (oxymorphone HCl, IV or oral) once their pain score is ≥4 on the FLACC or ≥3 on the NIPS (day 1 time zero). The exact time when study drug was administered must be recorded. No food or oral liquid restrictions will be imposed around the time of dosing. Note: Laxative and antiemetic regimens may be used; all subjects will be allowed use of a laxative and antiemetic throughout the study. All medications taken by the subjects (including NCA rescue medication) will be recorded. **Reason for Change:** Modification to clarify 1)the treating physician will need to confirm that concomitant medications will not interfere with study drug pain assessments, 2) that tolerance to oral intake is only required prior to administration of oxymorphone HCl oral solution (and not IV), and 3) add detail to the recording of concomitant medication	~~When subjects are showing signs of tolerating oral intake, their~~ **When subjects in Groups A and B are showing signs of tolerating oral intake and subjects in Groups C and D are showing signs of awakening and arousal, their** IV analgesic regimen should be discontinued and the subject will be closely monitored for pain. **The pain scores will be recorded at least hourly until time of study drug dosing. Once their pain score is ≥3 on the NIPS (day 1 time zero) or is ≥4 on the FLACC, study drug (oxymorphone HCl, either IV or oral) can be administered. Prior to study drug administration, the treating physician should review all intra-operative and post-operative medications previously administered (excluding Nurse-controlled analgesia (Section 8.1.4) to ensure that the administration time, half-life and potency of any of these medications will not impact the study drug dose pain assessments. The treating physician must confirm the subject's ability to tolerate oral liquids prior to administering study oxymorphone HCl oral solution. The exact time when study drug was administered must be recorded. No food or oral liquid restrictions will be imposed around the time of dosing.** Note: Laxative and antiemetic regimens may be used; all subjects will be allowed use of a laxative and antiemetic throughout the study. All medications taken by the subjects (including NCA rescue medication) **must be recorded with precise dose administered in mg or cc, frequency of administration, and indication.**

Section	Original Text (Reason for Change)	Revised Text
Section 8.1.4, Nurse Controlled Analgesia; Synopsis, Nurse Controlled Analgesia, Section 8.1.5, Single-dose Phase, Synopsis, Single-dose Phase	**Original Text:** Intermittent PRN dosing, with or without a background infusion (using the background infusion dosing guidelines referenced in Table 6), in accordance with individual institutions' usual standard practices for postoperative opioid analgesia in this population is permissible. NCA (section 8.1.4) will be initiated coincident with the first administration of study drug (refer to section 8.1.5 [single-dose phase] and section 8.1.6 [multiple-dose phase]). **Reason for Change:** Added timeframe of administration of NCA relative to study drug for additional clarification.	Intermittent PRN dosing, with or without a background infusion (using the background infusion dosing guidelines referenced in Table 6), in accordance with individual institutions' usual standard practices for postoperative opioid analgesia in this population is permissible. NCA (section 8.1.4) will be initiated coincident with the first administration of study drug (refer to section 8.1.5 [single-dose phase] and section 8.1.6 [multiple-dose phase]) **but not earlier than the first administration of study drug.**
Section 8.1.5, Single-dose Phase	**Original Text:** No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive rescue by morphine-NCA as needed. For groups A and B, non-opioid analgesics (acetaminophen and/or NSAIDS) per SOC may be used 6 hours following the first dose of study drug. Subjects will undergo subsequent pain assessments as noted in **Table 3**. **Reason for Change:** Clarify that for all groups non-opioid analgesics are permitted to treat breakthrough pain not earlier than 6 hours after administration of study drug.	No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive rescue by morphine-NCA as needed. ~~For Groups A and B, non-opioid analgesics (acetaminophen and/or NSAIDS) per SOC may be used 6 hours following administration of study drug~~ **Non-opioid analgesics (acetaminophen and/or non-steroidal anti-inflammatory drugs [NSAIDS] per SOC may be used to treat breakthrough pain not earlier than 6 hours following administration of study drug.**
Section 8.1.5, Single-dose Phase, Synopsis, Single-dose Phase	**Original Text:** Once subjects are tolerating oral intake and their analgesic regimen has been discontinued per standard of care, baseline assessments will be collected (Table 3). **Reason for Change:** Clarify that only subjects in Groups A and B need to tolerate oral intake prior to receiving oxymorphone oral liquid.	**Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.** Once **the subject's** analgesic regimen has been discontinued per standard of care, baseline assessments will be collected **as documented in Table 3 and section 8.1.3**

Section 8.1.6 Multiple-dose Phase; Section 3, Schedule of Assessments, Table 4, footnote "a"; Synopsis, Multiple-dose Phase	**Original Text:** Once subjects are tolerating oral intake and their analgesic regimen has been discontinued per standard of care, they will be randomized and enter the multiple-dose phase. Baseline assessments (Table 4) will be collected following randomization. All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time they will be administered study drug (oxymorphone HCl immediate release oral liquid for Groups A and B; IV oxymorphone HCl for Groups C and D) or placebo. Morphine-NCA (section 8.1.4) will be initiated coincident with study drug/placebo administration, and this time will be designated as day 1 time zero. **Reason for Change:** 1) Clarify requirements for all Groups to be randomized to multiple-dose phase. 2) Clarify age groups for use of the FLACC and NIPS 3) Clarify that subjects in Groups A and B, only, must tolerate oral intake before receiving oxymorphone oral liquid 4) Clarification of timing of morphine-NCA	~~Once subjects are tolerating oral intake and their analgesic regimen has been discontinued per standard of care, they will be randomized and enter the multiple-dose phase~~ **Prior to entering the multiple-dose phase, when subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will be randomized and enter multiple-dose phase of the study.** **Prior to entering the multiple dose-phase, when subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they will be randomized and enter the multiple-dose phase of the study.** Baseline assessments (Table 4) will be collected following randomization. **The FLACC will be used for subjects in Groups A and B. The NIPS will be used for subjects in Groups C and D.** All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time they will be administered study drug (oxymorphone HCl immediate release oral liquid for Groups A and B; IV oxymorphone HCl for Groups C and D) or placebo. **Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.** Morphine-NCA (section 8.1.4) will be

Section	Original Text (Reason for Change)	Revised Text
		initiated coincident **with but not earlier than**-study drug/placebo administration, and this time will be designated as day 1 time zero.
Section 8.1.7, End of Treatment/ Early Termination	**Original Text:** At the completion of the single- or multiple-dose phases, EOT assessments and procedures will occur at 24 hours after initial study drug administration or upon early discontinuation. **Reason for Change:** Clarify that EOT assessments and procedures must be conducted 24 hours after the last study drug administration, instead of 24 hours after the initial dose, in the case of early study withdrawal.	At the completion of the single- or multiple-dose phases, EOT assessments and procedures will occur at 24 hours after **the ~~initial~~ last** study drug administration or upon early ~~discontinuation~~ **study withdrawal**
Section 8.3 Study Drug Administration	**Original Text:** Study drug in the form of oral liquid will be provided for subjects in age groups A and B. **Reason for Change:** Add instructions in case subjects spit out a dose.	Study drug in the form of oral liquid will be provided for subjects in age groups A and B. **If a subject in groups A or B does not consume the entire dose, the subject should not be redosed until the next time scheduled dose, if applicable**
Section 8.3 Study Drug Administration	**Original Text:** Following surgery, when subjects are tolerating oral intake, their SOC postoperative analgesic regimen will be discontinued. All subjects will then be closely monitored for pain (pain scores will be recorded at least hourly) and they will be administered study drug or placebo once their pain score is ≥4 on the FLACC or ≥3 on the NIPS (day 1 time zero). **Reason for Change** Define criteria for discontinuation of post-operative analgesic regimen will be discontinued and by which subjects in Groups A and B can start receiving oxymorphone oral liquid.	Following surgery, when subjects **in Groups A and B** are **showing signs of** tolerating oral intake **and subjects in Group C and D are showing signs of awakening and arousal** their SOC postoperative analgesic regimen will be discontinued. All subjects will then be closely monitored for pain (pain scores will be recorded at least hourly) and they will be administered study drug or placebo once their pain score is ≥4 on the FLACC or ≥3 on the NIPS (day 1 time zero). **Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.**

Section	Original Text (Reason for Change)	Revised Text
Section 9.1, Subject Inclusion Criteria, Synopsis, Subject Inclusion Criteria	**Original Text:** **Postoperative** 9. Has demonstrated the ability to tolerate clear fluids following surgery according to the SOC at each institution. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions. The ability to tolerate small amounts (1 to 2 oz.) of clear liquids without emesis (over 30 to 60 minutes) would support readiness for study participation and oral intake once the physician has ordered the diet advanced to clear liquids and the subject has ingested fluids by mouth without nausea or vomiting. **Reason for Change:** Clarify that postoperatively only subjects in Groups A and B need to show signs of tolerating oral liquids and that prior to administration of the solution and that prior to administration of oxymorphone IR solution, only subjects in Groups A and B need to have the ability to tolerate oral liquids.	**Postoperative** **9. For Groups A and B: Has demonstrated signs of** ~~Has demonstrated the ability. Subjects are showing signs~~ **tolerating oral intake,** ~~to tolerate clear fluids following surgery according to the SOC at each institution.~~ All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions. ~~The ability to tolerate small amounts (1 to 2 oz.) of clear liquids without emesis (over 30 to 60 minutes) would support readiness for study participation and oral intake once the physician has ordered the diet advanced to clear liquids and the subject has ingested fluids by mouth without nausea or vomiting~~. **Prior to Administration of Oxymorphone HCl Oral Solution** **For Groups A and B: Has demonstrated the ability to tolerate clear liquids, following surgery according to the SOC at each institution. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions. The ability to tolerate small amounts (1 to 2 oz.) of clear liquids without emesis (over 30 to 60 minutes) would support readiness for study participation and oral intake once the physician has ordered the diet advanced to clear liquids and the subject has ingested fluids by mouth without nausea or vomiting.**

Section	Original Text (Reason for Change)	Revised Text
Section 10.1.5, Follow-up	**Original Text:** The date of EOT or ET from the study will be recorded by the Investigator (or assigned designee) and will be the official EOT/ET for each subject. Study participation will end with the completion of the 14-day follow-up telephone call. **Reason for Change**: To clarify that all types of analgesics are permitted during follow-up.	The date of EOT or ET from the study will be recorded by the Investigator (or assigned designee) and will be the official EOT/ET for each subject. **Subjects may take analgesics (opioid or non-opioid) according to SOC after EOT.** Study participation will end with the completion of the 14-day follow-up telephone call.
Section 10.2, Prior and Concomitant Medications and Procedures	**Original Text:** For groups C and D: During the single-dose phase, no analgesics other than the study drug will be permitted during the 24-hour assessment period (except NCA rescue) For groups A and B: During the single-dose phase, no analgesics other than the study drug (except NCA rescue) will be permitted for 6 hours following the study drug dose. **Reason for Change:** To clarify that non-opioid analgesics are allowed after 6 hours instead of after 24 hours for all age groups. Consolidation of bullet points for all age groups.	~~For groups C and D: During the single-dose phase, no analgesics other than the study drug will be permitted during the 24-hour assessment period (except NCA rescue)~~ ~~For Groups A and B: During the single-dose phase, no analgesics other than the study drug (except NCA rescue) will be permitted for 6 hours following the study drug dose.~~ **For all age groups: During the single-dose phase, no analgesics other than the study drug (except NCA) will be permitted for 6 hours after study drug administration. Non-opioid analgesics (acetaminophen and/or NSAIDs) per SOC may be used to treat breakthrough pain not earlier than 6 hours after administration of study drug.**
Section 10.2, Prior and Concomitant Medications and Procedures	**Original Text:** Nursing mothers may not receive opioids during the study period. **Reason for Change:** Clarification	Nursing mothers **should be advised** ~~may~~ **not to** receive opioids during the study period.
Section 10.2, Prior and Concomitant Medications and Procedures	**Original Text:** OTC acetaminophen or SOC may be administered for fever only for groups C and D. Groups A and B may be given non-opioid analgesics (acetaminophen and/or NSAIDS) per SOC 6 hours following the first dose of study drug. **Reason for Change:** To eliminate redundancy due to text that has been newly added	**Across all age groups, acetaminophen or SOC may be administered for subjects who develop fever during the study period.** ~~OTC acetaminophen or SOC may be administered for fever only for groups C and D. Groups A and B may be given non-opioid analgesics (acetaminophen and/or NSAIDS) per SOC 6 hours following the first dose of study drug.~~

Section	Original Text (Reason for Change)	Revised Text
Section 10.2, Prior and Concomitant Medications and Procedures	**Original Text:** During the multiple-dose phase, no analgesics other than the study drug will be permitted during the 24-hour assessment period (except NCA rescue). **Reason for Change:** Clarify that the prohibition of analgesic use during the 24 hour assessment period of the multiple dose phase applies to all age groups.	During the multiple-dose phase **(all age groups),** no analgesics other than the study drug will be permitted during the 24-hour assessment period (except NCA rescue).
Section 12.1.1 Adverse Events	**Original Text:** All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease. **Reason for Change:** Instruct when worsening of the existing condition should be documented as an AE.	All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease**. Post-operative pain should be captured as an AE after the EOT.**
Section 13.1.1, Blood Sample Collection	**Original Text:** Blood collection may be performed using an existing line (arterial or venous) 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 be established only as required for the clinical management of the subject and not solely for study purposes; otherwise, the subject's participation in the study will be early terminated. **Reason for Change:** To indicate that loss of a line will not result in termination of study participation	Blood collection may be performed using an existing line (arterial or venous) 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 be established only as required for the clinical management of the subject and not solely for study purposes;~~ otherwise, the subject's participation in the study will be early terminated.~~
Section 14.5.2, Secondary Efficacy Analysis	**Original Text:** The FLACC ranges from 0 to 10; while the NIPS ranges from 0 to 7. Before any statistical analysis, NIPS will be normalized in reference to FLACC by dividing by 7 and multiplying by 10. **Reason for Change:** Clarification that the text is referring to the NIPS assessments.	The FLACC ranges from 0 to 10; while the NIPS ranges from 0 to 7. Before any statistical analysis, **all** NIPS **assessments** will be normalized in reference to FLACC by dividing by 7 and multiplying by 10.

Section	Original Text (Reason for Change)	Revised Text
Section 15.1 Study Drug Identity	**Original Text:** The study drugs are EN3319 oxymorphone HCl prepared as an oral immediate-release solution, commercially available OPANA® (Oxymorphone Hydrochloride) Injection 1 mg/mL and sodium chloride 0.9% solution for injection as placebo for oxymorphone HCl IV solution. Oxymorphone oral liquid and IV products are light sensitive and must be protected from light. **Reason for Change:** OPANA IV is no longer commercially available	The study drugs are EN3319 oxymorphone HCl prepared as an oral immediate-release solution, matching placebo liquid, ~~commercially available OPANA®~~ oxymorphone HCl IV solution ~~(Oxymorphone Hydrochloride) Injection 1 mg/mL~~ and sodium chloride 0.9% solution for injection as placebo for oxymorphone HCl IV solution. Oxymorphone oral liquid and IV products are light sensitive and must be protected from light.
Section 15.2 Study Drug Packaging and Labeling	**Original Text:** OPANA (Oxymorphone Hydrochloride) Injection 1 mg/mL is supplied as 1 mL ampules, 10 ampules/box and will be provided with commercial labeling. Sodium chloride 0.9% solution for injection will be provided with commercial labeling for single use. **Reason for Change:** OPANA IV is no longer commercially available	~~OPANA (Oxymorphone Hydrochloride) Injection 1 mg/mL~~ **Oxymorphone HCl IV solution** is supplied as 1 mL **units,** 10 **units**/box and **each box** will be ~~provided~~ **labeled minimally** with ~~commercial labeling~~ **the following information (as appropriate): protocol number, study drug name, strength, dosage form, Class II designation, quantity, lot number, appropriate administration and storage instructions, sponsor's identification and address, appropriate cautionary statements.** Sodium chloride 0.9% solution for injection will be provided with commercial labeling for single use.
Sections 15.3; 15.4, 15.5, 15.6 Study Drug Storage, Study Drug Preparation, Study Drug Accountability Study Drug Handling and Disposal	**Original Text:**…OPANA IV… …ampules of oxymorphone HCl IV.. **Reason for Change:** OPANA IV is not commercially available. Oxymorphone HCL IV may not be manufactured in ampules.	~~…OPANA IV~~ **oxymorphone HCl** IV **solution** …**units** of oxymorphone HCl IV

SPONSOR CONTACT INFORMATION

Table 2: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided separately for your reference.

2. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3319 Oxymorphone HCl Immediate-release Oral Liquid and Oxymorphone HCl injection	
Name of Active Ingredient: Oxymorphone HCl	
Title of Study: An Open-label Single-dose and Randomized, Double-blind, Placebo-controlled Multiple-dose Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Oxymorphone HCl for Acute Moderate to Severe Postoperative Pain in Pediatric Subjects	
Study Center(s): Up to 25 sites	
Investigators: TBD	
Studied Period (years): Date first subject enrolled: April 2016 Estimated date last subject completed: TBD	**Phase of Development**: 3

Objectives:

Primary:

- To describe the efficacy of oxymorphone HCl in children aged 0 to <2 years for whom an opioid to treat acute moderate to severe postoperative pain of various etiologies may be an appropriate treatment option.

Secondary:

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

Methodology:

Study Design: This is a phase 3, post market study being conducted for Pediatric Research Equity Act (PREA) commitment, with an open-label, single-dose, dose selection phase and a randomized, double-blinded, placebo-controlled multiple-dose phase to characterize the efficacy, safety, tolerability, and PK of oxymorphone HCl in pediatric subjects with acute moderate to severe postoperative pain for whom an opioid may be determined to be an appropriate treatment option. It is a multicenter study conducted at up to 25 sites.

All subjects will be enrolled preoperatively up to 5 days before surgery with the expectation that they will require intravenous (IV) access after surgery and postoperative analgesia with an opiate medication.

Four (4) separate age groups of subjects will be enrolled in the study, with recruitment of older infants and toddlers preceding involvement of the youngest age subjects (Figure 1). Subjects will be stratified into groups by age as follows:

A. 6 months – <2 years (up to and inclusive of 279 days)
B. 61 days – <6 months (up to and inclusive of 179 days)
C. 31 days – 60 days
D. 0 – 30 days

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The study will consist of a screening period; a predose evaluation; a treatment phase (single-dose open-label phase and placebo-controlled, double-blinded, multiple-dose phase, each occurring after surgery) to evaluate efficacy, safety, tolerability, and PK; an end-of-treatment (EOT) assessment 24 hours after the last dose of study drug; and 2 follow-up contacts (at 3 ± 1 and 14 ±2 days after the last dose of study drug). For all age groups, the screening period will occur within 5 days before surgery. Eligible subjects whose parent or guardian provides consent will have study assessments performed at screening. Following surgery, subjects will receive standard of care (SOC), including IV analgesia with a non-oxycodone, non-oxymorphone medication that will not interfere with the measurement or metabolism of oxymorphone and does not have oxymorphone as a metabolite (eg, morphine). At this time, subjects will have a predose evaluation to re-confirm eligibility. After all subjects are post-operative, and subjects in Groups A and B are showing signs of tolerating oral intake and subjects in Groups C and D are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued, replaced by a morphine nurse-controlled analgesia (NCA) paradigm and they will enter either the single-dose or multiple-dose phase of the study (depending on study progression). The study will initiate with oldest age subjects first (Group A), and each subsequently younger age group (B, C, and D) will enter the study only after the preceding age group has completed enrollment and the data is reviewed by an independent data monitoring committee (IDMC) to evaluate efficacy, safety, tolerability, and PK (ie, Group A must complete enrollment and IDMC review before Group B can open for enrollment, etc.). The study will be implemented in 2 phases and will be conducted in each age group separately and sequentially: • Beginning with Group A, each group must complete the single-dose phase and IDMC review before the next age group can open enrollment in the single-dose phase. • Beginning with Group A, each age group must complete the multiple-dose phase and IDMC review before the next age group can open enrollment in the multiple-dose phase. • Each age group must complete their respective single-dose phase and IDMC review before proceeding to the multiple-dose phase. The first cohort of subjects from Group A entering the study will receive a dose of 0.05 mg/kg for the single-dose phase, and doses for all subsequent cohorts (across all age groups and dose phases) will be determined based on recommendation of the IDMC following each cohort review. The total duration of the study, excluding screening, for subjects in the open-label, dose-selection phase will be approximately 15 days from the first dose of study drug to last follow-up. The total duration of the study, excluding screening, for subjects in the multiple-dose phase will be up to 17 days from the first dose of study drug to last follow-up. Nurse-controlled Analgesia (NCA): Postoperative morphine consumption via NCA will be used as a surrogate measure for analgesic efficacy.[1] NCA is an established form of postoperative analgesia, similar in nature to other demand-led analgesic regimens (eg, Patient-controlled analgesia [PCA]), but tailored for patients who are too young or unable to use PCA.[2] The dose of NCA rescue medication will be based on weight and age

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according to well-established standards,[1,2] and will be administered by a blinded nurse observer trained in appropriate pain assessment techniques. Under this NCA paradigm, morphine analgesia may be administered using a conventional PCA pump using bolus dosing with or without a background infusion rate as described in Table 6. Intermittent dosing as needed, or when necessary (PRN), with or without a background infusion (using the background infusion dosing referenced in Table 6), in accordance with individual institutions' usual standard practices for postoperative opioid analgesia in this population is permissible. NCA will be initiated coincident with the first administration of study drug but not earlier than the first administration of study drug. The NCA guidelines detailed below provide a baseline framework for postoperative morphine-NCA and may be adjusted to be consistent with institutional SOC.

Guidelines for Morphine Nurse-Controlled Analgesia [a]

Age Group	Starting Background (mcg/kg/h)	Maximum Background (mcg/kg/h)	Bolus Dose (mcg/kg)	Lockout (minutes)	Maximum Bolus/h [b]
A and B	Up to 5	Up to 30	10-15	10	3
C and D	0	Up to 15	10	10	3

[a] Adapted from *Pediatr Anesth*. 2010; 20(2):126-134 and *Br J Anaesth*. 2007; 98(3):372-379.

[b] Subjects should be titrated to minimal effective analgesia requiring up to 3 boluses per hour. If more than 3 boluses per hour are required, background may be increased by 5 mcg/kg/h up to the maximum background.

Initiation: Nurse-controlled analgesia (NCA) should be initiated concomitant with first administration of study drug.

Single-dose Phase:

The open-label, single-dose phase will use oxymorphone HCl immediate-release oral liquid (Groups A and B) or oxymorphone HCl IV (Groups C and D) for PK assessments and to determine which dose (for each age group) to take forward into the multiple-dose phase (Figure 1).

For each age group, up to 3 cohorts of 5 subjects will receive oxymorphone HCl (either immediate-release oral liquid or IV, based on age) and will follow per protocol instructions for up to 24 hours. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. Once the subject's analgesic regimen has been discontinued per standard of care, baseline assessments (section 3) will be collected. All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until their pain score is ≥4 on the Face, Leg, Activity, Cry, and Consolability (FLACC) scale or ≥3 on the Neonatal Infant Pain Scale (NIPS), at which time the baseline dosing assessments will be done and they will be administered study drug. The FLACC will be used for subjects in Groups A and B and the NIPS will be used for subjects in Groups C and D. Background morphine NCA (section 8.1.4) will be initiated coincident with but not earlier than the first administration of study drug and this time will be designated as time zero of day 1. Bolus morphine administration may be given per standard of care. No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive rescue by morphine-NCA as needed. Subjects will undergo subsequent pain assessments as noted in **Table 3**. All pain assessments will be conducted using an age-appropriate pain instrument (FLACC or NIPS). PK and additional assessments will occur at fixed intervals throughout the single-dose phase, as outlined in section 3.

[3] Czarnecki ML, Salamon KS, Jastrowski Mano KE, Ferrise AS, Sharp M, Weisman SJ. A preliminary report of parent/nurse-controlled analgesia (PNCA) in infants and preschoolers. *Clin J Pain*. 2011;27(2):102-107.

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Selection of Doses: Single-dose Phase: The first cohort of subjects from Group A will receive 0.05 mg/kg oxymorphone HCl immediate-release oral liquid. Data from the initial cohort will be assessed by the IDMC for efficacy, safety, tolerability, and PK, at which time the IDMC will make a recommendation for the dose for the second cohort of subjects from Group A. Each cohort of age groups will progress through the single-dose phase in the same manner (ie, completion of cohort followed by IDMC data review and dose recommendation for the next cohort) until either 3 doses are assessed in the single-dose phase for each age group or the IDMC recommends that an age group proceeds to the multiple-dose phase.

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The starting dose for the first cohort of subjects of Group B will be determined based on IDMC recommendation following review of data from Group A. Doses for subsequent cohorts of Group B will be determined based on IDMC recommendation following completion of prior Group B cohorts (up to 3 cohorts may be tested in the single-dose phase for each age group). Because Groups C and D will utilize an IV formulation of oxymorphone HCl, the IDMC will also be provided PK modeling data aggregated from Groups A and B (by the Sponsor) to assist in their determination of the proper starting dose. The starting dose for Group D will be determined by the IDMC following completion of Group C, with doses for subsequent cohorts of Group D subjects determined in the same manner as described above. For any cohort or age group, the Sponsor may choose to utilize a dose in the single-dose phase other than that recommended by the IDMC, but will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. Likewise, the Sponsor may choose to end the single-dose phase for any age group after 2 cohorts have been tested, and will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. All such changes must be endorsed as "safe to proceed" by the IDMC before being implemented in the study.

Multiple-dose Phase:

Following review of data related to the efficacy, safety, tolerability, and PK from the single-dose phase, the IDMC will provide a recommendation for a dose (for each age group) to be carried forth into the double-blind, placebo-controlled multiple-dose phase to assess efficacy of oxymorphone HCl versus placebo. The determination of dose to be tested in the multiple-dose phase will be made independently for each age group. The IDMC will make their dose recommendation after equal consideration of the following factors:

1) Analgesic efficacy in the single-dose phase (no morphine-NCA bolus doses required for at least 3 hours following dosing).
2) PK and analgesic efficacy data from the multiple-dose phase of the preceding age group where applicable.
3) Minimal drug-related adverse event (AE) profile (determined at the discretion of the IDMC).
4) Optimal safety and tolerability profile (determined at the discretion of the IDMC).

In the event that no dose tested in the single-dose phase meets these criteria, the IDMC will provide a dose recommendation for testing in the multiple-dose phase that they deem safe for testing (the dose may be below the lowest dose tested in the single-dose phase, but not above the highest tested dose). For any cohort or age group, the Sponsor may choose to utilize a dose for the multiple-dose phase other than that recommended by the IDMC, but will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. All such changes must be endorsed as "safe to proceed" by the IDMC before being implemented in the study.

The multiple-dose phase will include a double-blinded assessment of oxymorphone HCl versus placebo conducted in the same manner as the single-dose phase (ie, the same progression of age groups, beginning with Group A, followed by Group B, etc.), but only a single dose level will be tested in each age group (Figure 1). New cohorts of 10 subjects per age group will be randomized 1:1 to receive study drug as either oxymorphone HCl (N=5 per age group) at the dose established following IDMC review in the single-dose phase or placebo (N=5 per age group) every 4-6 hours PRN. Prior to entering the multiple-dose phase, when subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will be randomized and enter multiple-dose phase of the study.

Prior to entering the multiple dose-phase, when subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they

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will be randomized and enter the multiple-dose phase of the study. Baseline assessments (section 3) will be collected following randomization. All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until
their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time they will be administered study drug (oxymorphone HCl immediate release oral liquid for Groups A and B; IV oxymorphone HCl for Groups C and D) or placebo. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. The FLACC will be used for Groups A and B and the NIPS will be used for Groups C and D. Morphine-NCA (section 8.1.4) will be initiated coincident with study drug/placebo administration, but not earlier than the first administration of study drug, and this time will be designated as time zero of day 1. No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive morphine-NCA rescue as needed. Subjects will undergo subsequent assessments at half-hour intervals post first dose in the multiple-dose phase (section 3). The study drug will be administered every 4 to 6 hours as needed (q4-6h PRN). Following dose 1, subsequent doses should be administered no less than 4 hours apart, and at least 20 minutes have elapsed since the last bolus NCA rescue. The last dose of study drug will be administered no later than 18 hours post first dose (All subjects must receive a minimum of 3 doses of study drug in the multiple-dose phase). Pain assessments will be conducted every half-hour for the remainder of the multiple-dose phase, or until early termination from the study. All pain assessments will be conducted using an age-appropriate pain instrument (FLACC or NIPS). PK and additional assessments will occur at fixed intervals throughout the multiple-dose phase, as outlined in section 3. At 24 hours after the last dose of study drug, all subjects (in both the single-dose and multiple-dose phase) will undergo an end-of-treatment assessment. Subjects will also receive a follow-up contact from a member of the study staff 3 ±1 and 14 ±2 days after the last dose of study drug. Safety will be assessed by monitoring AEs; assessments of cardiac, respiratory, and neurological function (Modified Ramsay Sedation Scale); clinical laboratory test results; vital sign measurements; and physical examination findings. PK in this study will be characterized using population PK modeling and analysis. Blood samples collected from the single-dose phase will be based on a 4-hour dosing interval since this is the specified period for evaluation of the dose strength. Blood samples will be collected from each subject according to the randomized subject number. Subjects with even subject numbers will have blood samples collected at 0.5, 2, 3, 4, and 8 hours after dosing. Subjects with odd subject numbers will have blood samples collected at 1, 2, 3, 4, and 8 hours after dosing. A window of ±10 minutes is allowed. In the multiple-dose phase, PK blood samples will be collected at each trough (ie, just before each dose). Population PK analyses will be used to estimate the clearance from multiple trough samples collected in the same subject. The date/time and study drug dose, as well as the date/time of each sample collection, must be recorded accurately. However, no specific schedule needs to be followed other than that each sample be collected as a trough sample just before the next dose. If any other source of oxymorphone is administered (including oxycodone, which has oxymorphone as a metabolite), no further PK samples will be collected (in either phase of the study). The population PK modeling and analysis will pool the available data from both phases of this study to estimate the oral clearance and oral volume of distribution using age, weight, and other potential covariates.

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Number of Subjects Planned: Up to 60 subjects (5 subjects per dose per age group, with up to 3 doses per age group) for the single-dose phase and another 40 subjects (10 subjects per age group) for the multiple-dose phase are planned to ensure sufficient subjects for assessment of the efficacy, safety, tolerability, and PK profiles of oxymorphone HCl. The maximum number of subjects planned for both phases of the study is 100 subjects as follows:

Single-dose Phase:

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

Multiple-dose Phase:

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

Grand Total (N): 100

Diagnosis and Inclusion/Exclusion Criteria: Acute moderate to severe postoperative pain for which an opioid analgesic is an appropriate treatment option.

Inclusion Criteria:

1. Is male or female <2 years of age at the time of surgery.
2. Must weigh at least 3 kg.
3. Is scheduled to have a surgical procedure for which opioid analgesia will be needed to manage postoperative pain for at least 18 hours following intraoperative and/or postoperative IV analgesia.
4. Is generally healthy as documented by medical history; physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; 12-lead electrocardiograms (EKGs); clinical laboratory assessments; and general observations. Any abnormalities or deviations from the acceptable range that might be considered clinically relevant by the study physician or investigator will be evaluated on a case-by-case basis, agreed upon by the Principal Investigator (or sub-investigator), and documented in study files before enrolling the subject in the study.
5. The subject's parent or guardian has been informed of the nature of the study and has provided written informed consent.

Postoperative:

6. Is anticipated to require an analgesic regimen using a short-acting opioid (non-oxycodone and non-oxymorphone) analgesic after surgery (according to SOC as defined in the protocol).
7. Is an inpatient expected to be hospitalized for 24 hours after dosing with study drug.
8. Has an indwelling access catheter for blood sampling.

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9. For Groups A and B: Subjects are showing signs of tolerating oral intake, following surgery according to the SOC at each institution. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions.

Prior to Administration of Oxymorphone HCl Oral Solution

10. For Groups A and B: Has demonstrated the ability to tolerate clear liquids, following surgery according to the SOC at each institution. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions. The ability to tolerate small amounts (1 to 2 oz.) of clear liquids without emesis (over 30 to 60 minutes) would support readiness for study participation and oral intake once the physician has ordered the diet advanced to clear liquids and the subject has ingested fluids by mouth without nausea or vomiting.

Exclusion Criteria:

1. Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or nervous system(s) or psychiatric disease that would contraindicate participation, as determined by the Investigator.
2. Has any clinical laboratory test result outside the accepted range that has been confirmed upon re-examination and deemed to be clinically significant.
3. Has a clinically significant illness or condition any time before dosing with study drug that would contraindicate participation, as determined by the Investigator.
4. Has a life expectancy <8 weeks.
5. For age groups A and B: Has a malabsorption, gastroenterologic, or abdominal condition that would interfere with the absorption of study drug.
6. Has evidence of increased intracranial pressure.
7. Has a respiratory condition requiring intubation or resulting in active bronchiolitis, asthma, stridor, or difficulty breathing due to congestion and increased nasal secretions, including oxygen (O_2) saturation ≤92%.
8. Has a history of seizures.
9. Subject (and/or mother if subject is nursing) has used medications with actions characteristic of monoamine oxidase inhibitors (MAOIs) within 14 days before the start of the study drug is prohibited. Standard daily pediatric multivitamins may be taken until enrollment into the study but will be restricted during the study.
10. Subject (and/or mother if subject is nursing) has received preoperative opioids for more than 72 consecutive hours.
11. Subject (and/or mother if subject is nursing) has received oxycodone or oxymorphone within 48 hours prior to screening.
12. Subject (and/or mother if subject is nursing) has ingested caffeine- or xanthine-containing products (eg, theophylline) within 48 hours before dosing. These products are also prohibited during periods when blood samples are collected.
13. Has a history of relevant drug allergies, food allergies, or both (ie, allergy to oxymorphone or other opioid analgesics) that could interfere with the study.
14. Parent or legal guardian is unable to provide consent for any reason (eg, mental or physical disabilities, language barriers, or is unavailable).

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15. Subject (and/or mother if subject is nursing) has participated in a clinical study of an unapproved drug within the previous 30 days.
16. Is not suitable for entry into the study in the opinion of the Investigator.

Investigational Product, Dosage, and Mode of Administration: EN3319 oxymorphone HCl immediate-release oral liquid (Groups A and B) 1 mg/mL dosed at 0.05 mg/kg by mouth, with subsequent doses to be determined by IDMC. Oxymorphone HCl IV solution (Groups C and D) 1 mg/mL at doses to be determined by IDMC.

Duration of Study:

Screening period – up to 5 days

Treatment period – up to 24 hours

Follow-up telephone contact – 3±1 and 14 ±2 days after the last dose of study drug

Reference Therapy, Dosage, and Mode of Administration: Morphine NCA

Age Group	Starting Background (mcg/kg/h)	Maximum Background (mcg/kg/h)	Bolus Dose (mcg/kg)	Lockout (minutes)	Maximum Bolus/h
A and B	Up to 5	Up to 30	10-15	10	3
C and D	0	Up to 15	10	10	3

Criteria for Evaluation:

Efficacy: Analgesic efficacy will be characterized for subjects in all age groups by assessing morphine demand using NCA. The incidence, amount of NCA rescue medication (both basal infusion and bolus morphine doses), and time to first bolus rescue used in each group will also be examined. Pain assessments using age-appropriate instruments (NIPS and FLACC) will also be utilized.

Pharmacokinetics:

Non-compartmental PK parameters such as AUC, T_{max}, and C_{max} will be determined after a single dose of oxymorphone. Oxymorphone plasma concentration-time data after multiple dosing will be evaluated using population PK analysis methods. Full details of the population PK modeling and analysis will be documented in a separate population PK analysis plan.

All data available for oxymorphone dosing and sample concentrations with elapsed time from the last dose will be reviewed for use in the analysis. A structural and error model will be selected based on oxymorphone plasma concentration time profiles.

Once the structural model has been selected, covariates will be added to the model. Covariates that will be studied include age and weight and others as appropriate.

Safety and Tolerability:

Safety will be assessed by the monitoring and recording of AEs; assessments of cardiac, respiratory, and neurological function; clinical laboratory tests; vital signs; and physical examination findings.

Statistical Methods:

Sample Size Considerations:

Efficacy:

The primary endpoint for efficacy is cumulative morphine demand via NCA. To detect a difference in effect size of 0.9, 20 subjects for each group (active treatment group pooled across all age groups and vs. placebo group pooled across all age groups) will have 80% power at 2-sided significance level of 0.05.

Pharmacokinetics:

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Earlier PK studies in adults have indicated that the best fitting model was 2 compartmental and that the inter- and intra-subject coefficient of variation (CV [%]) for clearance and volume of distribution were 54 and 20, respectively. If each subject provides 3 data points in the ranges of absorption and terminal elimination phases, the total CV(%) (combination of the inter- and intra-subject CV[%]) is approximately 60. Based on this assumption, a total of 34 subjects are needed to provide estimates of clearance and volume of distribution if their 95% confidence interval (CI) is within the range of 0.6 to 1.4 of the point estimates with 90% power.
For the single-dose phase, 5 subjects from each age group will receive oxymorphone (up to 60 total subjects, depending on IDMC recommendations for each age group). For the multiple-dose phase, 10 subjects from each age group will be randomized to receive either oxymorphone or placebo (40 total subjects). This will provide up to 80 subjects that are evenly distributed over the 4 age groups for the final population PK modeling and analysis. Analysis Populations: A population PK analysis will be performed using data from both single-dose and multiple-dose phases. The PK population will include all subjects who receive oxymorphone HCl (immediate-release oral liquid or IV formulation) and have plasma concentration data from at least 1 time point from either single-dose or multiple-dose phase to facilitate the population PK modeling and analysis. *Single-dose Phase*: The safety population for the single-dose phase will include all subjects who receive at least 1 dose of study drug. All safety analyses and demographic/baseline characterization for the single-dose phase will be performed using this population. The single-dose PK population will include all subjects who receive oxymorphone HCl (immediate-release oral liquid or IV formulation) and provide sufficient data points to facilitate the calculation for non-compartmental PK parameters. The evaluable population will include all subjects who receive at least 1 dose of the study medication and provide a minimum of 2-hour efficacy and safety data to facilitate the dose selection decision. All efficacy analyses for the single-dose phase will be performed on this population. *Multiple-dose Phase:* The safety population for the multiple-dose phase will include all subjects who receive at least 1 dose of study drug or placebo. All safety analyses for the multiple-dose phase will be performed using this population and in all safety analyses, subjects will be attributed to the treatment that they actually received regardless of their assigned randomized treatment. The intent to-treat (ITT) population will include all randomized subjects who receive at least 1 dose of study drug during the multiple-dose phase and complete at least 1 post dose pain intensity assessment. All efficacy analyses and demographic/baseline characterization will be performed using this population treatment they actually receive. The per-protocol population (PP) will include all subjects in ITT population who did not violate the protocol in any fundamental manner related to the evaluation of efficacy. This population will be used for supporting the primary efficacy analysis. ***Statistical Analysis***: Pharmacokinetic Analyses: The PK analysis will be conducted using population PK modeling and analysis methods as described in the Food and Drug Administration (FDA) Guidance for Industry Population Pharmacokinetics. Details of the population PK modeling and analysis will be documented in a separate population PK analysis plan. Results of these analyses will be documented in a separate report.

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Single-dose PK will also be characterized using non-compartmental methods. Efficacy Analyses: The primary endpoint (cumulative morphine demand via NCA) will be analyzed using a mixed effect model with subject as random effect and treatment and age group as fixed effect. The least square means for each treatment group (active treatment and placebo groups) and the difference between the treatment groups (active vs. placebo) as well as their 95% CIs will be calculated using the model.
Incidence of NCA rescue medication use, and time to the first use of bolus rescue will be analyzed using logistic regression, and Cox models, respectively. Safety Analyses: Adverse events (AEs) will be coded using the latest major version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized overall and by preferred term and system organ class. AEs will also be summarized by severity and relationship to study drug. Serious adverse events (SAEs) and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from baseline for assessments of cardiac, respiratory, and neurological function (Modified Ramsay Sedation Scale); clinical laboratory test results; and vital sign measurements will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Physical examination findings will be presented in a listing.

3. SCHEDULE OF EVENTS

Table 3: Schedule of Assessments/Procedures for the Single-dose Phase

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

Table 3: Schedule of Assessments/Procedures for the Single-dose Phase (Continued)

Footnotes:

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

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

[c] See section 8.1.3 and section 8.1.4 for Baseline Dosing Assessment Procedures and NCA Information. All baseline assessment procedures should be completed prior to dosing the subject. After subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will enter either the single-dose e phase of the study. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.

After subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they will enter either the single-dose phase of the study.

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

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

[f] Respiratory assessment Includes oxygen saturation.

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

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

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

[j] The FLACC will be used for subjects in Groups A and B . The NIPS will be used for subjects in Groups C and D.

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

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

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

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

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

[3] Czarnecki ML, Salamon KS, Jastrowski Mano KE, Ferrise AS, Sharp M, Weisman SJ. A preliminary report of parent/nurse-controlled analgesia (PNCA) in infants and preschoolers. *Clin J Pain*. 2011;27(2):102-107.

[4] Berde CB, Walco, GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics*. 2012;129(2):354-364.

[5] Howard RF, Lloyd-Thomas A, Thomas M, et al. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Pediatr Anesth*. 2010;20(2):126-134.

Table 4: Schedule of Assessments/Procedures for the Multiple-dose Phase

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

Table 4: Schedule of Assessments/Procedures for the Multiple-dose Phase (Continued)

Footnotes:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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[6] Czarnecki ML, Salamon KS, Jastrowski Mano KE, Ferrise AS, Sharp M, Weisman SJ. A preliminary report of parent/nurse-controlled analgesia (PNCA) in infants and preschoolers. *Clin J Pain*. 2011;27(2):102-107.

[7] Berde CB, Walco, GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop. *Pediatrics*. 2012;129(2):354-364.

[8] Howard RF, Lloyd-Thomas A, Thomas M, et al. Nurse-controlled analgesia (NCA) following major surgery in 10,000 patients in a children's hospital. *Pediatr Anesth*. 2010;20(2):126-134.

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5. LIST OF ABBREVIATIONS

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

Table 5: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AUC	Area under the concentration versus time curve
BL	Baseline; occurs at the time when postoperative oral dosing with an opioid analgesic commences according to each institution's standard of care
BLQ	Below limit of quantification
CF	Clear fluids
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CRF	Case report form
CRO	Contract research organization
CV	Coefficient of variation
CYP	Cytochrome P450
DAT	Diet-as-tolerated
DEA	Drug Enforcement Administration
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EKG	Electrocardiogram
EOT	End-of-Treatment
ER	Extended-release
ET	Early termination
FDA	Food and Drug Administration
FF	Full fluids
FLACC	Face, Legs, Activity, Cry, Consolability scale

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
HCl	Hydrochloride
IB	Investigator Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IR	Immediate-release
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LAR	Legally authorized representative
LC-MS/MS	Liquid chromatography dual mass spectrometry
MAA	Marketing Authorization Application
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Nurse-controlled analgesia
NDA	New Drug Application
NIPS	Neonatal Infant Pain Scale
NSAID	Nonsteroidal anti-inflammatory drug
O_2	Oxygen
OTC	Over-the-counter
PCA	Patient-controlled analgesia
PCS	Potentially clinically significant
Ped-IMMPACT	Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
PK	Pharmacokinetics
PREA	Pediatric Research Equity Act
PRN	Pro re nata (as needed, or when necessary)
PVRM	Pharmacovigilance and Risk Management

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation or specialist term	Explanation
q4-6h	Every 4 to 6 hours
SAE	Serious adverse event
SAS®	Statistical Analysis System
SD	Standard deviation
SOC	Standard of care
SPC	Summary of Product Characteristics
$t_{½}$	Terminal half-life
TBD	To be determined
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
VAS	Visual Analog Scale

6. INTRODUCTION

6.1. Background

Oxymorphone HCl (14-hydroxydihydromorphinone) is a semisynthetic opioid agonist derived from thebaine with a more rapid onset of action and a significantly higher analgesic potency compared to the structurally-related compound morphine. Oxymorphone was first synthesized and developed in the 1950s; oxymorphone-containing products were first approved by the Food and Drug Administration (FDA) in 1959. Developed by Endo Pharmaceuticals Inc., oxymorphone HCl extended-release (ER) tablets (EN3202; OPANA® ER) and oxymorphone HCl immediate-release (IR) tablets (EN3203; OPANA®) were approved by the FDA on June 22, 2006. Oxymorphone is a Schedule II controlled substance.

Oxymorphone IR is indicated for the management of moderate to severe pain in adults where the use of an opioid is appropriate; oxymorphone IR tablets have been developed in strengths of 5 mg and 10 mg. Oxymorphone ER is indicated for the relief of moderate to severe pain in subjects requiring continuous, around-the-clock opioid treatment for an extended period of time; oxymorphone ER tablets have been developed in strengths of 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg. Additional details of the physical, chemical, and pharmaceutical properties of oxymorphone HCl immediate-release oral liquid and oxymorphone ER are provided in the Investigator's Brochure (IB) and in the OPANA Prescribing Information. In the present study, an oral liquid formulation of oxymorphone IR has been developed at a concentration of 1 mg/mL for use in subjects aged 61 days and older. Subjects aged 0 to 60 days will be administered oxymorphone HCl injectable formulation (oxymorphone HCl injection).

6.2. Summary of Nonclinical Studies

Nonclinical pharmacology and toxicology studies conducted between 1952 and 1970 have been reviewed.(1) The results of those studies indicate that the pharmacology and toxicology profile of oxymorphone is similar to that of other opioids. This is consistent with more recent toxicology studies conducted with oxymorphone.(2,3) Results of nonclinical studies are summarized in the IB and in the OPANA Prescribing Information.

6.3. Summary of Known Risks and Benefits

Oxymorphone ER and oxymorphone IR tablets were studied in an adult clinical development program; several pharmacokinetic (PK) studies used both dosage forms. The properties of the oxymorphone molecule found in the adult clinical PK studies are the same regardless of the formulation (see the IB and the OPANA Prescribing Information. Therefore, conclusions concerning bioavailability and the effects of food, other drugs, age and gender, liver disease, and renal impairment can be drawn independent of the formulation. A total of at least 16 clinical PK and bioavailability studies have been conducted to support the development and proposed labeling of oxymorphone ER and oxymorphone IR tablets. Results from these studies are summarized in the IB.

The efficacy and/or safety of oxymorphone were assessed in at least 14 adult clinical studies. Evaluations of the clinical efficacy of oxymorphone included the assessment of pain relief in 3 models: acute postoperative pain (oxymorphone ER and oxymorphone IR); chronic

non-malignant pain, specifically, lower back pain, osteoarthritis, and neuropathic pain (oxymorphone ER); and chronic cancer pain (oxymorphone ER). Postoperative pain studies were multicenter, double-blind, randomized, parallel group, placebo-controlled studies of limited duration (ie, 8 hours to 3 days), some of which also included an active control group. Single, fixed doses of oxymorphone were used in all of these studies; multiple doses were also evaluated in some studies. Chronic non-malignant and cancer pain studies included multicenter, double-blind, randomized, parallel group, placebo-controlled (and in some cases active-controlled) studies of varying duration up to 2 years. Safety was evaluated in all clinical studies.

The safety, PK, and effectiveness of oxymorphone IR has also been investigated in children aged >12 to 17 with acute postoperative pain requiring an opioid. A starting dose of 5 mg oxymorphone every 4 to 6 hours was well tolerated and is appropriate for these patients. Based on available data, the safety findings are consistent with the established safety profile of oxymorphone. The effectiveness of oxymorphone was shown in the improvement in pain intensity scores using a 100-mm visual analog scale (VAS) seen throughout the treatment period.

In the clinical development of the study drug, oxymorphone ER and IR have been shown to be potent opioid analgesics and that the efficacy and safety are not dependent on a patient's metabolizer status (see OPANA ER Prescribing Information).(4)

For the current study, an oral liquid formulation of oxymorphone HCl (EN3319) has been developed for weight-based dosing in populations unable to swallow tablets. The bioavailability and bioequivalence properties of this new formulation are identical in nature to the OPANA tablet formulation, and are summarized in the IB.

6.4. 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 postoperative 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. Particularly for neonates, postoperative pain care can play an important role in outcomes, as adverse circulatory and respiratory events may manifest following inadequate interventions.(4) Inadequate treatment of pain in neonates may also have significant implications beyond the neonatal period, perhaps resulting in long-lasting changes in pain behavior.(12)

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 efficacy, safety, tolerability, and PK data for oxymorphone HCl in children (aged 0 days to 2 years) experiencing postoperative pain.

6.4.1. Study Design Rationale

This is a Phase 3 study with an open-label, single-dose, dose selection phase and a randomized, double-blinded, active controlled multiple-dose phase to characterize the efficacy, safety, tolerability, and PK of oxymorphone HCl immediate-release oral liquid in pediatric subjects with acute moderate to severe postoperative pain for whom an oral opioid is determined to be an appropriate treatment option. The oxymorphone HCl immediate-release oral liquid starting doses chosen for the study are based on an established equivalent morphine sulfate dose (0.3 mg/kg by mouth every 3 to 4 hours) in children being treated for acute pain.(13) Doses utilized for subjects receiving the intravenous (IV) formulation of oxymorphone HCl will be determined by an independent data monitoring committee (IDMC) following review of safety, efficacy, and PK data obtained in older subjects.

Randomization in the multiple-dose phase will be used to avoid bias in the assignment of patients to treatment and to enhance the validity of statistical comparisons between treatment groups. Blinding to treatment assignment during the multiple-dose phase will be used to reduce potential bias during data collection and evaluation of endpoints.

The study subjects will be stratified into 4 age groups:

A. 6 months – <2 years *(up to and inclusive of 729 days)*

B. 61 days – <6 months *(up to and inclusive of 179 days,*

C. 31 days – 60 days

D. 0 – 30 days

The study will enroll the older age group (6 months – <2 years) first as a conservative approach aimed at safe drug administration in the less at-risk populations. Completion of the older age groups will help highlight any unexpected PK and/or pharmacodynamic (PD) results prior to exposure in younger (ie, more at-risk) subjects should they occur. Data from the older age groups will also help to more accurately predict safety and efficacy in the younger study populations. The age groups were selected due to age-related differences in this pediatric population that include:(8)

- **Body Compartments**: Younger infants have significantly different body compartment composition (ie, fat, muscle, water differences) that impact volume of distribution for water-soluble drugs.
- **Plasma Protein Binding**: Younger infants have decreased albumin concentration and α_1-acid glycoprotein.
- **Hepatic enzymes**: Younger infants have immature cytochrome P450 (CYP) subtypes and glucuronyl transferases.
- **Renal filtration/excretion**: Younger infants have decreased glomerular filtration.
- **Metabolic Rate**: Younger infants have increased oxygen (O_2) demand, decreased airway caliber, increased work of breathing, decreased control of airway musculature, and decreased ventilatory responses to O_2 and carbon dioxide (CO_2).

The study will initiate with oldest age subjects first (Group A), and each subsequently younger age group (B, C, and D) will enter the study only after the preceding age group has completed

enrollment and the data is reviewed by an IDMC to evaluate efficacy, safety, tolerability, and PK (ie, Group A must complete enrollment and IDMC review before Group B can open for enrollment, etc.). The study will be implemented in 2 phases and will be conducted in each age group separately and sequentially:

- Beginning with Group A, each group must complete the single-dose phase and IDMC review before the next age group can open enrollment in the single-dose phase.
- Beginning with Group A, each age group must complete the multiple-dose phase and IDMC review before the next age group can open enrollment in the multiple-dose phase.
- Each age group must complete their respective single-dose phase and IDMC review before proceeding to the multiple-dose phase.

Beginning with Group B, in order to proceed to the multiple-dose phase, each age group must complete their respective single-dose phase and the preceding age group must have completed their respective multiple-dose phase. As the study proceeds to progressively younger age groups, the IDMC will therefore review single-dose and multiple-dose data to better inform their decision on choosing doses for the multiple-dose phase. This approach will provide the earliest possible indication of any concerns with drug accumulation or clearance as subjects proceed to the multiple-dose phase.

7. OBJECTIVES

7.1. Primary Objective

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

7.2. Secondary Objectives

The secondary objectives of this study are:

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

8. INVESTIGATIONAL PLAN

8.1. Study Design

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

All subjects will be enrolled preoperatively up to 5 days before surgery with the expectation that they will require IV access after surgery and postoperative analgesia with an opiate medication.

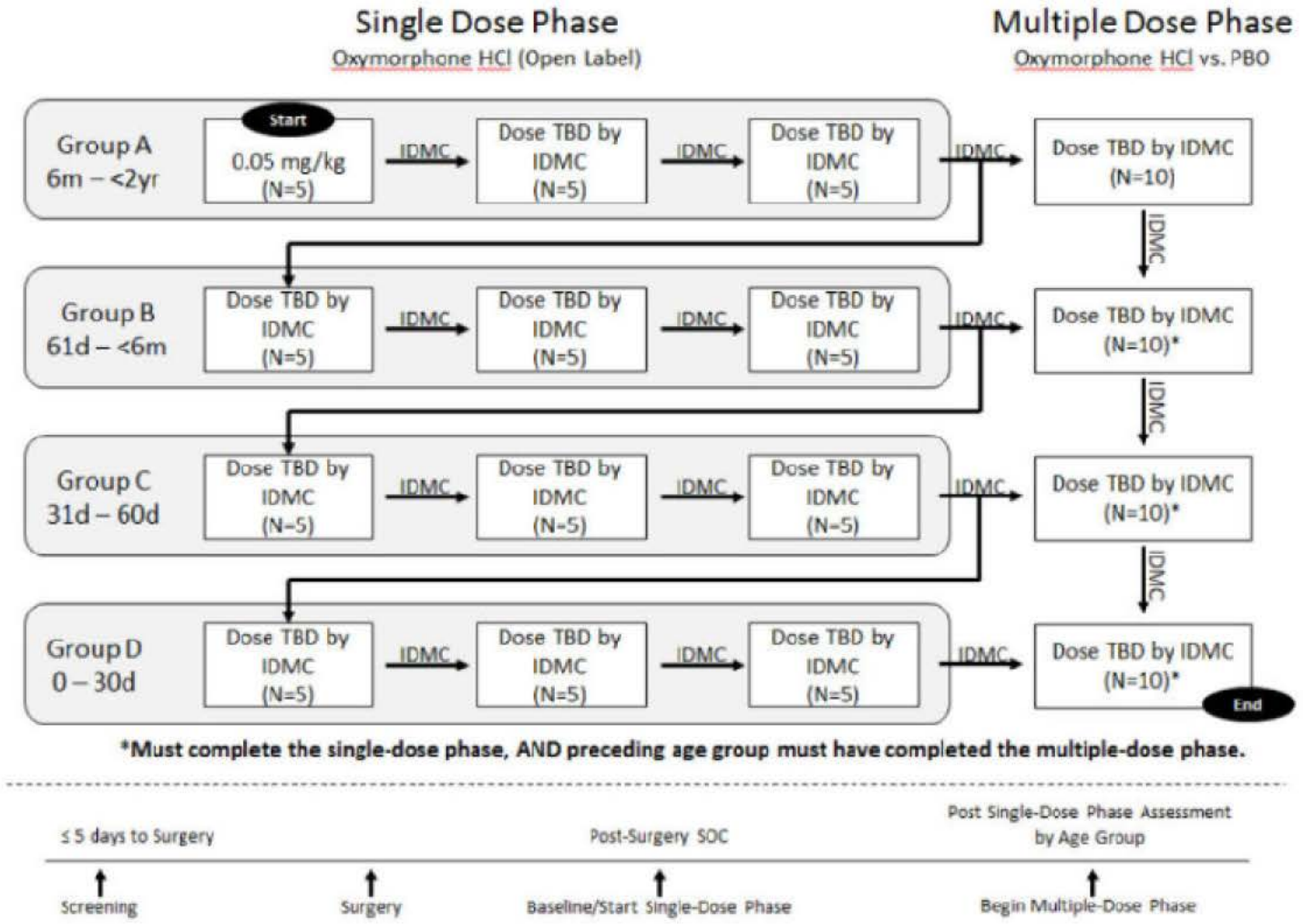
Four (4) separate age groups of subjects will be enrolled in the study, with recruitment of older infants and toddlers preceding involvement of the youngest age subjects (Figure 1).

The study will consist of a screening period; a post-surgery evaluation; a treatment phase (single-dose open-label phase and placebo-controlled, double-blinded, multiple-dose phase, each occurring after surgery) to evaluate efficacy, safety, tolerability, and PK; an end-of-treatment (EOT) assessment 24 hours after the last dose of study drug; and 2 follow-up contacts (at 3 ±1 and 14 ±2 days after the last dose of study drug). The total duration of the study, excluding screening, for subjects in the open-label, dose-selection phase will be approximately 15 days from the first dose of study drug to last follow-up. The total duration of the study, excluding screening, for subjects in the multiple-dose phase will be up to 17 days from the first dose of study drug to last follow-up.

For all age groups, the screening period will occur within 5 days before surgery.

Eligible subjects whose parent or guardian provides written consent will have study assessments performed at screening.

Figure 1: Study Design



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

8.1.1. Screening Phase

The Investigator, or designee, will identify a potential candidate for the EN3319-304 study. The Investigator, or designee, will obtain informed consent per Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) requirements and will screen the subject at any time within 5 days prior to surgery. Informed consent will be obtained via parent or legal guardian prior to initiation of any study-related procedures. After the informed consent has been signed, and a unique subject number has been assigned, screening assessments/procedures will be completed (see Table 3 and Table 4 Blood samples for baseline clinical laboratory tests as detailed in Table 9 may be collected at any time within 5 days prior to surgery. Clinical labs drawn as part of the standard of care (SOC) (including the intraoperative period) will be acceptable for study purposes provided they are taken prior to first surgical incision and assessed by the Investigator prior to administration of the first dose of study drug (see Table 9 for a list of analytes). Details on selection of subjects will be based on their anticipated need for opioids for management of pain following surgery. The Investigator will explain the study 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).

Screening activities will include:

- Obtaining written informed consent from parent(s)/legal guardian(s) (section 18.3).
- Assessing entry criteria: inclusion/exclusion criteria (section 9.1 and section 9.2) will be assessed during the screening phase.
- 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 EKG.
- Measuring vital signs (section 12.8).
- Obtaining clinical laboratory tests (section 12.7): Blood samples for baseline clinical laboratory tests may be collected at any time within 5 days prior to surgery. Clinical labs drawn as part of the SOC (including the intraoperative period) will be acceptable for study purposes provided they are taken prior to first surgical incision and assessed by the Investigator prior to administration of the first dose of study drug (see Table 9 for a list of analytes).
- Completing a respiratory assessment (section 12.10).
- Completing a neurology assessment (section 12.11 and Appendix A).

- Collecting AEs/SAEs (section 12).
- Recording prior and concomitant medications: medications taken within 30 days prior to signing consent as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (Appendix B). All appropriate restrictions on concomitant medication usage during the preoperative period must be followed per Appendix B.

8.1.2. Post-surgery Evaluation

Each subject will undergo surgery. Following surgery, subjects will receive SOC, including IV analgesia with a non-oxycodone, non-oxymorphone medication that will not interfere with the measurement or metabolism of oxymorphone and does not have oxymorphone as a metabolite. At this time, subjects will have a post-surgery evaluation to re-confirm eligibility. Details of the surgical procedure(s) will be recorded, 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).

Post-surgery evaluation procedures will include:

- Assessing entry criteria: inclusion/exclusion criteria (section 9.1 and section 9.2 will be assessed during the screening phase and confirmed prior to beginning baseline assessments/procedures.
- Begin continuous pulse oximetry if not already initiated as part of SOC (section 12.10).
- Begin telemetry if not already initiated as part of SOC (section 12.12).
- Measuring vital signs (section 12.8).
- Completing a respiratory assessment (section 12.10).
- Completing a neurological assessment (section 12.11 and Appendix A).
- Recording of surgical details (procedure[s], AEs, etc.) including medications (Appendix B) type of procedure(s), date of procedure(s), surgical start/stop time, and anesthesia/analgesia start and stop time.

If not already obtained at screening, post-surgery evaluation procedures may include:

- Recording medical/surgical history: all previously existing and current medical conditions including any past surgical procedures.
- 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.

- Obtaining clinical laboratory tests (section 12.7): Clinical labs drawn as part of the SOC (including the intraoperative period) will be acceptable for study purposes provided they are taken prior to first surgical incision and assessed by the Investigator prior to administration of the first dose of study drug (see Table 9 for a list of analytes).
- Collecting AEs/SAEs (section 12).
- Recording prior and concomitant medications: medications taken within 30 days prior to signing consent as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (Appendix B). All appropriate restrictions on concomitant medication usage during the preoperative period must be followed per Appendix B.
- After subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will enter either the single-dose or multiple-dose phase of the study (depending on study progression). Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid.
- After subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they will enter either the single-dose or multiple-dose phase of the study (depending on study progression).

8.1.3. Baseline Dosing Assessments (Day 1, Time 0)

Baseline dosing assessments and procedures should be completed prior to administration of study drug. They include the following:

- Assessing current pain intensity (immediately prior to first administration of study drug): each subject will provide a baseline level of pain intensity using an age-appropriate pain assessment instrument (Face, Legs, Activity, Cry, Consolability [FLACC] scale or Neonatal Infant Pain Scale [NIPS] (Appendix C or Appendix D, respectively) prior to first dose of study drug administration as well as just before administration of each dose of study drug during the multiple-dose.
- Measuring vital signs (section 12.8).
- Continuous pulse oximetry (section 12.10).
- Telemetry (section 12.12).
- Completing a respiratory assessment (section 12.10).
- Completing a neurological assessment (section 12.11 and Appendix A).

Blood sample for baseline PK analysis should be drawn immediately prior to first administration of study drug

- Dosing the subject with study drug (All baseline dosing assessments should be completed prior to administration of study drug)

- When subjects in Groups A and B are showing signs of tolerating oral intake and subjects in Groups C and D are showing signs of awakening and arousal their IV analgesic regimen should be discontinued and the subject will be closely monitored for pain. The pain scores will be recorded at least hourly until time of study drug dosing. Once their pain score is ≥3 on the NIPS (day 1 time zero) or is ≥4 on the FLACC, study drug (oxymorphone HCl, either IV or oral) can be administered.
- Prior to study drug administration, the treating physician should review all intra-operative and post-operative medications previously administered (excluding Nurse-controlled analgesia (Section 8.1.4) to ensure that the administration time, half-life and potency of any of these medications will not impact the study drug dose pain assessments. The treating physician must confirm the subject's ability to tolerate oral liquids prior to administering study oxymorphone HCl oral solution. The exact time when study drug was administered must be recorded. No food or oral liquid restrictions will be imposed around the time of dosing. Note: Laxative and antiemetic regimens may be used; all subjects will be allowed use of a laxative and antiemetic throughout the study. All medications taken by the subjects (including NCA rescue medication) must be recorded with precise dose administered in mg or cc, frequency of administration, and indication.
- Food consumption will be recorded from the period 1 hour prior to administration of study drug through end of treatment (EOT) assessment; record all times that any food was consumed and what food was consumed (diet-as-tolerated [DAT], DAT-soft, full fluids [FF], clear fluids [CF], water, formula, breast milk).
- Nurse-controlled analgesia (section 8.1.4) will be started coincident with first administration of study drug.

- Updating and recording all concomitant medications: medications taken within 30 days prior to signing consent as well as ongoing medications. Note: Preoperative, intraoperative, and postoperative medications will be recorded (Appendix B). For single-dose cohorts, non-opioid analgesics (acetaminophen and/or non-steroidal anti-inflammatory drugs [NSAIDS] per SOC may be used to treat breakthrough pain not earlier than 6 hours following administration of study drug.
- Across all age groups, acetaminophen or SOC may be administered for subjects who develop fever during the study period.
- Collecting AEs/SAEs (section 12.1).

The first cohort of subjects from Group A entering the study will receive a dose of 0.05 mg/kg for the single-dose phase, and doses for all subsequent cohorts (across all age groups and dose Phases) will be determined based on recommendation of the IDMC following each cohort review.

8.1.4. Nurse-controlled Analgesia (NCA)

Postoperative morphine consumption via NCA will be used as a surrogate measure for analgesic efficacy.(14). NCA is an established form of postoperative analgesia, similar in nature to other

demand-led analgesic regimens (eg, PCA), but tailored for patients who are too young or unable to use PCA.(15,16) The dose of NCA rescue medication will be based on weight and age according to well-established standards,(14-18) and will be administered by a blinded nurse observer trained in appropriate pain assessment techniques. Under this NCA paradigm, morphine analgesia may be administered using a conventional PCA pump using bolus dosing with or without a background infusion rate as referenced in Table 6. Intermittent PRN dosing, with or without a background infusion (using the background infusion dosing guidelines referenced in Table 6), in accordance with individual institutions' usual standard practices for postoperative opioid analgesia in this population is permissible. NCA (section 8.1.4) will be initiated coincident with the first administration of study drug (refer to Section 8.1.5 [single-dose phase] and Section 8.1.6 [multiple-dose phase]) but not earlier than the first administration of study drug. The morphine-NCA guidelines detailed below provide a baseline framework for postoperative morphine-NCA and may be adjusted to be consistent with institutional SOC.

Table 6: Guidelines for Morphine Nurse-controlled Analgesia [a]

Age Group	Starting Background (mcg/kg/h)	Maximum Background (mcg/kg/h)	Bolus Dose (mcg/kg)	Lockout (minutes)	Maximum Bolus/h [b]
A and B	Up to 5	Up to 30	10-15	10	3
C and D	0	Up to 15	10	10	3

Initiation: Nurse-controlled analgesia should be initiated concomitant with first administration of study drug.

[a] Adapted from *Pediatr Anesth*. 2010;20(2):126-134 and *Br J Anaesth*. 2007;98(3):372-379.

[b] Subjects should be titrated to minimal effective analgesia requiring up to 3 boluses per hour. If more than 3 boluses per hour are required, background may be increased by 5 mcg/kg/h up to the maximum background.

8.1.5. Single-dose Phase

The open-label, single-dose phase will use oxymorphone HCl immediate-release oral liquid (Groups A and B) or oxymorphone HCl IV (Groups C and D) for PK assessments and to determine which dose (for each age group) to take forward into the multiple-dose phase (Figure 1). For each age group, up to 3 cohorts of 5 subjects will receive oxymorphone HCl (either immediate release oral liquid or IV, based on age. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. Once the subject's analgesic regimen has been discontinued per standard of care, baseline assessments will be collected as documented in Table 3 and Section 8.1.3. All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time baseline dosing assessments will be performed and they will be administered study drug. The FLACC will be used for subjects in Group A and Group B. The NIPS will be used for subjects in Group C and Group D. Morphine-NCA per SOC (section 8.1.4) will be initiated coincident but not earlier than the firststudy drug administration. Bolus morphine administration may be given per standard of care. No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive rescue by morphine-NCA as needed. Non-opioid analgesics (acetaminophen and/or non-steroidal anti-inflammatory drugs [NSAIDS] per SOC may be used to treat breakthrough pain not earlier than 6 hours following administration of study drug.

• Subjects will undergo subsequent pain assessments as noted in Table 3. All pain assessments will be conducted using an age-appropriate pain instrument (FLACC or NIPS). PK and additional assessments will occur at fixed intervals throughout the single-dose phase, as outlined in Table 3. Food consumption will be recorded from the period 1 hour prior to administration of study drug through EOT assessment; record all times that any food was consumed and what food was consumed (DAT, DAT-soft, FF, CF, water, formula, breast milk). The following assessments are to be completed during the single-dose phase.

Following administration of study drug, procedures and assessments will include the following:

- Blood samples for PK analysis should be collected at 0.5 (for subjects with even subject numbers – see Table 3, footnote "n") **or** 1.0 hour (for subjects with odd subject numbers – see Table 3, footnote "n"), and at 2.0, 3.0, 4.0, and 8.0 hours. A window of ±10 minutes is allowed.
- Post-dose vital signs, respiratory assessments, and neurological assessments will be collected at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, and 8.0 hours.
- Telemetry is required for all subjects.
- Continuous pulse oximetry.
- AEs and concomitant medications will be monitored throughout the single-dose phase.
- Pain assessments (using FLACC or NIPS; see Appendix C or Appendix D, respectively) will be recorded at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, and 8.0 hours.
- Morphine requirements (via NCA) will be continuously monitored and recorded, including all boluses and changes in background infusion.

8.1.6. Multiple-dose Phase

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

Prior to entering the multiple-dose phase, when subjects in Groups A and B are postoperative, and are showing signs of tolerating oral intake their SOC analgesic regimen will be discontinued and they will be randomized and enter multiple-dose phase of the study.

Prior to entering the multiple dose-phase, when subjects in Groups C and D are post-operative, and are showing signs of awakening and arousal, their SOC analgesic regimen will be discontinued and they will be randomized and enter the multiple-dose phase of the study.

Baseline assessments (

Table 4) will be collected following randomization. The FLACC will be used for subjects in Groups A and B. The NIPS will be used for subjects in Groups C and D. All subjects will then be closely monitored for pain and their pain score will be recorded at least hourly until their pain score is ≥4 on the FLACC or ≥3 on the NIPS, at which time they will be administered study drug (oxymorphone HCl immediate release oral liquid for Groups A and B; IV oxymorphone HCl for Groups C and D) or placebo. Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. Morphine-NCA (section 8.1.4) will be initiated coincident with but not earlier than study drug/placebo administration, and this time will be designated as day 1 time zero. No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive morphine-NCA rescue as needed. Subjects will undergo subsequent pain assessments at half-hour intervals post first dose in the multiple-dose phase (

Table 4). Following dose 1, subsequent doses should be administered q4-6h PRN but no less than 4 hours apart, and at least 20 minutes have elapsed since the last bolus NCA rescue. The last dose of study drug will be administered no later than 18h post first dose. (All subjects must receive a minimum of 3 doses of study drug in the multiple-dose phase). PK and additional assessments will occur at fixed intervals throughout the multiple-dose phase, as outlined in section 3. Food consumption will be recorded from the period 1 hour prior to administration of study drug through EOT assessment; record all times that any food was consumed and what food was consumed (DAT, DAT-soft, FF, CF, water, formula, breast milk).

Following first administration of study drug, procedures and assessments will include the following:

- Blood samples for PK analysis should be collected immediately prior to each dose. Post-dose vital signs, respiratory assessments, and neurological assessments will be recorded at 0.5, 1, 2, 3, and 4 hours after administration of first dose of study drug; and at 0.5, 1, and 2 hours after administration of subsequent doses.
- Continuous telemetry.
- Continuous pulse oximetry.
- AEs and concomitant medications will be monitored throughout the multiple-dose phase.
- Pain assessments (using FLACC or NIPS; see Appendix C or Appendix D, respectively) will be recorded every 0.5 hours through EOT.
- Morphine requirements (via NCA) will be continuously monitored and recorded, including all boluses and changes in background infusion.

8.1.7. End-of-treatment/Early Termination

At the completion of the single- or multiple-dose phases, EOT assessments and procedures will occur at 24 hours after thelast study drug administration or upon early study withdrawal. Each subject will be required to complete all EOT/ET assessments and procedures unless consent has been withdrawn. EOT assessments will include:

- Ongoing collection of AEs/SAEs (section 12).

- Performing physical examination: a brief physical examination, excluding length and weight, to assess the subject's overall health and physical status.
- Measuring vital sign (section 12.8).
- For the single-dose phase, collecting a blood sample for PK assessments (at 24 hours or upon EOT, if possible).
- For multi-dose phase, no blood sample for PK assessments will be drawn at EOT.
- Obtaining clinical laboratory tests (section 12.7): clinical laboratory tests as part of SOC will be acceptable.
- Assessing respiratory and neurological function (section 12.10, section 12.11 and Appendix A).
- Telemetry and pulse oximetry will be ongoing to EOT or ET.
- Updating and recording concomitant medications (including NCA rescue medications).
- Pain assessment (FLACC or NIPS; Appendix C or Appendix D, respectively) will be recorded.
- Recording of food consumption from the period 1 hour prior to administration of study drug through EOT assessment; record all times that any food was consumed and what food was consumed (DAT, DAT-soft, FF, CF, water, formula, breast milk).
- Converting subjects to a marketed opioid upon discharge, if required.
- Scheduling the 3-day and 14-day follow-up telephone call: assessment to include ongoing or new AEs, SAEs, and associated concomitant medications. The complete Schedule of Events is provided in Table 3 and Table 4

8.2. Selection of Doses

This study is designed to characterize the efficacy, safety, tolerability, and PK of single-dose and multiple-dose postoperative treatment utilizing oxymorphone HCl immediate-release oral liquid in children aged 0 to <2 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,(19) 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 one-half of the predicted equianalgesic starting dose of oral morphine. Once the 2 age groups receiving the oral liquid formulation of oxymorphone HCl have completed the single-dose phase, data from these groups will be used to model the predicted required exposure for analgesia in the younger age groups, and results from the

modeling will be submitted as part of the IDMC's review materials to determine the starting dose for age Group C (the first group in the study to receive parenteral [IV] oxymorphone HCl).

8.2.1. Single-dose Phase

The first cohort of subjects from Group A will receive 0.05 mg/kg oxymorphone HCl immediate-release oral liquid. Data from the initial cohort will be assessed by the IDMC for efficacy, safety, tolerability, and PK, at which time the IDMC will make a recommendation for the dose for the second cohort of subjects from Group A. Each cohort of age groups will progress through the single-dose phase in the same manner (ie., completion of cohort followed by IDMC data review and dose recommendation for the next cohort) until either 3 doses are assessed in the single-dose phase for each age group or the IDMC recommends that an age group proceeds to the multiple-dose phase.

The starting dose for the first cohort of subjects of Group B will be determined based on IDMC recommendation following review of data from Group A. Doses for subsequent cohorts of Group B will be determined based on IDMC recommendation following completion of prior Group B cohorts (up to 3 cohorts may be tested in the single-dose phase for each age group). Because Groups C and D will utilize an IV formulation of oxymorphone HCl, the IDMC will also be provided PK modeling data aggregated from Groups A and B (by the Sponsor) to assist in their determination of the proper starting dose. The starting dose for Group D will be determined by the IDMC following completion of Group C, with doses for subsequent cohorts of Group D subjects determined in the same manner as described above. For any cohort or age group, the sponsor may choose to utilize a dose in the single-dose phase other than that recommended by the IDMC, but will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. Likewise, the sponsor may choose to end the single-dose phase for any age group after 2 cohorts have been tested, and will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. All such changes must be endorsed as "safe to proceed" by the IDMC before being implemented in the study.

8.2.2. Multiple-dose Phase

Following review of data related to the efficacy, safety, tolerability, and PK from the single-dose phase, the IDMC will provide a recommendation for a dose (for each age group) to be carried forth into the double-blind, placebo-controlled multiple-dose phase to assess efficacy of oxymorphone HCl vs. placebo. The determination of dose to be tested in the multiple-dose phase will be made independently for each age group. The IDMC will make their dose recommendation after equal consideration of the following factors:

1) Analgesic efficacy in the single-dose phase (no morphine-NCA bolus doses required for at least 3 hours following dosing).
2) PK and analgesic efficacy data from the multiple-dose phase of the preceding age group.
3) Minimal drug-related AE profile (determined at the discretion of the IDMC).
4) Optimal safety and tolerability profile (determined at the discretion of the IDMC).

In the event that no dose tested in the single-dose phase meets these criteria, the IDMC will provide a dose recommendation for testing in the multiple-dose phase that they deem safe for

testing (the dose may be below the lowest dose tested in the single-dose phase, but not above the highest tested dose). For any cohort or age group, the Sponsor may choose to utilize a dose for the multiple-dose phase other than that recommended by the IDMC, but will notify the IDMC of any such changes and provide rationale for the change prior to implementing the change in the study. All such changes must be endorsed as "safe to proceed" by the IDMC before being implemented in the study.

8.3. Study Drug Administration

Study drug in the form of oral liquid will be provided for subjects in age groups A and B. If a subject in groups A or B does not consume the entire dose, the subject should not be redosed until the next time scheduled dose, if applicable. A parenteral formulation of the study drug will be provided for subjects in age groups C and D. Subjects randomized to receive placebo in the double-blind multiple-dose phase will be administered an oral liquid or parenteral formulation (depending on age group) that is identical in appearance to the active study drug.

The selection and timing of drug dosing will be as presented in Table 3 and

Table 4 (Schedule of Events).

Following surgery, when subjects in Groups A and B are showing signs of tolerating oral intake and Subjects in Group C and D are showing signs of awakening and arousal their SOC postoperative analgesic regimen will be discontinued. All subjects will then be closely monitored for pain (pain scores will be recorded at least hourly) and they will be administered study drug or placebo once their pain score is ≥4 on the FLACC or ≥3 on the NIPS (day 1 time zero). Subjects in Groups A and B must be able to tolerate oral intake prior to receiving oxymorphone oral liquid. Background morphine-NCA (section 8.1.4) will be initiated coincident with study drug/placebo administration. No food or oral liquid restrictions will be imposed around the time of dosing. All subjects will receive morphine-NCA rescue as needed. The study drug will be administered every 4 to 6 hours as needed (q4-6h PRN) in the double-blind multiple-dose phase. Following dose 1, subsequent doses should be administered no less than 4 hours apart, and at least 20 minutes have elapsed since the last bolus NCA rescue. The last dose of study drug will be administered no later than 18h post first dose. All subjects must receive a minimum of 3 doses of study drug in the multiple-dose phase.

8.3.1. Age Groups A and B

Subjects in age groups A and B will receive an oral formulation of oxymorphone HCl (or an oral liquid placebo matched in color and flavor). Morphine-NCA will be administered by IV catheter.

8.3.2. Age Groups C and D

Subjects in age groups C and D will receive a parenteral formulation of oxymorphone HCl (or a matched placebo appropriate for parenteral administration) administered as a bolus dose through their existing IV catheter (already in place for morphine-NCA).

8.4. Discussion of Study Design, Including the Choice of Control Groups

This is a Phase 3, post market PREA commitment with an open-label, single-dose, dose selection phase and a randomized, double-blinded, placebo-controlled multiple-dose phase to characterize

the safety, tolerability, PK, and efficacy of oxymorphone HCl immediate-release oral liquid in pediatric subjects with acute moderate to severe postoperative pain. The study design and the use of placebo as a control are necessary to provide reliable scientific evidence of efficacy, safety, tolerability, and PK to ensure a reliable evaluation of the balance of benefits and risks.

Within each treatment cohort and age group, subjects will receive open-label oxymorphone HCl immediate-release oral liquid (Age Groups A and B) or IV (Age Groups C and D) in the single-dose phase, and either oxymorphone HCl or placebo in a 1:1 ratio in the multiple-dose phase. Enrollment will be approximately evenly distributed across each of the age groups. Sites will access an Interactive Web Response System (IWRS) for assignment of treatment phase and dose for all subjects. The age groups of subjects are:

A. 6 months – <2 years (up to and inclusive of 729 days)

B. 61 days – <6 months (up to and inclusive of 179 days)

C. 31 days – 60 days

D. 0 – 30 days

The study will initiate with oldest age subjects first (Group A), and each subsequently younger age group (B, C, and D) will enter the study only after the preceding age group has completed enrollment and the data is reviewed by an IDMC to evaluate efficacy, safety, tolerability, and PK (ie, Group A must complete enrollment and IDMC review before Group B can open for enrollment, etc.). The study will be implemented in 2 phases and will be conducted in each age group separately and sequentially:

- Beginning with Group A, each group must complete the single-dose phase and IDMC review before the next age group can open enrollment in the single-dose phase.
- Beginning with Group A, each age group must complete the multiple-dose phase and IDMC review before the next age group can open enrollment in the multiple-dose phase.

Each age group must complete their respective single-dose phase and IDMC review before proceeding to the multiple-dose phase. Up to 3 doses may be tested in each age group in the single-dose phase, and only a single dose level (determined independently for each age group) will be used to assess efficacy versus placebo in the double-blind multiple-dose phase.

8.4.1. Single-dose Phase

The treatment assignment for the single-dose phase is summarized in Table 7.

Table 7: Treatment Assignment – Single-dose Phase

Age Group	Oxymorphone HCl (Max N)
6 months – <2 years[a]	15
61 days – <6 months[b]	15
31 days – 60 days	15
0 – 30 days	15

Age Group	Oxymorphone HCl (Max N)
Total	**60**

[a] Up to and inclusive of 729 days.
[b] Up to and inclusive of 179 days.

8.4.2. Multiple-dose Phase

The multiple-dose phase will proceed using the same age group stratification used in the single-dose phase. Subjects will be randomized to receive either oxymorphone HCl or placebo in a 1:1 ratio. The treatment assignment for the multiple-dose phase is summarized in Table 8.

Table 8: Treatment Assignment – Multiple-dose Phase

Age Group	Oxymorphone HCl (N)	Placebo (N)
6 months – <2 years[a]	5	5
61 days – <6 months[b]	5	5
31 days – 60 days	5	5
0 – 30 days	5	5
Total	**20**	**20**

[a] Up to and inclusive of 729 days.
[b] Up to and inclusive of 179 days.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Subject Inclusion Criteria

In order to be eligible to participate in the study, subjects must meet the following criteria:

1. Is male or female <2 years of age at the time of surgery.
2. Must weigh at least 3 kg.
3. Is scheduled to have a surgical procedure for which opioid analgesia will be needed to manage postoperative pain for at least 18 hours following intraoperative and/or postoperative IV analgesia.
4. Is generally healthy as documented by medical history; physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; 12-lead electrocardiograms (EKG); clinical laboratory assessments; and general observations. Any abnormalities or deviations from the acceptable range that might be considered clinically relevant by the study physician or Investigator will be evaluated on a case-by-case basis, agreed upon by the principal Investigator (or sub-investigator), and documented in study files before enrolling the subject in the study.
5. The subject's parent or guardian has been informed of the nature of the study and has provided written informed consent.

Postoperative

6. Is anticipated to require an analgesic regimen using a short-acting opioid (non-oxycodone or non-oxymorphone) analgesic after surgery (according to SOC as defined in the protocol).
7. Is an inpatient expected to be hospitalized for 24 hours after dosing with study drug.
8. Has an indwelling access catheter for blood sampling.
9. For Groups A and B: Has demonstrated signs of tolerating oral intake. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions.

Prior to Administration of Oxymorphone HCl Oral Solution

10. For Groups A and B: Has demonstrated the ability to tolerate clear liquids, following surgery according to the SOC at each institution. All infants and children should be able to demonstrate strong suck and swallow reflexes and neurologic alertness and stability sufficient to handle oral secretions. The ability to tolerate small amounts (1 to 2 oz.) of clear liquids without emesis (over 30 to 60 minutes) would support readiness for study participation and oral intake once the physician has ordered the diet advanced to clear liquids and the subject has ingested fluids by mouth without nausea or vomiting.

9.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or nervous system(s) or psychiatric disease that would contraindicate participation, as determined by the Investigator.
2. Has any clinical laboratory test result outside the accepted range that has been confirmed upon re-examination and deemed to be clinically significant.
3. Has a clinically significant illness or condition any time before dosing with study drug that would contraindicate participation, as determined by the Investigator.
4. Has a life expectancy <8 weeks.
5. For age groups A and B: Has a malabsorption, gastroenterologic, or abdominal condition that would interfere with the absorption of study drug.
6. Has evidence of increased intracranial pressure.
7. Has a respiratory condition requiring intubation or resulting in active bronchiolitis, asthma, stridor, or difficulty breathing due to congestion and increased nasal secretions, including O_2 saturation ≤92%.
8. Has a history of seizures.
9. Subject (and/or mother if subject is nursing) has used medications with actions characteristic of monoamine oxidase inhibitors (MAOIs) within 14 days before the start of the study drug is prohibited. Standard daily pediatric multivitamins may be taken until enrollment into the study but will be restricted during the study.
10. Subject (and/or mother if subject is nursing) has received preoperative opioids for more than 72 consecutive hours.
11. Subject (and/or mother if subject is nursing) has received oxycodone or oxymorphone within 48 hours prior to screening.
12. Subject (and/or mother if subject is nursing) has ingested caffeine- or xanthine-containing products (eg, theophylline) within 48 prior to screening. These products are also prohibited during periods when blood samples are collected.
13. Has a history of relevant drug allergies, food allergies, or both (ie, allergy to oxymorphone or other opioid analgesics) that could interfere with the study.
14. Parent or legal guardian is unable to provide consent for any reason (eg, mental or physical disabilities, language barriers, or is unavailable).
15. Subject (and/or mother if subject is nursing) has participated in a clinical study of an unapproved drug within the previous 30 days.
16. Is not suitable for entry into the study in the opinion of the Investigator.

9.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An AE
- Lack of efficacy
- Use of an opioid antagonist (eg, naloxone)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc.)
- Withdrawal by subject (reason must be specified)
- The subject was "lost to follow-up"
- Unblinding of a subject based on medical need
- Sponsor decision to terminate trial
- Investigator decision

Other Reasons (reason must be specified)

If a subject discontinues from the study, all EOT procedures should be conducted as detailed in section 3. The date a subject discontinues the treatment and the reason for discontinuation will be recorded in the source documentation and electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no EOT procedures are required except for the collection of AE information. This information should be recorded in the source documentation and the eCRF.

9.3.1. Replacement of Subjects

9.3.1.1. Single-dose Phase

In the single-dose phase, up to 3 dose cohorts of 5 subjects may be studied (doses to be determined by IDMC) for each age group (see Table 7). Enrollment in each cohort will continue until at least 5 evaluable subjects are completed. To be considered an evaluable subject, each subject must meet the following criteria:

1. Receive expected dose of study drug
2. Complete at least 4 hours of post-dose assessments
3. Complete at least 3 PK assessments

9.3.1.2. Multiple-dose Phase

In the multiple-dose phase, a single dose cohort (dose to be determined by IDMC) will be studied for each age group (see Table 8). Subjects will not be replaced in the double-blind multiple-dose phase.

10. TREATMENT OF SUBJECTS

10.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 3. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

10.1.1. Subject Screening

Investigators will be expected to maintain a screening log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

10.1.2. Pretreatment/Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to randomization/study entry (depending on study phase), pretreatment/screening assessments will be performed according to the Schedule of Events outlined in section 3.

10.1.3. Study Entry

A subject whose parent or guardian gives written informed consent and who satisfies all eligibility criteria may be entered into the study. The following demographic information will be required for study entry:

- Subject initials
- Date of birth
- Gender
- Weight

Demographic (and other study specific details) will be entered into the IWRS. At the end of the randomization procedure, the subject will be assigned a unique subject identification number in sequential order.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by -1001, -1002, -1003, and so on.

10.1.4. Study Assessments

All study assessments will be conducted in accordance with section 8 and the Schedule of Events outlined in section 3.

10.1.5. Follow-up

A documented follow-up telephone call will be required 3 days and 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 EOT or ET.

The date of EOT or ET from the study will be recorded by the Investigator (or assigned designee) and will be the official EOT/ET for each subject. Subjects may take analgesics (opioid or non-opioids) according to SOC after EOT. Study participation will end with the completion of the 14-day follow-up telephone call.

10.2. Prior and Concomitant Medications and Procedures

Drugs that are allowed and not allowed as concomitant medications for either episodic or chronic use are described in this section. 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 hours post first dose of study drug) will be recorded. Surgical medications will be captured on the Surgical Medications eCRF. 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 starting with the post-operative period:

- For all age groups: During the single-dose phase, no analgesics other than the study drug (except NCA) will be permitted for 6 hours after study drug administration. Non-opioid analgesics (acetaminophen and/or NSAIDs) per SOC may be used to treat breakthrough pain not earlier than 6 hours after administration of study drug.
- Nursing mothers should be advised not to receive opioids during the study period.
- During the multiple-dose phase (all age groups), no analgesics other than the study drug will be permitted during the 24-hour assessment period (except NCA rescue).
- Across all age groups, acetaminophen or SOC may be administered for subjects who develop fever during the study period.
- 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 postoperative 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 IV opioid pain medication until the completion of study observations.
- SOC may be given for 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.

10.2.1. Prohibited Medications

During the study, the following medications are prohibited:

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

10.3. Treatment Compliance

Discrepancies between the number of doses administered and the amount of returned drug will be recorded in the drug accountability log. The Investigator (or an authorized designee) will perform a review for compliance by reviewing the source documentation and eCRF against used and 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 will be carefully investigated by the Sponsor. Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (section 12.6.1.1).

10.4. Blinding and Randomization

Subjects will be stratified by 4 different age groups as outlined in Table 7 and Table 8. During the multiple-dose phase, subjects within each age group will be randomized to receive either oxymorphone HCl or placebo in a 1:1 ratio.

Site personnel will be trained on the randomization component of the study.

10.4.1. Blinding

The multiple-dose phase of this study is double-blinded. Subjects, parents, study staff (with the exception of the Pharmacist), clinical staff, vendor staff (eg, CRO) with the exception of the

packaging and labeling vendor, and the Sponsor (with the exception of the clinical supplies staff) and its designees will be blinded to the study treatment being received by each subject. In addition, an unblinded monitor will conduct study medication reconciliation at the site. The blind will only be broken in cases of medical need, and every attempt will be made to discuss the case with the Medical Monitor prior to unblinding. Instructions for unblinding subjects during the course of the study will be provided. Breaking the code at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as an SAE according to instructions in section 12.5.2. Otherwise, the study will be unblinded only after database lock and after all Sponsor-required authorizations have been documented.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Measurements

11.1.1. Morphine Consumption via NCA

NCA is an established form of postoperative analgesia, similar in nature to other demand-led analgesic regimens (eg, PCA), but tailored for patients who are too young or unable to use PCA.(14-18). The primary efficacy variable will be the cumulative total amount of morphine required for analgesia (including background infusion and boluses).

11.2. Secondary Efficacy Measurements

The Investigator, or designee will conduct pain assessments at the designated times during the study (Table 3 and

Table 4) using the FLACC or NIPS (Appendix C and Appendix D, respectively).

Selection of pain scales in children is complex because there is no single instrument suitable for all ages. While the use of a 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 FLACC.(20)

11.2.1. 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.(20) 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.(21) The FLACC scale (Appendix C) 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 (Appendix C).(22) There are extensive reliability and validity data on the FLACC, including preverbal children.(22,23) The FLACC uses items similar to other well-established instruments, but with a more easily understood 0 to 10 scale.(24) 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.(20) 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.(22-26) In the current study, the FLACC will be used in all subjects aged 61 days to <2 years for pain assessment (Groups A and B). Each rater will receive training on completing this observer-reported pain assessment; completion of the training will be documented.

11.2.2. Neonatal Infant Pain Scale (NIPS)

The NIPS is a validated behavioral assessment tool for measurement of pain in neonates (both preterm and full-term neonates).(27) It was developed at the Children's Hospital of Eastern Ontario and consists of 6 behavioral parameters with descriptors and potential scores for each descriptor. The behavior parameters include facial expression, cry, breathing patterns, arm movement, leg movement, and state of arousal. Each behavior (except cry) has descriptors for 2 possible scores of 0 and 1. Cry has 3 descriptors (no cry, whimper, and vigorous cry) for a maximum score of 2. The NIPS is shown in Appendix D. The NIPS will be used in this study for subjects aged 0 to 60 days (inclusive), encompassing all subjects in age groups C and D. The NIPS was chosen because it has shown excellent inter-rater reliability (r=0.92-0.97) and internal consistency (α=0.87-0.95).(28)

12. ASSESSMENT OF SAFETY

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, EKG, X-ray, etc.), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs will be captured once a subject has signed the informed consent. AEs include:

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

A treatment-emergent adverse event (TEAE) is any condition that was not present prior to treatment with study medication 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 recorded on the AE page of the eCRF, regardless of whether associated with the use of study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

12.1.2. Serious Adverse Events

A serious adverse event (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)

- 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 medication regardless of time to diagnosis)
- Is considered an important medical event

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 other serious 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.

12.2. Monitoring Adverse Events

AEs will be monitored throughout the study. Study site personnel will record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

12.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

12.4. Intensity Assessment

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 an AE changes, the greatest intensity during that continuous episode should be recorded.

12.5. Reporting Adverse Events and Serious Adverse Events

12.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate eCRF page, whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of all AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 14 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 14 days after the subject's last study visit, whichever comes first.

12.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study, must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 14 days after the last dose of study medication. SAEs that occur within 14 days, following cessation of the study treatment, or within 14 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (Table 2).

All SAEs should be sent via the email address, or faxed to the fax number, provided in Table 2.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the IRB per their IRB policy.

12.5.2.1. Follow-Up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and an autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

12.6. Special Reporting Situations

12.6.1. Overdose/Misuse/Abuse

12.6.1.1. 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 (section 10.3) 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 medication eCRF.

All AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 12.5.2, 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.

12.6.1.2. Misuse/Abuse

AEs associated with misuse or abuse will be appropriately reported as AEs or SAEs, and monitored per section 12.5.

12.6.2. AEs/SAEs Experienced by Non-Subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. Serious adverse events occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 12.5.2. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

12.7. Clinical Laboratory Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events as outlined in section 3. Clinical laboratory tests will be performed by a local laboratory. Clinical laboratory test data will be reviewed by the Investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the local laboratory.

The Investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the Investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate (section 12.1.1 and section 12.1.2, respectively.

Clinical laboratory parameters that will be measured in this study are listed in Table 9.

Table 9: Clinical Laboratory Tests

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

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

12.8. Vital Signs

Vital sign measurements will be documented as described in section 3. These parameters include pulse rate, respiratory rate, and systolic and diastolic blood pressure. Length and weight should only be recorded at screening.

The Investigator will review all vital sign values for clinical significance. Any vital sign value meeting the Investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate (section 12.1.1 and section 12.1.2, respectively).

12.9. Physical Examination

A complete physical examination will be performed at screening or pre-dose evaluation. A brief physical exam excluding height and weight will be performed at the EOT assessments. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The Investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (section 12.1.1 and section 12.1.2, respectively).

12.10. 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 via continuous oxygen pulse oximetry. Oxygen saturation will be recorded at the time of vital sign assessment (see Table 3 and
- Table 4 for timing of assessments). 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 [section 12.1.1 and section 12.1.2, respectively]).
- 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.

12.11. 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, as follows:

- Level of sedation will be assessed using the Modified Ramsay Sedation Scale (Appendix A), where a score of >6 will be recorded as an SAE per definitions in section 12.1.2.

12.12. Telemetry

This study involves the use of a strong opioid for the treatment of acute pain. While it is generally well known that opioids can suppress central ventilatory drive, neonates and infants less than 12 months appear to be particularly sensitive to postoperative opioid-induced respiratory depression.(29) Because of this documented sensitivity, following administration of the study drug, telemetry (eg, bedside EKG monitor) and continuous pulse oximetry will be implemented for the duration of the study period . Monitors should be set to alarm according to

definitions described in section 12.10, and alarm times should be recorded as an AE if they are determined to be of clinical significance by the Investigator, or designee.

13. ASSESSMENT OF PHARMACOKINETICS

13.1. Study Drug Concentration Measurements

13.1.1. Blood Sample Collections

Blood collection may be performed using an existing line (arterial or venous) 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 be established only as required for the clinical management of the subject and not solely for study purposes. 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 for subjects weighing ≥6 kg. For subjects weighing between 3 and <6 kg, only up to 0.5 mL of discard volume will be allowed.

Calculation and evaluation of the following PK variables only for single-dose administration will be performed for all subjects participating in study: Single-dose Phase - C_{max}, T_{max}, AUC_{0-t} (see Table 11 for definitions).

For subjects with body weights 3 to <6 kg, 0.5-mL blood samples will be obtained and placed into 2.0-mL dipotassium ethylenediaminetetraacetic acid (K_2EDTA) tubes for the single-dose phase, and 0.5-mL blood samples will be obtained and placed into 2.0-mL K_2EDTA tubes for the multiple-dose phase. For subjects with body weights 6 to <10 kg, 1.2-mL blood samples will be obtained and placed into 2.0-mL K_2EDTA tubes for the single-dose phase, and 1.2-mL blood samples will be obtained and placed into 2.0-mL K_2EDTA tubes for the multiple-dose phase. For subjects with body weights ≥10 kg, 1.2-mL blood samples will be obtained and placed into 2.0-mL K_2EDTA tubes at each blood collection time point for both phases (see Table 3 and Table 4). The samples will be obtained at the times designated in section 3.

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 2 aliquots. 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 PK 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 13.1.2.

13.1.2. 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 the criteria in Table 10 and Appendix E (based on Investigator feedback and values reviewed in Aladangady et al and Howie).(30,31) This volume limitation includes discard volume, which should be limited to between 0.5 and 1.0 mL depending upon the dead space of the blood collection tubing (see Appendix E footnotes) for subjects weighing ≥6 kg. For subjects weighing between 3 and <6 kg, a discard volume only up to 0.5 mL will be allowed. The blood volume of the study population is estimated to be 75 to 80 mL/kg (human blood volume peaks at 105 mL/kg by the end of the first month, and then decreases progressively over the ensuing months).(31) The minimum weight limit for participation in the study is 3 kg. Refer to Appendix E for required sample volumes for PK analyses.

Table 10: Blood Volumes

Body Weight	Blood Volume (mL/kg)	Total Volume (estimate) (mL)	(≤3%) Total Volume of Blood Allowed for Study (mL)
3 kg – <6 kg	85	255	7.65[a]
6 kg – <10 kg	95[b]	570	17.1[a]
≥10 kg	75	750	22.5[a]

[a] Inclusive of up to 2.5 mL (1.25 mL at screening and 1.25 mL at end-of-treatment) for clinical laboratory testing

[b] Blood volume is higher in the neonatal period (from 85 mL/kg to a peak of 105 mL/kg by the end of the first month, and then decreases progressively over the ensuing months).(31) Mean of (85 + 105 mL/kg)/2 = 95 mL/kg.

13.1.3. 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 months to <2-year-olds has completed the single-dose phase of the study; samples from all 5 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.

13.1.4. 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).

14. STATISTICAL CONSIDERATIONS AND METHODS

14.1. Determination of Sample Size

14.1.1. Efficacy

The primary endpoint for efficacy is cumulative morphine demand via NCA. To detect a difference in effect size of 0.9, 20 subjects for each group (active treatment group pooled across all age groups vs. placebo group pooled across all age groups) will have 80% power at 2-sided significance level of 0.05.

14.1.2. Pharmacokinetics

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

For the single-dose phase, 5 subjects from each age group will receive oxymorphone (up to 60 total subjects, depending on IDMC recommendations for each age group). For the multiple-dose phase, 10 subjects from each age group will be randomized to receive either oxymorphone or placebo (40 total subjects). This will provide up to 80 subjects that are evenly distributed over the 4 age groups for the final population PK modeling and analysis.

PK in this study will be characterized using population PK modeling and analysis. Blood samples collected from the single-dose phase will be based on a 4-hour dosing interval since this is the specified period for evaluation of the dose strength. Four (4) blood samples will be collected from each subject according to the randomized subject number. Subjects with even subject numbers will have blood samples collected at 0.5, 2, 3, and 4 hours after dosing. Subjects with odd subject numbers will have blood samples collected at 1, 2, 3, and 4 hours after dosing. . A window of ±10 minutes is allowed.

In the multiple-dose phase, PK blood samples will be collected just before each dose (ie, at each trough). Population PK analyses will be used to estimate the clearance from multiple trough samples collected in the same subject. The date/time and study drug dose, as well as the date/time of each sample collection, must be recorded accurately. However, no specific schedule needs to be followed other than that each sample be collected as a trough sample just before the next dose.

If any other source of oxymorphone is administered (including oxycodone, which has oxymorphone as a metabolite), no further PK samples will be collected.

The population PK modeling and analysis will pool the available data from both phases of this study to estimate the oral clearance and oral volume of distribution using age, weight, and other potential covariates.

14.2. Subject Populations

14.2.1. Analysis Populations

A population PK analysis will be performed using data from both single-dose and multiple-dose phases. The PK population will include all subjects who receive oxymorphone HCl (immediate-release oral liquid or IV formulation) and have plasma concentration data from at least 1 time point from either single-dose or multiple-dose phase to facilitate the population PK modeling and analysis.

14.2.1.1. Single-dose Phase

The safety population for the single-dose phase will include all subjects who receive at least 1 dose of study drug. All safety analyses and demographic/baseline characterization for the single-dose phase will be performed using this population.

The single-dose PK population will include all subjects who receive oxymorphone HCl (immediate-release oral liquid or IV formulation) and provide sufficient data points to facilitate the calculation for non-compartmental PK parameters.

The evaluable population will include all subjects who receive at least 1 dose of the study medication and provide a minimum of 4 hours of post-dose assessments and at least 3 PK assessments to facilitate the dose selection decision. All efficacy analyses for the single-dose phase will be performed on this population.

14.2.1.2. Multiple-dose Phase

The safety population for the multiple-dose phase will include all subjects who receive at least 1 dose of study drug or placebo. All safety analyses for the multiple-dose phase will be performed using this population and in all safety analyses, subjects will be attributed to the treatment that they actually received regardless of their assigned randomized treatment.

The intent-to-treat (ITT) population will include all randomized subjects who receive at least 1 dose of study drug during the multiple-dose phase and complete at least 1 post-dose pain intensity assessment. All efficacy analyses and demographic/baseline characterization will be performed using this population and in all efficacy analyses subjects will be attributed to the randomized treatment regardless of the treatment they actually receive.

The per-protocol (PP) population will include all subjects in ITT population who do not violate the protocol in any fundamental manner related to the evaluation of efficacy. This population will be used for supporting the primary efficacy analysis.

14.3. Subject Disposition

The number and percentage of subjects enrolled/randomized, completed, prematurely discontinued and reasons for premature discontinuation during treatment periods will be presented for each treatment/dose group and age group. Screen failures and the associated failure reasons will be tabulated.

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

14.4. Demographics and Other Baseline Characteristics

Demographics and baseline characteristics of the subjects who participated in single-dose phase will be summarized by age group and dose group using single-dose phase safety population.

Demographics and baseline characteristics of the subjects who participated in multiple-dose phase will be summarized by age group and treatment group using ITT population.

The descriptive summaries will include frequency tables for all categorical variables and numbers, mean, standard deviation, minimum and maximum for all continuous variables.

14.5. Efficacy Analyses

The primary analysis of this study will compare the cumulative morphine demand via NCA during the multiple-dose phase. The null hypothesis is there is no difference between the 2 treatment groups; while the alternative hypothesis is that the treatments are different. The 2-sided significance level is 0.05.

The primary analysis will be performed on both ITT and PP populations, with ITT as the primary population. All other efficacy analyses will be performed on ITT population only.

14.5.1. Primary Efficacy Variable

The primary endpoint (cumulative morphine demand via NCA) will be analyzed using a mixed effect model with subject as random effect and treatment and age group as fixed effect. The least square means for each treatment group (active treatment and placebo groups) and the difference between the treatment groups (active vs. placebo) as well as their 95% CIs will be calculated.

In addition, the cumulative morphine demand via NCA will be summarized by treatment group and by treatment group and age group using N, mean, SD, minimum, median, and maximum.

The curves of the mean cumulative morphine demand via NCA over time by treatment group will be presented.

14.5.2. Secondary Efficacy Analysis

As the pain assessment, the FLACC (used for subjects between the ages of 6 months and 2 years) and the NIPS (used for subjects 0 to <6 months) will be measured after the first dose of study drug until EOT for both single-dose and multiple-dose phases.

The FLACC ranges from 0 to 10; while the NIPS ranges from 0 to 7. Before any statistical analysis, all NIPS assessments will be normalized in reference to FLACC by dividing by 7 and multiplying by 10.

For the single-dose phase, the pain assessment will be summarized descriptively by age group and dose group at each time point.

For the multiple-dose phase, the pain assessment will be summarized descriptively by treatment group and by treatment and age group at each time point. In addition, a mixed effects linear model with treatment and age group as fixed effect and subject as random effect will be used. The least squared means and 95% CIs will be calculated using this model for each treatment group and the difference between treatment groups.

Incidence of NCA rescue medication use and time to the first use of bolus rescue will be analyzed using logistic regression, and Cox models, respectively.

14.5.3. Supportive Analyses

The primary endpoint will be repeated based on the PP population as a supportive analysis.

14.6. Safety Analyses

Safety variables include prior, concomitant, and follow-up medications, study drug exposure, treatment compliance, AEs, laboratory parameters, vital signs, and physical examinations, as well as respiratory and neurological assessments. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

14.6.1. Prior, Concomitant, and Follow-up Medication

Prior, concomitant, and follow-up medication use will be summarized using the number and percentage of subjects by dose and age group for the single-dose phase and treatment for the multiple-dose phase.

14.6.2. Study Drug Exposure

During the single-dose phase, each subject will receive only 1 dose of the study medication. During the multiple-dose phase, the number of doses and cumulative dose received by each subject will be summarized by treatment, age group and overall.

14.6.3. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity. An AE that occurs more than 14 days or 5 half-lives, whichever is longer, after the last dose of study drug will not be counted as a TEAE.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

The distribution of TEAEs by severity and relationship to study drug will be summarized. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and treatment group, and sorted by decreasing frequency for the test treatment. SAEs will be displayed separately for those events occurring before the first study drug dosing date and all subsequent ones.

These tabulations will be stratified by age group and dose group for the single-dose phase and treatment group for the multiple-dose phase.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

14.6.4. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each assessment and at the end of treatment will be presented by age and dose group for the single-dose phase and by treatment group for the multiple-dose phase.

14.6.5. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

14.6.6. Physical Examination

For each body system, the number and percentage of subjects with transitions from normal or not done at baseline to abnormal post-baseline will be presented by treatment group. The percentages will be calculated relative to the number of subjects having normal or missing assessments at baseline who also had a post-baseline physical examination. A listing of physical examination data for all subjects will also be provided.

14.6.7. Other Safety Measurements

Continuous pulse oximetry, respiratory assessment, neurological assessment will summarized descriptively by age and dose groups for the single-dose phase and by treatment group for the multiple-dose phase.

14.7. Pharmacokinetic Analyses

14.7.1. Calculation of Pharmacokinetic Variables

PK variables (C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{½}$, CL, and V_d) will be estimated for the single-dose phase from the plasma concentration data using standard non-compartmental methods. Actual sample times, rather than scheduled times, will be used in the computation of PK parameters. 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 PK 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 PK variable are summarized in Table 11.

Table 11: Pharmacokinetic Variables

Variable	Definition
$AUC_{0\text{-}inf}$	Area under the *plasma/serum* concentration versus time curve from time 0 to infinity, calculated as $AUC_{0\text{-}t} + C_t/\lambda_n$
$AUC_{0\text{-}t}$	Area under the *plasma/serum* concentration versus time curve from time 0 to the last measured concentration (C_t), calculated by linear trapezoidal rule
CL	Clearance
C_{max}	Observed maximum *plasma/serum* concentration; the highest concentration observed during a dosage/application interval
$t_{½}$	Terminal half-life, calculated as $\ln(2)/\lambda_n$
T_{max}	The time at which C_{max} was observed
V_d	Apparent volume of distribution

14.7.2. Analysis of Pharmacokinetic Results

PK variables will be summarized by age group using N, mean, median, standard deviation (SD), geometric mean, CV, minimum, median, and maximum following dosing in the single-dose phase.

The PK analysis will be conducted using population PK modeling and analysis methods as described in the FDA Guidance for Industry Population Pharmacokinetics. Details of the population PK modeling and analysis will be documented in a separate population PK analysis plan. Results of these analyses will be documented in a separate report.

14.8. Interim Analysis

No interim analysis is planned for this study.

14.9. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, NC).

15. STUDY DRUG MATERIALS AND MANAGEMENT

15.1. Study Drug Identity

The study drugs are EN3319 oxymorphone HCl prepared as an oral immediate-release solution, matching placebo liquid, oxymorphone HCl IV solution, and sodium chloride 0.9% solution for injection as placebo for oxymorphone HCl IV solution. Oxymorphone oral liquid and IV products are light sensitive and must be protected from light.

15.2. Study Drug Packaging and Labeling

Oxymorphone HCl immediate-release oral liquid 1 mg/mL and matching placebo will be provided in single subject bottles. Each bottle will be labeled minimally with the following information (as appropriate): protocol number, study drug name, strength, dosage form, Class II designation, quantity, lot number, appropriate administration and storage instructions, sponsor's identification and address, appropriate cautionary statements.

Oxymorphone HCl IV solution is supplied as 1 mL units, 10 units/box and each box will be labeled minimally with the following information (as appropriate): protocol number, study drug name, strength, dosage form, Class II designation, quantity, lot number, appropriate administration and storage instructions, sponsor's identification and address, appropriate cautionary statements. Sodium chloride 0.9% solution for injection will be provided with commercial labeling for single use.

15.3. Study Drug Storage

Oxymorphone HCl oral liquid and oxymorphone HCl IV solution must be stored in a locked facility with restricted access 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° to 86°F) [see USP Controlled Room Temperature]. Oxymorphone HCl oral liquid and oxymorphone HCl IV solution are light sensitive and, therefore, must be stored in their original cardboard cartons.

15.4. Study Drug Preparation

Due to light sensitivity, both the oxymorphone HCl oral liquid bottles and the individual units of oxymorphone HCl IV solution must be maintained within the original cardboard carton other than during time of preparation in the pharmacy. The oxymorphone HCl oral liquid or oral liquid placebo dose should be dispensed with an oral syringe (1 mL); the IV oxymorphone solution or saline placebo should be dispensed with an appropriate sterile syringe. Refer to the Clinical Supplies Guidance Document within the Pharmacy Binder for specific instructions for determining and dispensing the appropriate dose. The concentration of both the oxymorphone HCl oral liquid and IV solution is 1 mg/mL. Any oxymorphone HCl oral liquid or IV solution drawn into a syringe should remain protected from light in an envelope or sleeve immediately following preparation until just prior to administration. Any oxymorphone HCl oral liquid drawn into a syringe for administration must be dispensed within 48 hours or returned to pharmacy.

15.5. Study Drug Accountability

The Principal Investigator is responsible for overall drug accountability, and is responsible for ensuring that appropriate site personnel record the receipt and use of all drugs supplied. The Principal Investigator is also responsible for ensuring the supervision of the storage and allocation of these supplies. Each bottle of oxymorphone HCl oral liquid and units of oxymorphone HCl IV solution will be allocated for use for a single subject. The pharmacy will be responsible for recording dispensed drug for both oxymorphone HCl oral liquid and oxymorphone HCl IV solution in the eCRF and in the appropriate drug accountability logs.

The 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 10.3 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 drugs will be followed in accordance with the individual site's standard procedures, which will be documented by the site.

15.5.1. Study Drug Handling and Disposal

The Principal Investigator will retain and store all bottles and unused units of study drug until inventoried by the Sponsor or Sponsor's representative. Any oxymorphone HCl IV solution units that have been used for dosing, however, should be disposed of per institution procedures. The Principal Investigator will return all unused oxymorphone HCl IV solution units and unused oxymorphone HCl oral liquid in the original bottles, including empty and partially empty oxymorphone HCl oral liquid bottles, and with appropriate documentation as specified by the Sponsor per the Clinical Supplies Guidance Document, to the Sponsor's return vendor.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Source Documents

Source documents include, but are not limited to, original documents, data and records such as hospital/ medical records (including electronic health 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 should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

16.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor (on-site and/or remotely) each investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

16.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The Investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

16.4. Institutional Review Board

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

16.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of 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. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites.

The 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 will be monitored and/or 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), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or 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 generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

18. ETHICS

18.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or Summary of Product Characteristics (SPC) as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

18.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56 and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

18.3. Subject Information and Consent

Each qualified subject's parent(s)/legal guardian(s) or legally authorized representative (LAR) 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 form and the consent 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. Each subject's parent(s)/legal guardian(s) or LAR will read and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that the subject may withdraw from the study at any time. 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.

In addition to obtaining informed consent/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent/assent process shall be recorded in source documents. Signed copies of the informed consent and/or assent will be given to the subject's parent(s)/guardian(s)/LAR and originals will be placed in the Investigator study files.

A unique subject identification number will be assigned according to section 10.1.3 at the time that the subject signs the informed consent form.

19. DATA HANDLING AND RECORDKEEPING

19.1. Data Collection

Data collection will involve the use of an electronic data capture (EDC) system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and will be reviewed and closed by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will be responsible to review eCRFs for all subjects at his/her site, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature at the end of the study.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

19.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the eCRF data for his/her files.

20. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo Pharmaceuticals Inc.

21. INVESTIGATOR OBLIGATIONS

21.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract.
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages.
- The IB acknowledgment of receipt page.
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable).
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 18.1.
- A copy of the IRB/IEC-approved informed consent form.
- A list of IRB/IEC members or DHHS Assurance Number.
- Laboratory certifications and normal ranges
- A financial disclosure agreement completed and signed by the Investigator and all sub-investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

21.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. 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.

21.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' 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 will report all AEs as required by the protocol (section 12.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

21.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or sub-investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.

Study drug that has Schedule II designation must be stored in a double-locked area (secure enclosure within a locked, controlled access location).

21.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

Endo Pharmaceuticals Inc. will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drug Application [NDA]/Marketing Authorization Application [MAA]).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo Pharmaceuticals Inc. must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

21.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

22. 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.

23. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

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APPENDIX A. MODIFIED RAMSAY SEDATION SCALE

Score Definition

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

The assessment is performed using a series of steps. A score of 2-3 is anxiolysis, 4-5 is moderate sedation, 6 is deep sedation, and 7-8 is general anesthesia.

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APPENDIX B. GUIDELINES FOR CAPTURE OF PRIOR AND CONCOMITANT MEDICATIONS

Item	Collect
Intra-operative/Post-op (up to Dosing)	
IV Fluids	N
Blood products	N
Vapor anesthetics (eg, isoflurane, desflurane, sevoflurane, nitrous oxide)	Y
O_2	N
IV anesthetics (eg, propofol, ketamine, etomidate, dexmedetomidine)	Y
Antibiotics	Y
Opioid analgesics	Y
Sedatives	Y
Local anesthetics	Y
Muscle relaxants (eg, succinylcholine, rocuronium, pancuronium)	Y
Muscle relaxant antagonists	Y
Anticholinergics (eg, atropine, glycopyrrolate)	Y
Inotropes (eg, epinephrine, phenylephrine, dopamine)	Y
Antiemetics (eg, ondansetron, dexamethasone)	Y
Non-opioid analgesics (eg, acetaminophen, tramadol, NSAIDs)	Y
Post Dosing	
IV Fluids	Y
Blood products	Y
O_2	Y
All medications regardless of route or indication	Y

APPENDIX C. FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY (FLACC)

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

Each of the 5 categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

Instructions for Use:

Patients who are awake: Observe for at least 1-2 minutes. Observe legs and body uncovered. Reposition patient or observe activity, assess body for tenseness and tone. Initiate consoling interventions if needed

Patients who are asleep: Observe for at least 2 minutes or longer. Observe body and legs uncovered. If possible reposition the patient. Touch the body and assess for tenseness and tone.

Face

Score 0 point if patient has a relaxed face, eye contact and interest in surroundings.

Score 1 point if patient has a worried look to face, with eyebrows lowered, eyes partially closed, cheeks raised, mouth pursed.

Score 2 points if patient has deep furrows in the forehead, with closed eyes, open mouth and deep lines around nose/lips.

Legs

Score 0 points if patient has usual tone and motion to limbs (legs and arms).

Score 1 point if patient has increase tone, rigidity, tense, intermittent flexion/extension of limbs.

Score 2 points if patient has hyper tonicity, legs pulled tight, exaggerated flexion/extension of limbs, tremors.

Activity

Score 0 points if patient moves easily and freely, normal activity/restrictions.

Score 1 point if patient shifts positions, hesitant to move, guarding, tense torso, pressure on body part.

Score 2 points if patient is in fixed position, rocking, side-to-side head movement, rubbing body part.

Cry

Score 0 points if patient has no cry/moan awake or asleep.

Score 1 point if patient has occasional moans, cries, whimpers, sighs.

Score 2 points if patient has frequent/continuous moans, cries, grunts.

Consolability

Score 0 points if patient is calm and does not require consoling.

Score 1 point if patient responds to comfort by touch or talk in ½ - 1 minute.

Score 2 points if patient requires constant comforting or is inconsolable.

Whenever feasible, behavioral measurement of pain should be used in conjunction with self-report. When self-report is not possible, interpretation of pain behaviors and decision-making regarding treatment of pain requires careful consideration of the context in which the pain behaviors were observed.

Each category is scored on a 0-2 scale, which results in a total possible score of 0-10. Assessment of Behavioral Score:

0 = Relaxed and comfortable

1-3 = Mild discomfort

4-6 = Moderate pain

7-10 = Severe discomfort/pain

Interpretation

Pain scores are coded as mild (0–3), moderate (4–6), and severe (7–10).[1] It is suggested that healthcare providers need to provide some type of analgesic for patients with pain scores of 6 or greater.[2]

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[1] Manworren RC, Hynan LS. Clinical Validation of FLACC: preverbal patient pain scale. *Pediatr Nurs*. 2003;29(2):140-146.

[2] Voepel-Lewis T, Merkel S, Tait AR, Trzcinka A, Malviya S. The reliability and validity of the Face, Legs, Activity, Cry, Consolability Observational Tool as a measure of pain in children with cognitive impairment. *Anesth Analg*. 2002;95(5):1224–1229.

APPENDIX D. NEONATAL INFANT PAIN SCALE (NIPS)

(1) Facial Expression; (2) Cry; (3) Breathing patterns; (4) Arms; (5) Legs; (6) State of Arousal.

Parameter	Finding	Points
Facial expression	Relaxed	0
	Grimace	1
Cry	No Cry	0
	Whimper	1
	Vigorous Cry	2
Breathing Patterns	Relaxed	0
	Change in breathing	1
Arms	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
Legs	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
State of Arousal	Sleeping	0
	Awake	0
	Fussy	1

Instructions for Use

The NIPS is an observational measure and is administered with the behavioral parameters and possible scores on the Y-axis. Scoring is permitted at one-minute intervals (along the X-axis), and can take place before, during, and after a procedure. The total score for a one-minute interval can range from 0 – 7.

Interpretation

Scores for each category are summed: the minimum score is 0, and the maximum score is 7. The primary limitation is that infants too ill to respond or that are receiving a paralytic agent may produce a falsely low score.

APPENDIX E. BLOOD SAMPLING INSTRUCTIONS

Visit/Phase	Amount Collected	Number of Samples Collected	Total Amount Collected Per Subject
Screening Serum Chemistry and Hematology [a]	1.25 mL	1	1.25 mL
For Subjects with Body Weights 3 - <6 kg			
Single-Dose Phase Pharmacokinetics	0.5 mL [b]	7	3.5 mL
Multiple-Dose Phase Pharmacokinetics	0.5 mL [b]	5	2.5 mL
For Subjects with Body Weights 6 - <10 kg			
Single-Dose Phase Pharmacokinetics	1.2 mL [c]	7	8.4 mL
Multiple-Dose Phase Pharmacokinetics	1.2 mL [c]	5	6.0 mL
For Subjects with Body Weights ≥10 kg			
Single-Dose Phase Pharmacokinetics	1.2 mL [c]	7	8.4 mL
Multiple-Dose Phase Pharmacokinetics	1.2 mL [c]	5	6.0 mL
End of Treatment Serum Chemistry and Hematology	1.25 mL	1	1.25 mL
Grand Total			
Single-Dose Phase for Subjects with Body Weights 3 - <6 kg			6.0 mL [b]
Multiple-Dose Phase for Subjects with Body Weights 3 - <6 kg			5.0 mL [b]
Single-Dose Phase for Subjects with Body Weights 6 - <10 kg			10.9 mL [c]
Multiple-Dose Phase for Subjects with Body Weights 6 - <10 kg			8.5 mL [c]
Single-Dose Phase for Subjects with Body Weights ≥10 kg			10.9 mL [c]
Multiple-Dose Phase for Subjects with Body Weights ≥10 kg			8.5 mL [c]

[a] Where possible, results from clinical laboratory tests performed as part of the standard of care (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. Preoperative or intraoperative (collected pre-first incision) test results must be available for review by the Investigator prior to dosing any subject. See Table 9 for list of analytes for clinical laboratory tests. Procedures for blood draws should follow institutional SOC. Refer to Table 10 for limitations on blood volumes.

[b] For all subjects weighing between 3 and <6 kg, only up to 0.5 mL of discard volume will be allowed.

[c] Includes up to 1.0 mL discard volume for all pharmacokinetic (PK) samples; a 0.5 mL discard volume should be used with short tubing (eg, tubing with a dead space of ≤0.5 mL) and up to a 1.0 mL discard volume should be used for longer tubing (eg, tubing with a dead space of >0.5 mL). Total blood volume drawn for research purposes must not exceed 3% of subject's total blood volume, which is assumed to be 75 to 80 mL/kg; the blood volume is higher in the neonatal period (from 85 mL/kg to a peak of 105 mL/kg by the end of the first month, and then decreases progressively over the ensuing months).[1] Refer to Table 10 for limitations on blood volumes.

[1] Howie SR. Blood sample volumes in child health research: review of safe limits. *Bull World Health Organ.* 2011;89(1):46-53.