CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
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Priority or Standard	**Standard**
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Division/Office	DAAAP/CDER/OND/ODE II
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Clinical Team Leader	Joshua Lloyd, M.D.
Division Director	Sharon Hertz, M.D.
Review Completion Date	(see electronic signature)
Established/Proper Name	Oxymorphone Hydrochloride
Trade Name	Opana®
Applicant	Endo Pharmaceuticals, Inc.
Dosage Form(s)	Oral tablet
Regulatory Action	Approval of labeling 1) Describing pediatric data required under PREA for the 2 to less than 17-year age group and 2) Recommending against the use of Opana Tablets in pediatric patients

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Glossary

AC	advisory committee
AE	adverse event
ASA	aspirin
AR	adverse reaction
APAP	acetaminophen
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ER	extended-release
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IR	immediate-release
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWR	Pediatric Written Request
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Opana (oxymorphone hydrochloride) is an immediate-release (IR) opioid product indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The drug was originally approved under NDA 021611 for the US market on June 22, 2006. The purpose of Supplement 16 is to fulfill the pediatric post-marketing requirement (PMR) study required under the Pediatric Research Equity Act (PREA). PMR 127-3 was issued to study the pharmacokinetics (PK) and safety of Opana in the pediatric population 2-17 years of age for the relief of moderate to severe acute pain where the use of an opioid is appropriate.

The Applicant conducted two pediatric studies in the 2-17 years age range to fulfill PMR 127-3. The approved tablet formulation was used in the study for the >12-17 years age group. The Applicant developed a new age-appropriate oral solution formulation for younger patients that was demonstrated to be bioequivalent to the marketed tablet formulation in a clinical pharmacology study conducted in adult healthy volunteers (refer to the clinical pharmacology review for more information). The oral solution was used in the study for the 2-12 years age group. The Applicant indicated that they only manufactured the oral solution formulation for use in the required pediatric studies and do not intend to market the oral solution formulation. Furthermore, the Applicant has not submitted adequate data to support marketing the oral solution formulation or the container closure system from a nonclinical pharmacology/toxicology perspective (refer to the nonclinical review for more details).

Based on the data submitted, the Applicant proposes to describe the PK and safety findings from the pediatric studies in various sections of labeling (i.e., [redacted] (b) (4), Section 8.4 Pediatric Use, and [redacted] (b) (4)); however, the Applicant is not seeking an indication in the pediatric population studied for this product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy data were not required for the 2-17 years age group because FDA allows extrapolation of efficacy from adults to pediatric patients two years of age and older for opioid analgesics when there is a demonstration of comparable exposures between the two populations.

Based on single-dose PK comparison, a 5 mg single dose of Opana tablets in patients aged >12-17 years will provide similar oxymorphone exposure to that of a 5 mg single dose in adults (excluding two patients who had markedly higher oxymorphone exposures from the analysis), and a dose between 0.05 and 0.1 mg/kg in patients aged 2-12 years will provide similar oxymorphone exposures to that of a 5 mg single dose in adults.

Although the submitted data established that comparable exposures were achieved between pediatric patients two years of age and older and adults, the pediatric study in >12-17 years age group demonstrated a very high proportion of discontinuations due to lack of efficacy at all dose levels studied during both the single- and multiple-dose treatment phases. The doses administered were expected to be comparable to effective starting doses in adults, suggesting that the doses studied might not have reached an efficacious range.

The study design precluded further evaluation of efficacy, as pain data collected from the two pediatric studies could not be interpreted due to limitations such as open-label design and lack of control group, and the findings from the study in the 2-12 years age group were further complicated by a direct switch from intravenous (IV) opioids to study medication without requiring certain levels of baseline pain intensity, concomitant use of additional opioids as rescue without standardization on their use, low levels of actual baseline pain intensity, and difficulty in assessing and interpreting pain from other stimuli in the younger age groups.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The benefits of using an opioid such as Opana in treating acute pain severe enough to require an opioid analgesic when alternative treatments are inadequate, have been established in the adult population. Comparison between PK profiles in adult and pediatric populations showed comparable exposures between the two populations. However, the ability to extrapolate efficacy from adults to the pediatric population aged 2-17 years based on comparable exposures between the two population is limited due to the high dropout rates due to lack of efficacy that was observed.

Known risks associated with the use of an opioid such as Opana in adults are described in the product labeling and will not be repeated here. Safety findings from the two pediatric studies were generally consistent with post-operative experiences and with the known safety profile of opioid analgesics. However, the safety database was limited by small sample sizes and high proportions of missing scheduled safety evaluations. Further, safety data are not available for higher and presumably more efficacious dose levels as the doses studied appear to be non-efficacious. Additionally, the findings of unexpected and otherwise unexplainable individual cases of higher exposures to oxymorphone in two of 24 patients included in the PK analysis raise safety concerns about potential toxicity in a subpopulation with variation in drug metabolism.

Therefore, the benefit/risk balance for the pediatric population has not been established, and it is unclear whether it would be similar to that of adults due to the concerns of questionable efficacy and the potential safety issues raised by higher than expected exposures in two patients.

A joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held on September 26, 2019, to discuss pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR as an example. The Advisory Committee (AC) voted against (16 No, 8 Yes, and 1 Abstain) including information from the pediatric studies in labeling, mostly due to the issues that were identified in our review (lack of efficacy of the doses studied, lack of safety data at higher presumably efficacious doses, and safety concerns with potentially higher systemic exposures in some pediatric patients) and due to the concern that the Applicant's proposed pediatric labeling may (b) (4) However, opioid products are often used off-label in the pediatric population, and it is important to convey the concerns that were identified in the review and by the AC to inform prescribers that this product should not be used in the pediatric population and the reasons why. Therefore, we will include information in the labeling to discourage off-label use of the product in the pediatric population emphasizing that OPANA tablets are not recommended for use in the pediatric population and that safety and effectiveness for pediatric patients aged 0-17 years have not been established. This labeling will also present the relevant pediatric study results, i.e., that there was no demonstration of efficacy at doses expected to be comparable to effective starting doses in adults and the finding of substantially higher systemic exposures to oxymorphone in two out of 24 patients.

In terms of fulfilling PMR for pediatric study under PREA, the pediatric studies of the age group of 2-17 years included in this submission have adequately addressed the PMR 127-3 for Opana.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain refers to pain of acute onset and short-term duration associated with disease, injury, or inflammation. • Untreated acute pain leads to not only short-term suffering, morbidity, and negative impact on quality of life but also risks of progression to chronic pain.	Acute pain in pediatric patients needs to be managed effectively to minimize suffering, morbidity and potential long-term negative consequences.
Current Treatment Options	• Non-pharmacologic management of acute pain includes rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, relaxation techniques, etc. • Two major pharmacologic classes of analgesics for treating acute pain includes opioid and non-opioid analgesics. • Severe pain (severe both in nature and pain intensity) requires opioid drugs or opioid-containing combinational products. • Availability of opioid-containing analgesics with pediatric labeling or indications is limited to certain opioid or opioid combination products such as: Opioids • Fentanyl transdermal (≥2 y) • Buprenorphine injection • Fentanyl citrate injection • Meperidine • OxyContin (>11 y) Combination Products • Codeine/APAP (≥3 y) • Hydrocodone/APAP (≥2 y) • Pentazocine/APAP • Dihydrocodeine/ASA/Caffeine • Codeine/ASA/Butalbital/Caffeine • Oxycodone/Ibuprofen	Although the Applicant is not seeking a pediatric indication for this product and has submitted a request to withdraw approval of NDA 021611 because Opana is no longer being marketed, addition of selected labeling statements on pediatric experience with oxymorphone to the product labeling would still be considered useful information for generic drug product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Pentazocine/Naloxone • Carisoprodol/ASA/Codeine • Butalbital/APAP • Butalbital/APAP/Caffeine • Off-label use of opioids in pediatric population is commonly recognized and raises questions and concerns about effectiveness and safety of such practice.	
Benefit	• PK data in the current submission showed comparable exposures between the adult and pediatric populations. • The 5-mg single dose in pediatric patients >12 to 17 years of age will provide similar oxymorphone exposure to that of a 5-mg single dose in adults, after excluding 2 outliers for whom many-fold higher exposure than the others were observed with no identified explanation. • A dose between 0.05 and 0.1 mg/kg in pediatric patients 2 to <6 and 6 to 12 years of age will provide similar oxymorphone exposures to that of a 5-mg single dose in adults. • Uncertainty about efficacy because of a large proportion (57%) of dropouts due to lack of efficacy in Study EN3203-010 • Uncertainty about population differences in half-life ($T_{1/2}$) that $T_{1/2}$ in the age group of >12 to 17 years is longer (range 12 - 20 hours in Study 010) and in the age group of 2 to 12 years is shorter (range 4.4- 7.5 hours in Study 302) than adults (range 7.25 to 9.43 hours by Opana labeling) based on cross study/information comparison.	Extrapolation of efficacy from adults to the pediatric populations based on comparable pharmacokinetic profiles between the two population is questionable for this product as suggested by high dropout rates due to lack of efficacy. There is uncertainty about efficacious dose range for pediatric use. Individual adjustment of dosage may be necessary based on response to pain relief and adverse reactions.
Risk and Risk Management	• Exposure in pediatric population consisted of 119 pediatric patients, 58 in the age group of >12 to 17 years exposed to the tablet formulation and 61 in the age group of 2 to 12 years exposed to the oral solution formulation. • Multiple-dose experience was limited to 30 pediatric patients, including 16 in the age group of >12 to 17 years and 14 in the age group of 2 to 12 years.	Safety findings were generally consistent with post-operative experiences and with known safety profile of opioid analgesics. Safety database was limited by small sample sizes and high proportions of missing scheduled safety

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Maximum exposures included exposure to 8-12 doses of 15 mg tablet by five patients aged >12 to 17 years and 8-12 doses of 0.2 mg/kg solution by seven patients aged 2 to 12 years. • Five cases of AE-related early dropouts were all due to CNS symptoms such as sedation, tremor, somnolence, and lethargy. • About two thirds (66%) reported any TEAEs with more AEs after multiple doses than a single dose (80% versus 60%). • Most commonly reported AEs (≥5%) included nausea, pyrexia, constipation, vomiting, and headache. • Most commonly observed (≥5 cases) clinically significant shifts in laboratory results included decreases in hematocrit, hemoglobin, RBC, albumin, protein, and calcium, and increase in glucose. • Unexplained overexposure in 2 of 24 patients aged >12 to 17 years dosed at 5 mg and 15mg initial level raises potential safety concerns.	evaluations. There are no safety data for higher, presumably more efficacious, doses The usefulness of safety data is debatable because of the uncertainty about efficacious dose range for pediatric use. The findings of unexpected and nonexplainable individual cases of overexposure raise safety concerns on potential toxicity in a subpopulation of pediatric patients.

1.4. Patient Experience Data

Not applicable.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Acute pain in pediatric patients needs to be managed effectively to minimize suffering, morbidity and potential long-term negative consequences. Opioid type analgesics are important in treating severe acute pain conditions such as post-operative pain after major surgery, sickle cell pain crisis, extensive trauma, etc. A major challenge in using opioids in treating pediatric pain is the lack of labeling information for pediatric use of the product, which leads to off-label practice using the dosage that may not be efficacious and/or safe. To address the unmet need for pediatric pain management pediatric labeling information from pediatric studies conducted under the Pediatric Research Equity Act (PREA) are necessary to inform safe and effective use of opioids in pediatric population.

2.2. Analysis of Current Treatment Options

Opioid-containing analgesics with pediatric labeling or indications and opioid analgesics without pediatric labeling are summarized in the table below.

Table 1 Opioid with and without Pediatric Labeling

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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Opana (oxymorphone hydrochloride) immediate-release (IR) tablet formulation was approved on June 22, 2006 for the indication of management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Opana ER, extended-release formulation was originally approved in 2006 for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. The original formulation was replaced in 2012 by a new formulation intended to make the drug resistant to physical and chemical manipulation for abuse by snorting or injecting. Post-marketing surveillance showed that there was a significant shift in the route of abuse from nasal to injection after drug reformulation. Injection abuse of reformulated Opana ER has been associated with a serious outbreak of hepatitis C and HIV, and cases of thrombotic microangiopathy. The issue was discussed at the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee held on March 13-14, 2017 (refer to https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-time-and-public-participation-information-joint-meeting-drug-safety-and-risk for detail). Because the benefits of reformulated Opana ER no longer outweigh its risks FDA requested drug removal from the market in 2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of original NDA approval pediatric studies of both oxymorphone IR and ER formulations under Pediatric Research Equity Act (PREA) were granted deferral (refer to the letter of approval of NDA 21610 (ER) and NDA 21611 (IR) dated June 22, 2006).

A Pediatric Written Request (PWR) was issued on March 16, 2007, (b) (4) [redacted] . (b) (4) [redacted] .

FDA revised the Post-Marketing Requirements (PMRs) from studying pediatric patients 0-17 years of age as one group to studying PK, efficacy, and safety in the age range of 0-2 years (PMR 127-2) and studying PK and safety in the age range of 2-17 years (PMR 127-3) as documented in a letter to the Sponsor under the NDA dated January 31, 2011. The new approach included extrapolation of efficacy from adults to pediatric patients two years of age and older for opioid analgesics and was based on the Agency's review of data presented at a pediatric pain workshop held in December 2009.

An agreement on the initial pediatric study plan (iPSP) was documented in the FDA's letter to the Sponsor under IND 58602 dated November 17, 2015. Subsequently, the agreed iPSP was submitted by the Sponsor on February 4, 2016 and contains statements related to PMR 127-2: Deferred study of efficacy, safety, and PK (single- and multiple-dose) under PREA for the relief of moderate to severe acute pain where the use of an opioid is appropriate in pediatric patients ages 0-2 years and PMR 127-3: Deferred study of safety and pharmacokinetics (single- and multiple-dose) under PREA for relief of moderate to severe acute pain where the use of an opioid is appropriate in patients ages 2-17 years.

The Sponsor requested a deferral extension of pediatric studies twice previously for the reasons of recruitment difficulties and slow enrollment and their requests were accepted as documented in the letters to the Sponsor dated June 24, 2013 and May 18, 2017.

The current NDA supplement was submitted on December 21, 2018 and contains one adult study comparing the liquid and tablet formulations and two pediatric PK and safety studies of patients in the age range of 2-17 year to meet PMR 127-3. The proposal was to add PK and safety findings to the pediatric-related labeling sections without using the data to support a pediatric indication or dosing recommendation.

[redacted] (b) (4) they submitted a request to withdraw approval of NDA 021611 [redacted] (b) (4) [redacted].

3.3. Foreign Regulatory Actions and Marketing History

[redacted] (b) (4) [redacted].

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The open-label PK studies were not inspected.

4.2. Product Quality

The tablet formulation has market approval with the original NDA. The oral solution formulation was developed as an age-appropriate formulation in order to study younger pediatric patients to fulfill PMR 127-3. The Applicant does not intend to market this formulation.

According to the CMC Review by Dr. Daneli Lopez-Perez, CMC data provided, batch results, stability data, and developmental information for the manufacture of the oral solution were considered adequate for use of the formulation in Study EN3319-302.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical data associated with the tablet formulation.

Although the Applicant does not intend to seek market approval of the oral solution formulation, several deficiencies related to approvability of the oral solution formulation were identified by the Nonclinical Pharmacology/Toxicology reviewer Dr. Bolan as summarized here. The (b) (4)

4.5. Clinical Pharmacology

PK information based on assessment by the Clinical Pharmacology reviewer Dr. David Lee is summarized in the table below.

Table 2 Single-Dose PK Summary Across Age Groups

PK parameter		Cmax (ng/mL)		AUC0-t (ng h/mL)		AUC0-inf (ng.h/mL)	
Age group	**Dose**	Mean (SD)*	***Outlier***	Mean (SD)*	***Outlier***	Mean (SD)*	***Outlier***
Adults	**5 mg**	**0.69 (0.34)**		**3.94 (1.67)**		**4.34 (1.86)**	
>12-17 years	**5 mg, 0.08 mg/kg* (0.086 mg/kg for outlier)**	**0.90** (0.69)	***4.00***	**4.57** (2.84)	***20.96***	**5.80** (4.08)	***22.26***
	10 mg, 0.16 mg/kg	**0.83** (0.69)		**3.77** (2.26)		10.22# (6.52#)	
	15 mg, 0.23 mg/kg* (0.28 mg/kg for outlier)	1.76 (1.02)	***33.55***	17.01 (15.68)	***467.26***	18.29 (9.10)	***746.34***
6-12 years	0.05 mg/kg	0.42 (0.21)		2.56 (2.00)		2.42 (0.052)	
	0.10 mg/kg	1.14 (0.85)		3.01 (0.77)		3.01 (0.95)	
	0.20 mg/kg	1.33 (0.77)		5.32 (4.53)		6.92 (4.02)	
2-<6 years	0.05 mg/kg	0.33 (0.22)		1.69 (0.94)		3.22 (1.56)	
	0.10 mg/kg	1.76 (1.62)		3.99 (2.09)		3.69 (3.12)	
	0.20 mg/kg	3.16 (1.65)		9.37 (5.81)		14.30 (5.01)	

Note: *The average weight-based dosing and the group mean (SD) are calculated by excluding the two outliers. One of the outliers EN3203-010-(b) (6) was in the 5 mg dose group and the second, EN3203-010-(b) (6) in the 15 mg dose group. #N=3

Dr. Lee concluded that the 5 mg single dose in patients >12 to 17 years of age will provide

similar oxymorphone exposure (after excluding the 2 outlier exposure cases from a sample of 24 exposed) to that of a 5 mg single dose in adults, and a dose between 0.05 and 0.1 mg/kg in patients 2 to 12 years of age will provide similar oxymorphone exposures to that of a 5 mg single dose in adults (refer to Dr. Lee's review for detail).

The subject with an outlier exposure in the 5 mg dose group had a similar mg/kg dose to the group mean but had Cmax and AUC about four times that of the group mean. The subject in the 15 mg dose group had slightly higher mg/kg dose than the group mean (0.28 versus 0.23 mg/kg) and had much higher exposure levels than the group mean, about 20 times higher Cmax, 27 times higher $AUC_{0\text{-}t}$, and 40 times higher $AUC_{0\text{-}inf}$. Neither the Applicant nor the review team could provide an explanation for the substantially high oxymorphone exposure levels in the two subjects identified as outliers.

The individual information on the two subjects revealed that the subject in the 5 mg dose group had no adverse events and the one in the 15 mg dose group dropped out early due to lack of efficacy regardless of the extremely high plasma concentrations and reported pruritus, fever, and asthma exacerbation as non-serious AEs, which were not as reasons for early discontinuation. Therefore, the outlier exposure in the 15 mg dose group may have been due to some sort of analytical error.

The study design and conduct of the two pediatric PK studies are also described in the Section 6 of this review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 Clinical Studies

Type	Study ID, NCT# site, date	Section	Design	Treatment	N	Population
PK (Relative bioavailability)	EN3319-101 One US sites 9/8/09-10/4/09	5.3.1.2	Single-center Single-dose Open-label 2-way crossover (fasted)	Oxymorphone oral solution 5 mg Opana oral tablet 5 mg	30	Adult 18-45 years of age healthy volunteers
PK, safety, & effectiveness	EN3203-010 10 US sites 2/17/09 to 4/18/11	5.3.5.2	Multicenter Single- and multiple-dose Open-label Dose escalation	Opana tablets 5 mg single dose 10 mg single dose 15 mg single dose 5 mg q4-6h for up to 48 hours 10 mg q4-6h for up to 48 hours 15 mg q4-6h for up to 48 hours	T58 13 9 11 9 8 8	Pediatric patients >12-17 years of age in need of opioid for acute postoperative pain
PK, safety, & effectiveness	EN3319-302 14 US sites 12/13/10 to 10/6/17	5.3.5.2	Multicenter Single- and multiple-dose Open-label Dose escalation	Oxymorphone oral solution 0.05 mg/kg single dose 0.1 mg/kg single dose 0.2 mg/kg single dose 0.2 mg/kg q4-6h for up to 48 hours	T61 20 12 13 16	Pediatric patients 2-12 years of age in need of opioid for acute postoperative pain

Note: T followed by a number in the table means total number of patients.

5.2. Review Strategy

The NDA contains three open-label pharmacokinetic (PK) studies, one adult and two pediatric studies, which were not designed for studying efficacy. For the two pediatric studies the study design and some results in terms of patient disposition, protocol deviations, demographic and baseline characteristics, and pain data will be summarized in the Review Section 6. PK findings are briefly summarized in the Review Section 4.5. Safety findings will be summarized by age group in the Review Section 8 with emphasis on pediatric studies.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Pediatric PK and safety studies

6.1.1. Study Design

Overview and Objective

Both Study EN3203-010 for the age group of >12 to 17 years and Study EN3319-302 for the age group of 2 to 12 years were open-label studies without a control group conducted to obtain PK and safety data to inform pediatric labeling.

Trial Design and Study Protocol

Key features of the two pediatric PK and safety studies are summarized in the table below.

Table 4 Summary of Study Design for the Two Pediatric Studies

Study	EN3203-010 (age >12 to 17 years)	EN3319-302 (age 2-12 years)
Title	An Open-Label, Ascending, Two-Part, Single- and Multiple-Dose Evaluation of the Safety, Pharmacokinetics, and Effectiveness of Oxymorphone for Acute Postoperative Pain in Pediatric Subjects	An Open-Label, Non-randomized, Multicenter, Ascending Dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety, and Tolerability of Oxymorphone HCl Immediate-Release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects
Formulation	5 and 10 mg tablet	Oral liquid
Age group	One age group	3 age groups: 6-12, 2 to <6 and 0-<2 years, where age 0-<2 years was terminated early & was limited to single dose
Design	Open-label Single-dose and multiple-dose Dose escalation (3 levels)	Open-label Single-dose and multiple-dose Dose escalation (3 levels)
Pain model	Postoperative pain	Postoperative pain
Population	Age >12-17 requiring an opioid to treat postoperative pain of various etiologies; (Exclusion: received preoperative opioids for >72 hours, previous exposure to oxymorphone, received codeine or oxycodone within 72 hours prior to study entry)	Age 2-12 switching from IV to oral opioid to treat acute postoperative pain of various etiologies; (Exclusion: received preoperative opioids for >72 hours, received oxycodone or oxymorphone within 48 hours prior to study entry)
Pain scale	100-mm VAS	Faces Pain Scale-Revised (FPS-R) for age 6-12 years; Face, Legs, Activity, Cry, Consolability (FLACC) for age 2-<6 years
Baseline PI	≥40 mm	Not specified
Treatment	Opana 5-mg, 10-mg, and 15-mg Single dose at 5, 10, & 15 mg Multiple dose at 5, 10, & 15 mg q4-6h for up to 48 hours	Oxymorphone oral liquid Single dose at 0.05, 0.1, & 0.2 mg/kg Multiple dose 0.2 mg/kg q4-6h for up to 48 hours
Rescue	Standard care (encouraging one-hour waiting)	Standard care (encouraging one-hour waiting)
PK sampling	0, 2, 4, 8, 12, & 24 hours post single dose; 0, 4, 8, 12, 24, 28, 32, 36, & 48 hours post the initial dose in the multiple-dose period	0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, & 24 hours post single dose; 0, 0.5, 1, 1.5, and 2 hours post Dose 1, immediately prior to Doses 2, 3, 4, 5, 6, 7, and at 0.5, 1, 1.5, and 2 hours post Dose 7 in the multiple- dose period
Safety	Adverse events (AEs)	Adverse events (AEs)

	Respiratory function (apnea monitoring & oxygen saturation) Neurological function Vital signs (frequent) Clinical laboratory tests (baseline, 24-h post single-dose, 48-h post the initial dose in the multiple-dose period)	Respiratory function (apnea monitoring & oxygen saturation) Neurological function Vital signs Clinical laboratory tests (baseline, 24-h post single dose, and 48-h post the initial dose in the multiple-dose period)
Efficacy data	• PI at 0, 0.25, 0.5, 1, 2, 3, 4, & 6 hours post single dose • PI at 0, 0.25, 0.5, 1, 2, 3, 4, (6) hours post initial dose and predose during repeated dosing • Rescue data	• PI at 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, & 24 hours post single dose • PI at 0, 0.5, 1, 1.5, and 2 hours post initial dose and predose during repeated dosing • Rescue data

Source: individual study reports and protocols.

6.1.2. **Study Results**

Patient Disposition

In Study EN3203-010, about 35% (20 of 58) of the >12-17 years age group completed the study. Early discontinuation accounted for about two thirds of the study population, including 22 of 33 (67%) patients in the single-dose phase and 16 of 25 (64%) patients in the multiple-dose phase, mostly (33 of 38 who had discontinued) due to lack of efficacy. The other cases of early dropouts were due to adverse events in two cases (both in multiple-dose phase), withdrew consent/assent in two cases, and Investigator's decision in one case. About 90% (52 of 58) were included in the PK analysis.

Table 5 Patient Disposition, Study EN3203-010

Study (EN3203-010) Patient Disposition							
	Single dose			**Multiple dose**			***Overall***
Opana tablet	**5 mg**	**10 mg**	**15 mg**	**5 mg**	**10 mg**	**15 mg**	
Enrolled (safety population)	13	9	11	9	8	8	*58*
Completed	7 (53.8)	0	4 (36.4)	3 (33.3)	1 (12.5)	5 (62.5)	*20 (34.5)*
Discontinued	6 (46.2)	9 (100)	7 (63.6)	6 (66.7)	7 (87.5)	3 (37.5)	*38 (65.5)*
Reasons for discontinuation							
Lack of efficacy	6 (46.2)	9 (100)	6 (54.5)	4 (44.4)	6 (75.0)	2 (25.0)	***33 (56.9)***
Adverse event	0	0	0	1 (11.1)	0	1 (12.5)	*2 (3.4)*
Withdrew consent/assent	0	0	1 (9.1)	1 (11.1)	0	0	*2 (3.4)*
Investigator's decision	0	0	0	0	1 (12.5)	0	*1 (1.7)*
Included in PK analysis	11 (84.6)	8 (88.9)	9 (81.8)	8 (88.9)	8 (100)	8 (100)	*52 (89.7)*

Source: Table 7 on page 33 and Table 8 on page 34 of the study report for EN3203-010.

In Study EN3319-302, most patients (41 of 45, or 91%) completed the study in the single-dose phase, including 36 of 38 (95%) in the age group of 2-12 years and 5 of 7 (71%) in the age group

of 0-<2 years. There were four cases of early discontinuation, including two cases of withdrawal by subject, one case of lack of efficacy, and one case of other reason. All patients were included in PK analysis.

Table 6 Patient Disposition, Study EN3319-302, Single-Dose Phase

Study (EN3319-302) Patient Disposition								
Age group, years	**6 to 12**			**2 to <6**			**0 to <2**	**Overall**
Oxymorphone solution, mg/kg	**0.05**	**0.10**	**0.20**	**0.05**	**0.10**	**0.20**	**0.05**	
Enrolled (safety population)	6	6	7	7	6	6	7	45
Completed	6 (100.0)	6 (100.0)	5 (71.4)	7 (100.0)	6 (100.0)	6 (100.0)	5 (71.4)	41 (91.1)
Discontinued	0	0	2 (28.6)	0	0	0	2 (28.6)	4 (8.9)
Reasons for discontinuation								
Withdrawal by subject	0	0	1 (14.3)	0	0	0	1 (14.3)	2 (4.4)
Lack of efficacy	0	0	0	0	0	0	1 (14.3)	1 (2.2)
Other	0	0	1 (14.3)	0	0	0	0	1 (2.2)
Included in PK analysis	6	6	7	7	6	6	7	45

Source: Table 8 on page 48 of the study report for EN3319-302.

In the multiple-dose phase, nine of 16 patients (seven of the 10 patients in the 6-12 years age group and two of the six patients in the 2-<6 years age group) completed the study. There were seven cases of early discontinuation, due to adverse events in three cases, physician's decision in three cases, and withdrawal by subject in one case in the two age groups (refer to table below for details per age group).

Table 7 Patient Disposition, Study EN3319-302, Multiple-Dose Phase

Study (EN3319-302) Patient Disposition			
Age group	**6 to 12 years**	**2 to <6 years**	**Overall**
Oxymorphone solution, multiple-dose	**0.20 mg/kg**	**0.20 mg/kg**	
Enrolled (safety population)	10	6	16
Completed	7 (70.0)	2 (33.3)	9 (56.3)
Discontinued	3 (30.0)	4 (66.7)	7 (43.7)
Reasons for discontinuation			
Adverse Event	2 (20.0)	1 (16.7)	3 (18.8)
Physician's decision	1 (10.0)	2 (33.3)	3 (18.8)
Withdrawal by Subject	0	1 (16.7)	1 (6.3)
Included in PK analysis	10	5 (83.3)	15 (93.8)

Source: Table 9 on page 49 of the study report for EN3319-302.

Protocol Deviations

In Study EN3203-010, all pediatric patients aged >12-17 years had at least one protocol deviation, when missing laboratory test results were included in the calculations, as shown in the table below. The deviation categories involved mostly failure to adhere to assessment schedule,

especially in terms of missing laboratory assessments (baseline and/or follow-up tests) and vital signs and/or respiratory assessments according to the Applicant's response to information requests dated June 5, 2019 and August 9, 2019.

Table 8 Protocol Deviation, Study EN3203-010

Study EN3203-010 Protocol Deviation							
	Single dose			**Multiple dose**			**Total**
Opana tablet	**5 mg**	**10 mg**	**15 mg**	**5 mg**	**10 mg**	**15 mg**	
N	13	9	11	9	8	8	58
# Patients with ≥ 1 deviation	13 (100)	9 (100)	11 (100)	9 (100)	8 (100)	8 (100)	58 (100)
Counts of specific deviation*							
Inclusion/Exclusion Criteria	3	1	1	1	2	0	8
Failure to adhere to assessment schedule	49	28	41	53	43	35	249
Laboratory assessment missing	26	18	22	18	16	16	116
Vital Signs and Respiratory Assessment missing	15	7	13	21	19	13	88
Vital Signs missing	5	2	4	6	1	2	20
Respiratory Assessment missing	1	0	1	2	6	2	12
Physical Examination Missing	1	1	0	2	0	0	4
PK Sampling Missing	1	0	1	2	0	0	4
Pain Assessment Missing	0	0	0	2	1	2	5
Total	52	29	42	54	45	35	257

*One patient may have multiple deviations in different categories.
Source: Table 1 on page 3 of the Response to Information Request (IR) submitted on April 1, 2019. Table 1 on pages 1-2 of the Response to IR submitted on June 5, 2019. Table 2 on page 4 of the Response to IR submitted on August 9, 2019.

In Study EN3319-302 all 61 pediatric patients in both age groups of 6-12 and 2-<6 years had at least one protocol deviation. The deviation categories involved mostly failure to adhere to assessment schedule, especially in terms of missing laboratory test results (baseline and/or follow-up tests), vital signs, respiratory and neurological assessments, and missing PK sampling.

Table 9 Protocol Deviations, Study EN3319-302

Study EN3319-302 Protocol Deviations					
	Single dose			**Multiple dose**	**Total**
Oxymorphone oral solution	**0.05 mg/kg**	**0.10 mg/kg**	**0.20 mg/kg**	**0.20 mg/kg**	**0.05-0.20 mg/kg**
N (age groups: 6-12, 2-<6, 0-<2 years)*	**Total (6-12 / 2-<6 / 0-<2y)**			**Total (6-12 / 2-<6y)**	**Total (6-12 / 2-<6 / 0-<2y)**
	20 (6/7/7)	12 (6/6)	13 (7/6)	16 (10/6)	61(29/25/7)
# Patients with ≥ 1 deviation	20 (100%)	12 (100%)	13 (100%)	16 (100%)	61 (100%)
Counts of specific deviation**					
Good Clinical Practice	2	0	3	5	10
Informed Consent Form Process	7	1	2	4	14

Inclusion/Exclusion Criteria	0	3	3	1	7
Investigational Product	0	0	0	9	9
Failure to adhere to assessment schedule	186 (58/63/65)	60 (20/40)	58 (37/21)	64 (42/22)	368 (157/146/65)
Clinical Laboratory Tests (lab)	61 (19/21/21)	19 (6/13)	23 (12/11)	20 (11/9)	123 (48/54/21)
Lab: Chemistry and/or Hematology Missing	41 (13/14/14)	14 (3/11)	16 (9/7)	16 (8/8)	87 (33/40/14)
Lab: Urine Drug Screen Missing	20 (6/7/7)	5 (3/2)	7 (3/4)	4 (3/1)	36 (15/14/7)
Vital Signs (VS)	31 (8/12/11)	11 (3/8)	11 (6/5)	7 (4/3)	60 (21/28/11)
VS: Missing	31 (8/12/11)	6 (3/3)	10 (5/5)	7 (4/3)	54 (20/23/11)
VS: Incomplete	0	4 (0/4)	1	0	5
VS: Timing error	0	1	0	0	1
Respiratory Assessment missing	20 (6/7/7)	4 (1/3)	5 (5/0)	3 (1/2)	32 (13/12/7)
Neurological Assessment missing	20 (6/7/7)	4 (0/4)	2 (2/0)	2 (1/1)	28 (9/12/7)
VS and Respiratory Assessment missing	0	4 (0/4)	0	0	4
Respiratory & Neurological Assessment missing	0	0	0	1	1
Physical Exam (PE)					
PE Incomplete	0	1	0	0	1
PE Missing	0	1	0	0	1
PE Timing Error	0	0	0	1	1
PK Sampling missing	20 (6/7/7)	5 (4/1)	7 (5/2)	11 (8/3)	43 (23/13/7)
Food Consumption Missing	3	0	0	1	4
Pain Assessment missing	21 (7/7/7)	11 (6/5)	10 (7/3)	18 (14/4)	60 (34/19/7)
Follow Up Visit Missing	11 (6/3/2)	0	0	0	11
Failure to adhere to visit window	0	0	0	1	1
Protocol Adherence – Other	2	0	1	0	3
Total	198	64	67	84	413

*Selected age group designation for more frequently reported deviation categories.
**One patient may have multiple deviations in different categories.
Source: Table 2 on page 3 of the Response to Information Request (IR) submitted on April 1, 2019. Table 2 to 5 on pages 4-6 of the Response to IR submitted on June 5, 2019. Table 4 on page 7 of the Response to IR submitted on August 9, 2019.

Demographic and Baseline Characteristics

In the single-dose phase of Study EN3203-010, the study population aged >12-17 years consisted of 73% female, 85% White, and 100% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 5, 10, and 15 mg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase the study population consisted of 56% female, 88% White, and 88% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups. Ranges of baseline weight, height, and BMI varied among the groups.

Table 10 Demographics and Baseline Characteristics, Study EN3203-010

Study EN3203-010, age >12 to 17 years								
Opana tablet	**Single dose**				**Multiple dose**			
	5 mg	**10 mg**	**15 mg**	**Subtotal**	**5 mg**	**10 mg**	**15 mg**	**Subtotal**
# Patients	N=13	N=9	N=11	N=33	N=9	N=8	N=8	N=25
Sex								
Male	4 (30.8%)	2 (22.2%)	3 (27.3%)	9 (27.3%)	5 (55.6%)	2 (25.0%)	4 (50.0%)	11 (44.0%)
Female	9 (69.2%)	7 (77.8%)	8 (72.7%)	24 (72.7%)	4 (44.4%)	6 (75.0%)	4 (50.0%)	14 (56.0%)
Age (years)								
Mean (SD)	14.9 (1.71)	15.3 (1.66)	14.6 (1.63)	14.9 (1.64)	15.0 (0.71)	15.3 (1.58)	15.5 (1.07)	15.2 (1.13)
Median	15.0	16.0	15.0	15.0	15.0	15.5	16.0	15.0
Min, max	12, 17	13, 17	12, 17	12, 17	14, 16	13, 17	14, 17	13, 17
Race								
White	11 (84.6%)	7 (77.8%)	10 (90.9%)	28 (84.8%)	9 (100%)	7 (87.5%)	6 (75.0%)	22 (88.0%)
Black or African American	2 (15.4%)	2 (22.2%)	1 (9.1%)	5 (15.2%)	0	1 (12.5%)	0	1 (4.0%)
Multiracial	0	0	0	0	0	0	2 (25.0%)	2 (8.0%)
Ethnicity								
Hispanic	0	0	0	0	2 (22.2%)	0	1 (12.5%)	3 (12.0%)
Not Hispanic	13 (100%)	9 (100%)	11 (100%)	33 (100%)	7 (77.8%)	8 (100%)	7 (87.5%)	22 (88.0%)
Weight (kg)	N=13	N=9	N=11	N=33	N=9	N=8	N=8	N=25
Mean (SD)	69.94 (22.648)	70.14 (15.016)	68.45 (16.197)	69.50 (18.201)	63.70 (11.141)	60.78 (7.322)	68.90 (15.709)	64.43 (11.845)
Median	65.00	70.70	66.00	66.00	60.00	63.10	64.45	63.00
Min, Max	33.9, 128.8	51.9, 99.3	45.4, 88.4	33.9, 128.8	53.3, 81.0	45.4, 68.0	51.2, 94.5	45.4, 94.5
Height (cm)	N=13	N=8	N=9	N=30	N=9	N=8	N=8	N=25
Mean (SD)	162.00 (8.700)	167.76 (7.462)	159.44 (6.189)	162.77 (8.118)	168.23 (8.823)	162.46 (9.374)	168.05 (7.138)	166.33 (8.589)
Median	162.50	168.35	160.20	162.75	168.00	161.00	166.50	163.80
Min, Max	152.0, 185.7	159.0, 179.0	146.5, 166.5	146.5, 185.7	156.0, 182.2	148.0, 173.5	159.6, 177.3	148.0, 182.2
BMI (kg/m^2)	N=13	N=8	N=9	N=30	N=9	N=8	N=8	N=25
Mean (SD)	26.19 (5.835)	25.15 (7.069)	27.38 (6.963)	26.27 (6.345)	22.52 (3.720)	23.11 (3.012)	24.26 (4.556)	23.26 (3.723)
Median	24.62	22.68	24.24	24.46	21.25	23.70	22.44	21.70
Min, Max	14.1, 37.4	19.3, 39.3	20.4, 41.2	14.1, 41.2	18.9, 30.0	18.4, 26.9	20.0, 30.6	18.4, 30.6

Source: Table 9 on pages 36-37 of the study report for EN3203-010.

Demographic and baseline characteristics for Study EN3319-302 are summarized by age group below. In the single-dose phase, the study population for the 6-12 years age group consisted of 47% female, 68% White, and 95% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 0.05, 0.10, and 0.20 mg/kg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase the study population consisted of 50% female, 70% White, and 100% Non-Hispanic. All ten patients received the 0.20 mg/kg dose.

Table 11 Demographics and Baseline Characteristics, Age 6-12 Years, Study EN3319-302

Study (EN3319-302), Age 6 to ≤12 years					
	Single dose				**Multi dose**
Oxymorphone oral solution	**0.05 mg/kg**	**0.10 mg/kg**	**0.20 mg/kg**	**Subtotal**	**0.20 mg/kg**
# Patients	N=6	N=6	N=7	N=19	N=10
Sex					
Male	5 (83.3)	4 (66.7)	1 (14.3)	10 (52.6)	5 (50.0)
Female	1 (16.7)	2 (33.3)	6 (85.7)	9 (47.4)	5 (50.0)
Age (years)				19	10
Mean (SD)	8.3 (1.75)	8.7 (1.86)	9.0 (2.16)	8.7 (1.86)	9.6 (1.90)
Median	7.5	9.0	9.0	9.0	9.5
Min, max	7, 11	6, 11	6, 12	6, 12	7, 12
Race					
White	4 (66.7)	3 (50.0)	6 (85.7)	13 (68.4)	7 (70.0)
Black or African American	2 (33.3)	1 (16.7)	0	3 (15.8)	3 (30.0)
Asian	0	2 (33.3)	0	2 (10.5)	0
American Indian or Alaska Native	0	0	1 (14.3)	1 (5.3)	0
Ethnicity					
Hispanic	0	0	1 (14.3)	1 (5.3)	
Not Hispanic	6 (100.0)	6 (100.0)	6 (85.7)	18 (94.7)	10 (100.0)
Weight (kg)	N=6	N=6	N=7	19	10
Mean (SD)	35.25 (11.725)	30.33 (17.731)	37.26 (20.613)	34.44 (16.615)	41.81 (18.103)
Median	39.80	23.45	33.10	33.10	38.80
Min, Max	20.1, 46.4	14.7, 64.2	19.7, 80.8	14.7, 80.8	20.5, 75.0
Height (cm)	N=6	N=5	N=7	18	10
Mean (SD)	129.83 (14.442)	130.54 (19.704)	130.80 (16.645)	130.41 (15.832)	141.61 (14.794)
Median	131.00	131.00	125.00	130.70	139.00
Min, Max	113.0, 153.0	98.5, 149.8	110.0, 158.1	98.5, 158.1	120.0, 163.7
BMI (kg/m^2)	N=6	N=5	N=7	18	10
Mean (SD)	20.35 (4.371)	17.52 (6.354)	20.59 (6.044)	19.66 (5.466)	20.03 (5.443)
Median	20.25	15.20	19.20	18.55	17.90
Min, Max	15.7, 26.6	12.8, 28.6	13.9, 32.3	12.8, 32.3	14.2, 30.7

Source: Table 5 and 6 on pages 44-46 of the study report for EN3319-302.

For the 2-<6 years age group in the single-dose phase, the study population consisted of 58% female, 74% White, and 90% Non-Hispanic. Mean age, weight, height, and BMI at baseline were basically balanced between the three dose groups of 0.05, 0.10, and 0.20 mg/kg. Ranges of baseline weight, height, and BMI varied among the groups.

In the multiple-dose phase the study population consisted of 100% male, 83% White, and 100% Non-Hispanic. All six patients received the 0.20 mg/kg dose.

Table 12 Demographics and Baseline Characteristics, Age 2 to <6 Years, Study EN3319-302

Study (EN3319-302), Age 2 to <6 years					
	Single dose				**Multi dose**
Oxymorphone oral solution	**0.05 mg/kg**	**0.10 mg/kg**	**0.20 mg/kg**	**Subtotal**	**0.20 mg/kg**
# Patients	N=7	N=6	N=6	N=19	N=6
Sex					
Male	5 (71.4)	3 (50.0)	0	8 (42.1)	6 (100.0)
Female	2 (28.6)	3 (50.0)	6 (100.0)	11 (57.9)	0
Age (years)				19	6
Mean (SD)	3.4 (1.27)	3.5 (1.38)	3.5 (1.38)	3.5 (1.26)	3.8 (1.17)
Median	3.0	3.5	3.5	3.0	4.0
Min, max	2, 5	2, 5	2, 5	2, 5	2, 5
Race					
White	4 (57.1)	4 (66.7)	6 (100.0)	14 (73.7)	5 (83.3)
Black or African American	3 (42.9)	1 (16.7)	0	4 (21.1)	1 (16.7)
Asian	0	1 (16.7)	0	1 (5.3)	0
Ethnicity					
Hispanic	0	0	2 (33.3)	2 (10.5)	
Not Hispanic	7 (100.0)	6 (100.0)	4 (66.7)	17 (89.5)	6 (100.0)
Weight (kg)	N=7	N=6	N=6	19	6
Mean (SD)	18.76 (4.026)	15.77 (4.303)	17.88 (4.869)	17.54 (4.336)	17.83 (2.701)
Median	18.20	14.70	17.65	17.40	16.70
Min, Max	12.7, 24.2	11.4, 22.8	12.7, 26.2	11.4, 26.2	16.0, 23.1
Height (cm)	N=7	N=6	N=5	18	5
Mean (SD)	106.36 (10.111)	96.82 (11.618)	107.42 (15.752)	103.47 (12.562)	101.06 (6.026)
Median	105.00	95.25	108.50	101.30	104.00
Min, Max	93.0, 120.5	82.5, 117.5	84.0, 124.0	82.5, 124.0	91.0, 105.8
BMI (kg/m^2)	N=7	N=6	N=5	18	5
Mean (SD)	16.43 (1.568)	16.70 (2.948)	16.24 (2.293)	16.47 (2.167)	17.78 (2.575)
Median	16.00	16.30	16.30	16.20	16.30
Min, Max	14.7, 18.6	14.0, 22.3	12.7, 18.5	12.7, 22.3	15.6, 21.4

Source: Table 5 and 6 on pages 44-46 of the study report for EN3319-302.

For the 0-<2 years age group the study population consisted of 86% male, 86% White, and 100% Non-Hispanic. All seven patients received a single dose of study medication at 0.05 mg/kg.

Table 13 Demographics and Baseline Characteristics, Age 0 to <2 Years, Study EN3319-302

Study (EN3319-302), Age 0 to < 2 years	
Treatment	**Oxymorphone oral solution 0.05 mg/kg**
# Patients	N=7
Sex	
Male	6 (85.7)
Female	1 (14.3)
Age (years)	
Mean (SD)	0.4
Median	0.53
Min, max	<1
Race	
White	6 (85.7)
Black or African American	1 (14.3)
Ethnicity	
Hispanic	0
Not Hispanic	7 (100.0)
Weight (kg)	
Mean (SD)	9.10 (3.106)
Median	8.70
Min, Max	4.0, 12.4
Height (cm)	
Mean (SD)	72.93 (9.760)
Median	73.00
Min, Max	55.0, 86.0
BMI (kg/m^2)	
Mean (SD)	16.51 (2.554)
Median	16.80
Min, Max	13.2, 20.7

Source: Table 5 on pages 44-45 of the study report for EN3319-302.

Measurements of Effectiveness (open-label with no control)

Study EN3203-010

Single-dose PID data from Study EN3203-010 were summarized in the table below. The maximum pain reduction from baseline was (b) (4) The results could not be interpreted without a control group for comparison. The very small sample size of 9-13 per treatment group would probably have made it difficult to show treatment differences even if a placebo control were included.

Table 14 Summary of PID (VAS) from Baseline by Treatment Group, Single-Dose, EN3203-010

Oxymorphone	5 mg (N=13)		10 mg (N=9)		15 mg (N=11)	
Time Point	**PI**	**PID**	**PI**	**PID**	**PI**	**PID**
Baseline	(b) (4)					
n						
Mean (SD), 100 mm VAS						
15 Minutes Post Dose						
n						
Mean (SD)						
30 Minutes Post Dose						
n						
Mean (SD)						
1 Hour Post Dose						
n						
Mean (SD)						
2 Hours Post Dose						
n						
Mean (SD)						
3 Hours Post Dose						
n						
Mean (SD)						
4 Hours Post Dose						
n						
Mean (SD)						
6 Hours Post Dose or Rescue						
n						
Mean (SD)						

Source: Table 10 on pages 39-40 of the study report.

The sample sizes for the dose groups were even smaller, <10 per treatment group in the multiple-dose phase. The maximum pain reduction during the initial dosing interval of the multiple-dose phase was (b) (4) . Dropout for lack of efficacy was (b) (4) .

Pain data were available from only 1-3 patients before the first repeated dose in the 5 mg dose group, by the 3rd repeated dose in the 10 mg dose group, and by the 8th repeated dose in the 15 mg dose group. Similarly, the results could not be interpreted without a control group for comparison.

Table 15 Summary of PID from Baseline by Treatment Group, Multiple-Dose, EN3203-010

Oxymorphone	5 mg (N=9)		10 mg (N=8)		15 mg (N=8)	
Time Point	**PI**	**PID**	**PI**	**PID**	**PI**	**PID**
Baseline	(b) (4)					
n						
Mean (SD)						
15 Minutes Post First Dose						
n						
Mean (SD)						
30 Minutes Post First Dose						
n						
Mean (SD)						
1 Hour Post First Dose						
n						
Mean (SD)						
2 Hours Post First Dose						
n						
Mean (SD)						
3 Hours Post First Dose						
n						
Mean (SD)						
4 Hours Post First Dose						
n						
Mean (SD)						
6 Hours Post First Dose						
n						
Mean (SD)						
Every 4 to 6 Hours Dose #1						
N						
Mean (SD)						
Every 4 to 6 Hours Dose #2						
n						
Mean (SD)						
Every 4 to 6 Hours Dose # 3						
N						
Mean (SD)						
Every 4 to 6 Hours Dose #4						
N						
Mean (SD)						
Every 4 to 6 Hours Dose #5						
N						
Mean (SD)						
Every 4 to 6 Hours Dose #6						
N						
Mean (SD)						
Every 4 to 6 Hours Dose #7						
N						
Mean (SD)						

Every 4 to 6 Hours Dose #8	(b) (4)
N	
Mean (SD)	
Every 4 to 6 Hours Dose #9	
N	
Mean (SD)	
Every 4 to 6 Hours Dose #10	
N	
Mean (SD)	
Every 4 to 6 Hours Dose #11	
N	
Mean (SD)	
Early Termination	
N	
Mean (SD)	

Source: Table 11 on pages 41-43 of the study report.

The number and proportion of patients taking rescue are summarized in the table below. Overall, there were (b) (4) Rescue consisted of standard care and was not standardized otherwise. Both the study medication and one or more rescue medication could have contributed to analgesic effects. Without a control group the results could not be interpreted.

Table 16 Number and Proportion of Patients Taking Rescue, Study EN3203-010

Oxymorphone IR	Single Dose				Multiple Dose			
	5 mg (N=13)	10 mg (N=9)	15 mg (N=11)	Overall (N=33)	5 mg (N=9)	10 mg (N=8)	15 mg (N=8)	Overall (N=25)
N (%) rescued	(b) (4)							

Source: Table 12 on page 45 of the study report.

Study EN3319-302

PI and PID data were presented in separate tables in the study report for Study EN3319-302. There were so many data inconsistencies in comparing PID data to corresponding PI data in the two tables that made it impossible to report the findings. The results were further complicated by the prior use of IV opioids before the start of study medication, concomitant use of other opioids as rescue during the study, lack of baseline pain intensity requirement (very low baseline PI of 2.4-4.5 in the single-dose phase and (b) (4) in the multiple-dose phase measured by a 11-point scale), and difficulty in measuring pain and interpreting pain from other stimuli in the younger age groups.

The number and proportion of patients taking rescue are summarized in the table below. Overall, there were (b) (4) of patients taking rescue in the single-dose phase and (b) (4)

(b) (4) taking rescue in the multiple-dose phase (refer to the table below for details on distribution of rescue use per age/dose group). Rescue consisted of standard care and was not standardized otherwise. Both the study medication and one or more rescue medication could have contributed to analgesic effects. Without a control group the results could not be interpreted.

Table 17 Number and Proportion of Patients Taking Rescue, Study EN3319-302

Age, years	6-12			2-<6			0-< 2	6-12	2-<6
Oxymorphone IR mg/kg	Single Dose							Multiple Dose	
	0.05 (N=6)	0.10 (N=6)	0.20 (N=7)	0.05 (N=7)	0.10 (N=6)	0.20 (N=6)	0.05 (N=7)	0.20 (N=10)	0.20 (N=6)
N (%) rescued	(b) (4)								

Source: Table 13 on page 61 and Table 17 on page 73 of the study report.

7. Integrated Review of Effectiveness

Not applicable.

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

7.1.2. Secondary and Other Endpoints

7.1.3. Subpopulations

7.1.4. Dose and Dose-Response

7.1.5. Onset, Duration, and Durability of Efficacy Effects

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

7.2.2. Other Relevant Benefits

7.3. Integrated Assessment of Effectiveness

8. Review of Safety

8.1. Safety Review Approach

The safety review is focused on pediatric safety data. Safety findings will be summarized by the age group and by dose level in each age group. Adult PK study is limited to a single dose at a relatively low dose level and thus safety data from the adult study will not be reviewed in detail.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Exposure by the number of doses per age group is summarized in the table below. A total of 149 patients had exposure to the study drug in one adult PK study and two pediatric PK and safety studies.

Exposure by formulation consisted of exposure to the tablet formulation in 30 adults and 58 pediatric patients aged >12-17 years and exposure to the liquid formulation in 29 of 30 adults and 61 pediatric patients aged 0-12 years.

Of the 119 pediatric patients, exposure to one dose of oxymorphone was reported in 89 pediatric patients including 42 patients aged >12-17 years, 19 patients aged 6-12 years, 21 patients aged 2-<6 years, and seven patients aged 0 to <2 years. Exposure to more than one dose (2-13 doses) was reported in 30 pediatric patients including 16 patients aged >12-17 years, 10 patients aged 6-12 years, and four patients aged 2-<6 years.

Maximum pediatric exposure by the number of doses included 13 doses taken by one patient and 12 doses by seven patients. Maximum pediatric exposure by dose level included exposure to 15 mg tablet in 19 patients aged >12-17 years and five of them had 8-12 doses, and exposure to 0.2 mg/kg solution in 29 patients aged 2-12 years and seven of them (in the 6-12 years age group) had 8-12 doses.

Table 18 Exposure by Number of Doses and Age Group, Safety Population

Age Group	Adult	Pediatric					Overall
		>12–17 years	6–≤12 years	2–<6 years	0–<2 years	Subtotal	
#patients	N=30	N=58	N=29	N=25	N=7	N=119	N=149
Study	EN3319-101	EN3203-010	EN3319-302				
Formulation	Tablet/solution	Tablet	Solution				
Dose level	*5 mg*	*5/10/15 mg*	*.05/.1/.2 mg/kg*	*.05/.1/.2 mg/kg*	*.05 mg/kg*		
Single dose	30 (tablet & 29 to solution)	33 (13/9/11)	19 (6/6/7)	19 (7/6/6)	7	78	108
Multiple dose	*Dose level*	*5/10/15 mg*	*0.2 mg/kg*	*0.2 mg/kg*			
Subtotal		25 (9/8/8)	10	6		41	
1 Dose		9 (3/3/3)		2		11	
2 Doses		2 (2/0/0)				2	
3 Doses		1 (1/0/0)	1	1		3	
4 Doses		1 (0/1/0)	1			2	

5 Doses		2 (1/1/0)		1		3	
6 Doses				2		2	
7 Doses			1			1	
8 Doses		1 (0/0/1)	1			2	
9 Doses		2 (1/1/0)				2	
10 Doses		1 (0/0/1)	3			4	
11 Doses		1 (0/0/1)				1	
12 Doses		4 (1/1/2)	3			7	
13 Doses		1 (0/1/0)				1	

Source: Table pending and Table 3 on page 4 of submission dated April 1, 2019.

8.2.2. **Relevant characteristics of the safety population:**

Demographics and baseline characteristics of the pediatric safety population are summarized by age group and described in detail in the Review Section 6.1.2.

8.2.3. **Adequacy of the safety database:**

Female pediatric patients had been included in all age groups in various proportions. The only age/dosage strata with no female patient was multiple-dose exposure to 0.2 mg/kg in the age group of 6 to 12 years. Overall, the individual age/dosage strata were small, mostly limited to less than 10 patients.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

Data inconsistency was detected in reporting missing laboratory test results between several different tables and many cases of missing lab tests were not counted in the shift tables for abnormal lab findings or in the tables summarizing protocol deviations. Very high proportions (100%) of study participants had one or more types of protocol deviation, especially in terms of missing laboratory assessments (baseline and/or follow-up tests), missing vital signs and/or respiratory assessments. Missing PK sampling and neurological assessments were also remarkable in Study EN3319-302.

8.3.2. **Categorization of Adverse Events**

The Applicant followed the FDA's guidance on reporting treatment emergent AEs, described cases of serious AEs and AE dropouts in narrative format, and provided shift tables for clinical laboratory tests and vital signs upon requests.

8.3.3. **Routine Clinical Tests**

Safety assessments, including monitoring of adverse events (AEs), respiratory function, neurological function, and vital signs at baseline and during and after the study and conducting

clinical laboratory tests at baseline and after the treatment, are considered adequate.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in any study.

8.4.2. Serious Adverse Events

No serious Adverse Events (SAEs) were reported in the adult Study EN3319-101.

SAEs are listed by age group and dosage as shown in the table below. Seven SAEs were reported in the two pediatric studies, three in the >12-17 years age group, three in the 6-12 years age group, and one in the 2-<6 years age group.

Table 19 List of SAEs in Pediatric Studies

Age Groups	**Age >12–17 years (n=58)**			**Age 6–≤12 years (n=29)**			**Age 2–<6 years (n=25)**			**Age 0–<2 years (n=7)**
Dose level	**5 mg**	**10 mg**	**15 mg**	**0.05 mg/kg**	**0.1 mg/kg**	**0.2 mg/kg**	**0.05 mg/kg**	**0.1 mg/kg**	**0.2 mg/kg**	**0.05 mg/kg**
Single dose	13	9	11	6	6	7	7	6	6	7
SAEs		***1***	***1***		***1***		***1***			
Multiple dose	9	8	8			10			6	
SAEs	***1***					***2***				

Source: Individual study reports.

Case narratives for SAEs were summarized in terms of exposure, SAE type, brief description of the events leading to SAE, concomitant medication, outcome of SAE, and the relationship of SAE with the study drug as shown in the table below. The seven SAEs included one case of atelectasis and fat embolism; one case of failure of spinal implant; one case of anemia, unequal pupils, blurred vision, and headache; one case of neutropenia and postoperative fever; one case of postoperative joint dislocation; one case of abdominal abscess; one case of wound dehiscence. All the SAEs resolved, mostly with treatments targeted at the SAEs, and were considered unlikely to be related to the study drug based on the case narratives provided.

Table 20 SAE Case Summary Based on Narratives

Patient	Study drug	SAE	Brief description	Concomitant medication	Outcome of SAE	Related to study drug
Study EN3203-010						
Age 17 white female	Opana 10 mg single dose	Atelectasis and fat embolism	Had left femur fracture undergoing surgery for intramedullary nailing, developed acute lung injury from fat emboli syndrome, and had bilateral basal atelectasis on chest X-ray	IV morphine, seretide, oxygen, paracetamol, methocarbamol, hydromorphone, fentanyl, docusate, and enoxaparin	Resolved with treatment	Unlikely
Age 12 white female	Opana 15 mg single dose	Failure of spinal implant	Underwent posterior spinal fusion surgery for severe idiopathic adolescent scoliosis, took one dose of study medication for leg pain, and discovered problems related to multiple screws on CT scan.	Cefazolin, diphenhydramine, Senokot-S, diazepam, macrogol, ketamine, hydromorphone, paracetamol, gabapentin, and hydrocortisone	Resolved with reinsertion of spinal implants	Unlikely
Age 15 white female	Opana 5 mg one dose	Anemia, pupils unequal, vision blurred, & headache	Underwent left femur and tibial osteotomy surgery and intramedullary nailing, progressively worsening anemia after surgery, multiple opioids including a single dose of study drug and several doses of morphine and oxycodone for post-operative pain, experienced double and blurred vision and headache, all resolved at initial discharge, worse after touching scopolamine patch (applied for nausea), presented with unequal pupil dilatation at hospital readmission, received blood transfusion for severe anemia	Enoxaparin, cefazolin, paracetamol, metoclopramide, prenatal vitamins, hydromorphone, ondansetron, hydromorphone, Sennoside, docusate, and bisacodyl	Resolved	Unlikely
Study EN3319-302						
Age 5 white female	0.05 mg/kg single dose	Neutropenia, Postoperative fever	Received oxymorphone oral liquid 1.2 mL single dose for pain post biopsy of abdominal mass, diagnosed with embryonal rhabdomyosarcoma, completed a week of chemotherapy, readmitted 9 days later for fever, urinary symptoms consistent with UTI, and neutropenia, which responded to antibiotics.	Coumadin (warfarin), oxycodone, OxyContin (oxycodone), Neupogen (filgrastim), Neurontin (gabapentin), and senna	Resolved with treatment	Unlikely

Age 11 white male	0.10 mg/kg single dose	Joint dislocation postoperative	Had medical history of slipped capital femoral epiphysis, and bilateral hip dislocation and femoral neck osteotomies, received oxymorphone oral liquid 6.4 mg single dose during recovery from bilateral hip dislocations and femoral neck osteotomies, had left hip dislocation detected by X-ray 5 days later.	Calcium gluconate, cefazolin, acetaminophen, ondansetron, diazepam, docusate, morphine and oxycodone	Resolved with treatment	Unlikely
Age 7 white male	0.20 mg/kg 8 doses	Abdominal abscess	Presented with a ruptured appendix and multiple abdominal abscesses and underwent open appendectomy, new abdominal abscesses by CT 4 days later leading to prolonged hospitalization	Oxymorphone oral liquid 4 mg q6 hours for 2 days	Resolved with treatment	Unlikely
Age 9 white male	0.20 mg/kg 3 doses	Wound dehiscence	Had rib cartilage harvest and stage 1 microtia repair, oxymorphone discontinued due to lethargy, wound dehiscence at follow-up visit 12 days later and had surgical repair.	Oxymorphone oral liquid 5-8 mg q4 hours, 3 doses	Resolved with treatment	Unlikely

Source: Table 14.3.3 on pages 169-172 of study report for Study EN3203-010 and Table 14.3.3. on pages 123-126 of study report for Study EN3319-302.

8.4.3. **Discontinuations Due to Adverse Events**

Cases of early discontinuation due to AEs are listed by the age group and dosage in the table below. One case was reported in the adult study. Five cases of early discontinuation were reported in pediatric studies during the multiple-dose phase with two in the >12-17 years age group, two in the 6-12 years age group, and one in the 2-<6 years age group.

Table 21 Case Summary for Study Discontinuation due to AEs

Age Groups	**Adult (n=30)**	**Age >12–17 years (n=58)**			**Age 6–≤12 years (n=29)**			**Age 2–<6 years (n=25)**			**Age 0–<2 years (n=7)**
Dose level	5 mg	5 mg	10 mg	15 mg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg	0.1 mg/kg	0.2 mg/kg	0.05 mg/kg
Single dose	30	13	9	11	6	6	7	7	6	6	7
AE Dropouts	***1***										
Multiple dose	0	9	8	8	0	0	10	0	0	6	0
AE Dropouts		***1***		***1***			***2***			***1***	

Source: Individual study reports.

Case narratives for early discontinuation due to AEs were summarized in terms of exposure, type of AE, brief description of the events leading to early discontinuation, concomitant medication,

outcome of AE, and the relationship of AE with the study drug as shown in the table below. The case in the adult study was due to herpes zoster, unlikely to be related to the study drug. Five pediatric cases of early discontinuation were due to CNS symptoms with two cases of sedation and one case each of tremor, somnolence, and lethargy. All pediatric cases resolved spontaneously and were considered to be probably related to the study drug based on the case narratives provided.

Table 22 Case Summary for Study Discontinuation due to AEs

Patient	Study drug	AE	Brief description	Concomitant medication	Outcome of AE	Related to study drug
Study EN3319-101						
Age 44 white Hispanic male	Opana 5 mg single dose	Herpes zoster	Received a single dose of Opana 5 mg in Period 1, developed herpes zoster prior to entering Period 2 and thus discontinued		Resolved	Unlikely
Study EN3203-010						
Age 16 white male	Opana 5 mg 3-dose	Sedation	Discontinued Opana 5 mg due to moderate sedation, other AEs: mild decrease in oxygen saturation, moderate hypertension, mild tachycardia, mild constipation next day, and mild urinary retention 2 days later	Fluticasone propionate, montelukast, loratadine, sertraline, midodrine, budesonide, salbutamol, cefazolin, paracetamol, Vicodin, Sennoside, fludrocortisone, bisacodyl	Resolved	Probably
Age 16 white male	Opana 15 mg 1-dose	Tremor	Discontinued Opana 15 mg due to moderate tremor, other AEs included mild pruritus, pyrexia, dizziness, and urinary retention	Morphine, ibuprofen, ketorolac, ondansetron, docusate, paracetamol, oxycodone, famotidine hydromorphone	Resolved	Probably
Study EN3319-302						
Age 9 black male	0.20 mg/kg 4-dose	Sedation	Discontinued oxymorphone oral liquid due to mild sedation		Resolved	Probably
Age 2 white male	0.20 mg/kg 1-dose	Somnolence	Discontinued oxymorphone oral liquid due to moderate somnolence		Resolved	Probably
Age 9 white male	0.20 mg/kg 3-dose	Lethargy	Discontinued oxymorphone oral liquid due to moderate lethargy		Resolved	Probably

Source: Table 14.3.3 on pages 174-175 of study report for Study EN3203-010 and Table 14.3.3. on pages 127-129 of study report for Study EN3319-302.

8.4.4. **Significant Adverse Events**

Refer to the cases identified as AE-related dropouts as described above.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs in the two pediatric studies

Treatment-emergent AEs or TEAEs are summarized in various ways: by age group subtotals including both single-and multiple-dose phases and by single-dose versus multiple-dose across age groups. Dose response is then explored in detail by presenting TEAEs by dose level per treatment phase (single- and multiple-dose) for the >12-17 years age group in Study EN3203-010 and for the three age groups in Study EN3319-302.

Common TEAEs per age group (single-and multiple-dose phases combined) and per study phase across age groups are summarized in the table below. For the entire pediatric population, two thirds of patients reported AEs with about 60% in the single-dose phase and 80% in the multiple-dose phase. Individual AEs reported noticeably more in the multiple-dose than the single-dose phase included constipation, nausea, dizziness, urinary retention, oxygen saturation decreased, and anemia. The number of patients with AEs and reporting rates varied between the age groups ranging from 57 to 79% in different age groups. The most common AEs (≥5%) for the entire pediatric population included (in order of decreasing reporting frequency) nausea, pyrexia, constipation, vomiting, pruritus, and headache. The next most common AEs included five cases (4%) of each of the following: peripheral edema, oxygen saturation decreased, muscle spasms, dizziness, and urinary retention. The AEs were generally consistent with common post-operative and opioid-related findings.

Table 23 Common TEAEs Per Age Group and Per Study Phase Across Age Group

Common AEs, N (%)	By age group				By study phase		
Subgroup	>12-17	6-12	2-<6	0-<2	SD, all age	MD, all age	Total
#patients in the subpopulation	N=58	N=29	N=25	N=7	N=78	N=41	N=119
#Patients with any AE	33 (56.9)	23 (79.3)	19 (76.0)	4 (57.1)	46 (59.0)	33 (80.5)	79 (66.4)
Blood and lymphatic system disorders							
Anemia	4 (6.9)	0	0	0	0	4 (9.8)	4 (3.4)
Gastrointestinal disorders							
Abdominal distension	2 (3.4)	0	2 (8.0)	0	2 (2.6)	2 (4.9)	4 (3.4)
Constipation	10 (17.2)	2 (6.9)	2 (8.0)	0	5 (6.4)	9 (22.0)	14 (11.8)
Nausea	11 (19.0)	6 (20.7)	1 (4.0)	0	7 (9.0)	11 (26.8)	18 (15.1)
Vomiting	5 (8.6)	5 (17.2)	2 (8.0)	1 (14.3)	6 (7.7)	7 (17.1)	13 (10.9)
General disorders and admin. site conditions							
Peripheral edema	0	0	3 (12.0)	2 (28.6)	4 (5.1)	1 (2.4)	5 (4.2)
Pyrexia	7 (12.1)	6 (20.7)	2 (8.0)	0	9 (11.5)	6 (14.6)	15 (12.6)
Injury, poisoning and procedural complications							
Postoperative fever	0	2 (6.9)	2 (8.0)	0	4 (5.1)	0	4 (3.4)
Procedural nausea	0	0	2 (8.0)	0	2 (2.6)	0	2 (1.7)
Procedural pain	0	1 (3.4)	2 (8.0)	0	3 (3.8)	0	3 (2.5)
Investigations	0	0	0	0	0	0	0
Oxygen saturation decreased	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)
Musculoskeletal and connective tissue disorders							
Muscle spasms	3 (5.2)	2 (6.9)	0	0	3 (3.8)	2 (4.9)	5 (4.2)
Nervous system disorders							
Dizziness	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)

Headache	4 (6.9)	2 (6.9)	0	0	0	6 (14.6)	6 (5.0)
Renal and urinary disorders							
Urinary retention	5 (8.6)	0	0	0	1 (1.3)	4 (9.8)	5 (4.2)
Skin and subcutaneous tissue disorders							
Pruritus	4 (6.9)	2 (6.9)	2 (8.0)	0	3 (3.8)	5 (12.2)	8 (6.7)

Source: the table below.

Table 24 Common TEAEs Per Study Phase for Each Age Group

Common AEs, N (%)	**Study EN3203-010**		**Study EN3319-302**				
Age group	**>12-17 years**		**6-12 years**		**2-<6 years**		**0-<2 years**
Study phase	Single-dose	Multi-dose	Single-dose	Multi-dose	Single-dose	Multi-dose	Single-dose
#patients in the subpopulation	N=33	N=25	N=19	N=10	N=19	N=6	N=7
#Patients with any AE	14 (42.4%)	19 (76.0%)	13 (68.4)	10 (100.0)	15 (78.9)	4 (66.7)	4 (57.1)
Blood and lymphatic system disorders							
Anemia	0	4	0	0	0	0	0
Gastrointestinal disorders							
Abdominal distension	0	2	0	0	2 (10.5)	0	0
Constipation	2 (6.1%)	8 (32.0%)	1 (5.3)	1 (10.0)	2 (10.5)	0	0
Nausea	4 (12.1%)	7 (28.0%)	2 (10.5)	4 (40.0)	1 (5.3)	0	0
Vomiting	2 (6.1%)	3 (12.0%)	1 (5.3)	4 (40.0)	2 (10.5)	0	1 (14.3)
General disorders and admin. site conditions							
Peripheral edema	0	0	0	0	2 (10.5)	1 (16.7)	2 (28.6)
Pyrexia	4 (12.1%)	3 (12.0%)	4 (21.1)	2 (20.0)	1 (5.3)	1 (16.7)	0
Injury, poisoning and procedural complications							
Postoperative fever	0	0	2 (10.5)	0	2 (10.5)	0	0
Procedural nausea	0	0	0	0	2 (10.5)	0	0
Procedural pain	0	0	1 (5.3)	0	2 (10.5)	0	0
Investigations							
Oxygen saturation decreased	1	4	0	0	0	0	0
Musculoskeletal and connective tissue disorders							
Muscle spasms	1 (3.0%)	2 (8.0%)	2 (10.5)	0	0	0	0
Nervous system disorders							
Dizziness	1 (3.0%)	4 (16.0%)	0	0	0	0	0
Headache	0	4 (16.0%)	0	2 (20.0)	0	0	0
Renal and urinary disorders							
Urinary retention	1	4	0	0	0	0	0
Skin and subcutaneous tissue disorders							
Pruritus	1 (3.0%)	3 (12.0%)	1 (5.3)	1 (10.0)	1 (5.3)	1 (16.7)	0

Source: Table 15 on pages 53-54 of study report for Study EN3203-010 and Table 28 on pages 102-105 and Table 29 on pages 107-108 of study report for Study EN3319-302.

TEAEs in Study EN3203-010

The next table summarizes common AEs defined as AEs reported in more than one patient from any of the dose groups during either the single-dose phase or the multiple-dose phase in Study EN3203-010 and is followed by a tabular summary of all AEs per dose group per study phase, which is presented as a reference.

In Study EN3203-010, which included the >12-17 years age group, more AEs were reported in the multiple-dose phase than the single-dose phase overall and in terms of the types of the individual AEs.

The most frequently reported individual AEs in the single-dose phase included four cases of pyrexia (all at 15 mg dose) and four cases of nausea (one at 5 mg dose, two at 10 mg dose, and one at 15 mg dose). Other more frequently reported AEs included two cases of constipation (one at 5 mg dose and one at 15 mg dose) and two cases of vomiting (one at 5 mg dose and one at 10 mg dose).

In the multiple-dose phase the most frequently reported individual AEs included eight cases of constipation (three at 5 mg dose, four at 10 mg dose, and one at 15 mg dose) and seven cases of nausea (four at 5 mg dose, two at 10 mg dose, and one at 15 mg dose). Other more frequently reported AEs included four cases of each of the following: anemia (one at 5 mg dose and three at 15 mg dose), oxygen saturation decreased (two at 5 mg dose and two at 15 mg dose), dizziness (one at 5 mg dose, two at 10 mg dose, and one at 15 mg dose), headache (three at 5 mg dose and one at 15 mg dose), and urinary retention (one at 5 mg dose and three at 15 mg dose), and three cases of each of the following: vomiting (two at 5 mg dose and one at 15 mg dose) and pyrexia (one at 5 mg dose and two at 15 mg dose).

The findings were generally consistent with what would be expected postoperatively and with the known safety profile associated with opioid analgesics. The data did not reveal any trend to suggest a dose response. However, this evaluation was limited due to small sample sizes for the dose/age subgroup and the short treatment duration as well as the relatively small difference in dose levels studied.

Table 25 Common AEs, More Than One Report in Any Dose Group, Study EN3203-010

Study EN3203-010	Single Dose of Oxymorphone IR				Multiple Dose of Oxymorphone IR			
System Organ Class/Preferred Term	5 mg (N=13)	10 mg (N=9)	15 mg (N=11)	Overall (N=33)	5 mg (N=9)	10 mg (N=8)	15 mg (N=8)	Overall (N=25)
#Patients with any AE	3 (23.1%)	4 (44.4%)	7 (63.6%)	**14 (42.4%)**	8 (88.9%)	5 (62.5%)	6 (75.0%)	**19 (76.0%)**
Blood and lymphatic system disorders								
Anemia	0	0	0	0	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Gastrointestinal disorders								
Constipation	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	**3 (33.3%)**	**4 (50.0%)**	1 (12.5%)	8 (32.0%)
Nausea	1 (7.7%)	**2 (22.2%)**	1 (9.1%)	4 (12.1%)	**4 (44.4%)**	**2 (25.0%)**	1 (12.5%)	7 (28.0%)
Vomiting	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	**2 (22.2%)**	0	1 (12.5%)	3 (12.0%)
General disorders and administration site conditions								
Pyrexia	0	0	**4 (36.4%)**	4 (12.1%)	1 (11.1%)	0	**2 (25.0%)**	3 (12.0%)
Investigations								
Oxygen saturation decreased	1 (7.7%)	0	0	1 (3.0%)	**2 (22.2%)**	0	**2 (25.0%)**	**4 (16.0%)**
Musculoskeletal and connective tissue disorders								
Muscle spasms	1 (7.7%)	0	0	1 (3.0%)	0	**2 (25.0%)**	0	2 (8.0%)
Nervous system disorders								
Dizziness	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	**2 (25.0%)**	1 (12.5%)	4 (16.0%)
Headache	0	0	0	0	**3 (33.3%)**	0	1 (12.5%)	4 (16.0%)
Renal and urinary disorders								
Urinary retention	0	0	1 (9.1%)	1 (3.0%)	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)

Source: the table below.

Table 26 TEAEs Reported in ≥5% in Either Treatment Phase, Study EN3203-010

Study EN3203-010	Single Dose of Oxymorphone IR				Multiple Dose of Oxymorphone IR			
System Organ Class/Preferred Term	5 mg (N=13)	10 mg (N=9)	15 mg (N=11)	Overall (N=33)	5 mg (N=9)	10 mg (N=8)	15 mg (N=8)	Overall (N=25)
#Patients with any AE	3 (23.1%)	4 (44.4%)	7 (63.6%)	14 (42.4%)	8 (88.9%)	5 (62.5%)	6 (75.0%)	19 (76.0%)
Blood and lymphatic system disorders	0	0	0	0	1 (11.1%)	0	3 (37.5%)	4 (16.0%)
Anemia	0	0	0	0	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Cardiac disorders	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Tachycardia	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Gastrointestinal disorders	2 (15.4%)	2 (22.2%)	1 (9.1%)	5 (15.2%)	5 (55.6%)	4 (50.0%)	3 (37.5%)	12 (48.0%)
Abdominal distension	0	0	0	0	0	1 (12.5%)	1 (12.5%)	2 (8.0%)
Constipation	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	**3 (33.3%)**	**4 (50.0%)**	1 (12.5%)	8 (32.0%)
Nausea	1 (7.7%)	**2 (22.2%)**	1 (9.1%)	4 (12.1%)	**4 (44.4%)**	**2 (25.0%)**	1 (12.5%)	7 (28.0%)
Vomiting	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	**2 (22.2%)**	0	1 (12.5%)	3 (12.0%)
General disorders and administration site conditions	1 (7.7%)	0	4 (36.4%)	5 (15.2%)	2 (22.2%)	0	2 (25.0%)	4 (16.0%)
Pyrexia	0	0	**4 (36.4%)**	4 (12.1%)	1 (11.1%)	0	**2 (25.0%)**	3 (12.0%)
Investigations	1 (7.7%)	0	0	1 (3.0%)	2 (22.2%)	0	2 (25.0%)	4 (16.0%)
Oxygen saturation decreased	1 (7.7%)	0	0	1 (3.0%)	**2 (22.2%)**	0	**2 (25.0%)**	**4 (16.0%)**
Musculoskeletal and connective tissue disorders	1 (7.7%)	0	0	1 (3.0%)	0	2 (25.0%)	1 (12.5%)	3 (12.0%)
Muscle spasms	1 (7.7%)	0	0	1 (3.0%)	0	**2 (25.0%)**	0	2 (8.0%)
Nervous system disorders	2 (15.4%)	2 (22.2%)	0	4 (12.1%)	4 (44.4%)	2 (25.0%)	2 (25.0%)	8 (32.0%)
Dizziness	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	**2 (25.0%)**	1 (12.5%)	4 (16.0%)
Headache	0	0	0	0	**3 (33.3%)**	0	1 (12.5%)	4 (16.0%)
Hypoesthesia	1 (7.7%)	1 (11.1%)	0	2 (6.1%)	0	0	0	0
Sedation	0	0	0	0	1 (11.1%)	0	1 (12.5%)	2 (8.0%)
Psychiatric disorders	0	0	0	0	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Anxiety	0	0	0	0	1 (11.1%)	1 (12.5%)	0	2 (8.0%)
Renal and urinary disorders	0	0	1 (9.1%)	1 (3.0%)	2 (22.2%)	0	3 (37.5%)	5 (20.0%)
Urinary retention	0	0	1 (9.1%)	1 (3.0%)	1 (11.1%)	0	**3 (37.5%)**	4 (16.0%)
Respiratory, thoracic and mediastinal disorders	1 (7.7%)	1 (11.1%)	1 (9.1%)	3 (9.1%)	1 (11.1%)	2 (25.0%)	1 (12.5%)	4 (16.0%)
Pleural effusion	0	0	0	0	0	1 (12.5%)	1 (12.5%)	2 (8.0%)
Skin and subcutaneous tissue disorders	1 (7.7%)	0	1 (9.1%)	2 (6.1%)	2 (22.2%)	1 (12.5%)	1 (12.5%)	4 (16.0%)
Pruritus	1 (7.7%)	0	0	1 (3.0%)	1 (11.1%)	1 (12.5%)	1 (12.5%)	3 (12.0%)

Source: Table 15 on pages 53-54 of study report for Study EN3203-010.

TEAEs in Study EN3319-302

The next table summarizes common AEs defined as AEs reported in more than one patient from any of the dose group during either the single-dose phase or the multiple-dose phase in each age group in Study EN3319-302 and is followed by a tabular summary of all AEs per dose group per study phase per age group, which is presented as a reference.

In Study EN3319-302, pediatric patients in all three age groups received a single dose at three dose levels of 0.05, 0.1, and 0.2 mg/kg. Only the 0.2 mg/kg was studied in the multiple-dose phase.

For the 6-12 years age group, more frequently reported individual AEs included four cases of

pyrexia (three at 0.1 mg/kg dose and one at 0.2 mg/kg dose) and two cases of each of the following: nausea (one at 0.1 mg/kg dose and one at 0.2 mg/kg dose), postoperative fever (one at 0.05 mg/kg dose and one at 0.1 mg/kg dose), and muscle spasms (both at 0.1 mg/kg dose) in the single-dose phase. More frequently reported individual AEs during the multiple-dose phase included four cases of nausea, four cases of vomiting, two cases of pyrexia, and two cases of headache.

For the 2-<6 years age group, more frequently reported individual AEs in the single-dose phase included two cases of each of the following: abdominal distension, peripheral edema, postoperative fever, procedural nausea, and procedural pain at 0.05 mg/kg dose level and constipation and vomiting at 0.1 mg/kg dose level. None of the AEs was reported by more than one patient during the multiple-dose phase.

More frequently reported individual AEs in the 0-<2 years age group were two cases of peripheral edema.

These more frequently reported individual AEs were mostly related to postoperative and gastrointestinal symptoms. Dose response was not studied in the multiple-dose phase and a single dose of the study drug is not expected to show any dose response in such small samples of 6-7 patients per dose group.

Table 27 Common AEs, More Than One Report in Any Dose Group, Study EN3319-302

EN3319-302	6 to ≤12 yrs				2 to <6 yrs				0 to <2 yrs
	Single dose			Multidose	Single dose			Multidose	Single dose
System Organ Class/Preferred Term	.05mg/kg (N=6)	0.1mg/kg (N=6)	0.2mg/kg (N=7)	0.2 mg/kg (N=10)	.05mg/kg (N=7)	0.1mg/kg (N=6)	0.2mg/kg (N=6)	0.2 mg/kg (N=6)	.05mg/kg (N=7)
#Patients with any AE	5 (83.3)	4 (66.7)	**4 (57.1)**	**10 (100.0)**	7 (100.0)	5 (83.3)	**3 (50.0)**	**4 (66.7)**	4 (57.1)
Gastrointestinal disorders									
Abdominal distension	0	0	0	0	**2 (28.6)**	0	0	0	0
Constipation	0	1 (16.7)	0	1 (10.0)	0	**2 (33.3)**	0	0	0
Nausea	0	1 (16.7)	1 (14.3)	**4 (40.0)**	0	0	1 (16.7)	0	0
Vomiting	0	0	1 (14.3)	**4 (40.0)**	0	**2 (33.3)**	0	0	1 (14.3)
General disorders and admin. site conditions									
Peripheral edema	0	0	0	0	**2 (28.6)**	0	0	1 (16.7)	**2 (28.6)**
Pyrexia	0	**3 (50.0)**	1 (14.3)	**2 (20.0)**	0	1 (16.7)	0	1 (16.7)	0
Injury, poisoning and procedural complications									
Postoperative fever	1 (16.7)	1 (16.7)	0	0	**2 (28.6)**	0	0	0	0
Procedural nausea	0	0	0	0	**2 (28.6)**	0	0	0	0
Procedural pain	1 (16.7)	0	0	0	**2 (28.6)**	0	0	0	0
Musculoskeletal and connective tissue disorders									
Muscle spasms	0	**2 (33.3)**	0	0	0	0	0	0	0
Nervous system disorders									
Headache	0	0	0	**2 (20.0)**	0	0	0	0	0

Source: the table below.

Table 28 TEAEs for Study EN3319-302

Study EN3319-302	6 to ≤12 yrs				2 to <6 yrs				0 to <2 yrs
	Single dose			Multidose	Single dose			Multidose	Single dose
System Organ Class/Preferred Term	.05mg/kg (N=6)	0.1mg/kg (N=6)	0.2mg/kg (N=7)	0.2 mg/kg (N=10)	.05mg/kg (N=7)	0.1mg/kg (N=6)	0.2mg/kg (N=6)	0.2 mg/kg (N=6)	.05mg/kg (N=7)
#Patients with any AE	5 (83.3)	4 (66.7)	4 (57.1)	10 (100.0)	7 (100.0)	5 (83.3)	3 (50.0)	4 (66.7)	4 (57.1)
Blood and lymphatic system disorders	0	0	0	0	1 (14.3)	0	0	1 (16.7)	0
Coagulopathy	0	0	0	0	0	0	0	1 (16.7)	0
Neutropenia	0	0	0	0	1 (14.3)	0	0	0	0
Cardiac disorders	0	0	0	0	1 (14.3)	1 (16.7)	0	0	0
Bradycardia	0	0	0	0	0	1 (16.7)	0	0	0
Sinus arrhythmia	0	0	0	0	0	1 (16.7)	0	0	0
Tachycardia	0	0	0	0	1 (14.3)	0	0	0	0
Gastrointestinal disorders	0	2 (33.3)	1 (14.3)	8 (80.0)	2 (28.6)	2 (33.3)	1 (16.7)	0	1 (14.3)
Abdominal distension	0	0	0	0	**2 (28.6)**	0	0	0	0
Constipation	0	1 (16.7)	0	1 (10.0)	0	**2 (33.3)**	0	0	0
Diarrhea	0	1 (16.7)	0	1 (10.0)	0	0	0	0	0
Ileus paralytic	0	0	0	1 (10.0)	0	0	0	0	0
Nausea	0	1 (16.7)	1 (14.3)	**4 (40.0)**	0	0	1 (16.7)	0	0
Vomiting	0	0	1 (14.3)	**4 (40.0)**	0	**2 (33.3)**	0	0	1 (14.3)
General disorders and admin. site conditions	0	3 (50.0)	1 (14.3)	4 (40.0)	3 (42.9)	3 (50.0)	0	2 (33.3)	3 (42.9)
Face edema	0	0	0	0	0	1 (16.7)	0	0	0
Fatigue	0	0	0	1 (10.0)	0	0	0	0	
General edema	0	0	0	1 (10.0)	1 (14.3)	0	0	0	0
Localized edema	0	0	0	0	0	0	0	0	1 (14.3)
Peripheral Edema	0	0	0	0	**2 (28.6)**	0	0	1 (16.7)	**2 (28.6)**
Peripheral swelling	0	1 (16.7)	0	0	1 (14.3)	1 (16.7)	0	0	0
Pyrexia	0	**3 (50.0)**	1 (14.3)	**2 (20.0)**	0	1 (16.7)	0	1 (16.7)	0
Infections and infestations	0	0	0	1 (10.0)	0	0	0	0	0
Abdominal abscess	0	0	0	1 (10.0)	0	0	0	0	
Injury, poisoning and procedural complications	5 (83.3)	1 (16.7)	0	2 (20.0)	4 (57.1)	0	0	0	0
Fall	1 (16.7)	0	0	0	0	0	0	0	0
Infusion site edema	0	0	0	1 (10.0)	0	0	0	0	
Joint dislocation	0	1 (16.7)	0	0	0	0	0	0	0
Postoperative fever	1 (16.7)	1 (16.7)	0	0	**2 (28.6)**	0	0	0	0
Procedural anxiety	1 (16.7)	0	0	0	0	0	0	0	0
Procedural nausea	0	0	0	0	**2 (28.6)**	0	0	0	0
Procedural pain	1 (16.7)	0	0	0	**2 (28.6)**	0	0	0	0
Procedural vomiting	1 (16.7)	0	0	0	0	0	0	0	0
Wound dehiscence	0	0	0	1 (10.0)	0	0	0	0	0
Investigations	0	0	0	1 (10.0)	1 (14.3)	0	0	0	1 (14.3)
ALT increased	0	0	0	0	0	0	0	0	1 (14.3)
AST increased	0	0	0	1 (10.0)	0	0	0	0	1 (14.3)
Clostridium test +	0	0	0	0	1 (14.3)	0	0	0	0
Hematocrit decreased	0	0	0	0	0	0	0	0	1 (14.3)
Hemoglobin decreased	0	0	0	0	0	0	0	0	1 (14.3)
RBC count decreased	0	0	0	0	0	0	0	0	1 (14.3)
WBC count decreased	0	0	0	0	0	0	0	0	1 (14.3)
Musculoskeletal and connective tissue disorders	0	2 (33.3)	0	1 (10.0)	0	1 (16.7)	0	0	0
Arthralgia	0	0	0	1 (10.0)	0	0	0	0	0
Foot deformity	0	0	0	0	0	1 (16.7)	0	0	0

Muscle spasms	0	**2 (33.3)**	0	0	0	0	0	0	0
Nervous system disorders	0	0	0	3 (30.0)	0	1 (16.7)	0	1 (16.7)	0
Cerebrospinal fluid leakage	0	0	0	0	0	1 (16.7)	0	0	0
Headache	0	0	0	**2 (20.0)**	0	0	0	0	0
Lethargy	0	0	0	1 (10.0)	0	0	0	0	0
Sedation	0	0	0	1 (10.0)	0	0	0	0	0
Somnolence	0	0	0	0	0	0	0	1 (16.7)	0
Vision blurred	0	0	0	1 (10.0)	0	0	0	0	0
Product issues	0	0	1 (14.3)	0	0	0	0	0	0
Device dislocation	0	0	1 (14.3)	0	0	0	0	0	0
Psychiatric disorders	0	0	1 (14.3)	0	0	0	0	0	0
Anxiety	0	0	1 (14.3)	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	1 (16.7)	0
Enuresis	0	0	0	0	0	0	0	1 (16.7)	0
Reproductive system and breast disorders	0	0	0	0	1 (14.3)	0	0	0	0
Edema genital	0	0	0	0	1 (14.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (10.0)	0	0	1 (16.7)	0	0
Atelectasis	0	0	0	1 (10.0)	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	1 (16.7)	0	0
Pleural effusion	0	0	0	1 (10.0)	0	0	0	0	0
Skin and subcutaneous tissue disorders	1 (16.7)	1 (16.7)	0	1 (10.0)	1 (14.3)	3 (50.0)	1 (16.7)	1 (16.7)	0
Pruritus	1 (16.7)	0	0	1 (10.0)	0	1 (16.7)	0	1 (16.7)	0
Blood blister	0	0	0	0	1 (14.3)	0	0	0	0
Dermatitis contact	0	1 (16.7)	0	0	0	0	0	0	0
Erythema	0	0	0	0	0	1 (16.7)	0	0	0
Rash	0	0	0	0	0	0	1 (16.7)	0	0
Swelling face	0	0	0	0	0	1 (16.7)	0	0	0
Surgical and medical procedures	0	1 (16.7)	0	1 (10.0)	0	0	0	0	0
Central venous catheterization	0	0	0	1 (10.0)	0	0	0	0	0
Incisional drainage	0	1 (16.7)	0	0	0	0	0	0	0
Vascular disorders	0	0	1 (14.3)	0	0	0	0	0	0
Hypotension	0	0	1 (14.3)	0	0	0	0	0	0

Source: Table 28 on pages 102-105 and Table 29 on pages 107-108 of study report for Study EN3319-302.

8.4.6. **Laboratory Findings**

Laboratory findings are summarized in terms of the number of patients with both baseline and post-treatment clinical laboratory results, the number of patients with baseline test values shifted to abnormal range post treatment, and the number of patients with clinically significant abnormal shift in laboratory tests, per dose group and per treatment phase in each study.

Study EN3203-010

High proportions of missing laboratory data in Study EN3203-010 were noticed during the review cycle. Among patients aged >12-17 years, few patients had both baseline and post treatment laboratory test results available for comparison during the single-dose phase. As

summarized in the table below only some of the individual lab tests had lab comparisons available, including one of 13 patients (none had chemistry labs) in the 5 mg dose group, four of nine patients in the 10 mg group and 1-3 of 11 patients in the 15 mg dose group. Overall, only less than a quarter of patients across dose groups had some lab comparisons. About one third of the individual tests scheduled could not be evaluated due to lack of results for comparison.

Clinically significant laboratory shifts were reported as one or two cases with decreases in hematocrit, hemoglobin, and RBC and increase in glucose in this very limited database.

Table 29 Shift in Clinical Laboratory Tests Post Single Dose, Study EN3203-010

Study EN3203-010 Lab test		**Single dose**											
		5 mg (N=13)			**10 mg (N=9)**			**15 mg (N=11)**			**Total (N=33)**		
		#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig
Hematology													
Basophils		0			0			2			2		
Eosinophils	N→L	0			0			2	1		2		
Hematocrit	N→L	1			4	2	1	3			8	2	1
Hemoglobin	N→L	1			4	2	1	3			8	2	1
Immature Grans	N→H	0			0			2	1		2	1	
Lymphocytes	H→L	1	1		0			2			3	1	
Monocytes	N→H	1	1		0			2	1		3	2	
Neutrophils	N→H	1	1		0			2	1		3	2	
Platelets	N→L	1			4			3			8		
PT		0			0			0			0		
PTT		0			0			0			0		
RBC	N→L	1			4	2	2	3			8	2	2
WBC	N→H	1			4			3	1		8	1	
Chemistry													
Albumin	N→L	0			0			0			0		
ALT	N→H	0			0			0			0		
AST	N→H	0			0			0			0		
Alkaline phosphatase		0			0			0			0		
Anion gap		0			0			0			0		
Bilirubin	N→H	0			0			0			0		
BUN	N→L	0			4	3		1			5	3	
Calcium	N→L	0			4			1			5		
Carbon Dioxide	N→H	0			4			1			5		
Chloride	N→L	0			4			1			5		
Creatinine		0			4			1			5		
Glucose	N→H	0			4	1	1	1			5	1	1
Ion Gap		0			4			0			4		
Potassium		0			4			1			5		
Protein	N→L	0			0			0			0		
Sodium	N→L	0			4	2		1			5	2	

Note #Labs means the number of patients with both baseline and follow-up laboratory test results;
#Shift means the number of patients with baseline laboratory results shifted to abnormal range;
#Sig means the shift is considered clinically significant.

Source: Table 14.3.4.1.2 on pages 199-207 and Table 14.3.4.2.2 on pages 237-243 in study report of Study EN3203-010. Table 9 on page 15 of the Response to Information Request (IR) submitted on April 1, 2019.

Missing data for comparing laboratory test results were also observed in the multiple-dose phase. As summarized in the table below some individual lab test comparisons were available in 1-4 of nine patients in the 5 mg dose group, 2-4 of eight patients in the 10 mg group, and 1-6 of eight patients in the 15 mg dose group during the multiple-dose phase. Overall, only up to about half of the study population across dose groups had some individual lab comparisons. Several individual lab tests could not be evaluated due to lack of results for comparison.

Clinically significant laboratory shifts were reported as decreases in hematocrit (10 cases), hemoglobin (six cases), RBC (five cases), albumin (eight cases), protein (five cases), and calcium (four cases), and increase in glucose (one cases).

Table 30 Shift in Clinical Laboratory Tests Post Multiple Doses, Study EN3203-010

Study EN3203-010 Lab test		**Multiple dose**											
		5 mg (N=9)			**10 mg (N=8)**			**15 mg (N=8)**			**Total (N=25)**		
		#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig
Hematology													
Basophils		1			2			5			8		
Eosinophils	N→L	1			2			5			8		
Hematocrit	N→L	3	2	2	4	4	4	6	4	4	13	10	10
Hemoglobin	N→L	3	2	2	4	3	2	6	2	2	13	7	6
Lymphocytes	H→L	1	1		2			5	1		8	2	
Monocytes	N→H	1			2	1		5	4		8	5	
Neutrophils	N→H	1			2	1		5			8	1	
Platelets	N→L	3	2		4			6	1		13	3	
PT		0			0			0			0		
PTT		0			0			0			0		
RBC	N→L	3	2	2	4	2	2	6	1	1	13	5	5
WBC	N→H	3			4	1		6			13	1	
Chemistry													
Albumin	N→L	2	2	2	3	2	2	5	4	4	10	8	8
ALT	N→H	2			3			5	1		10	1	
AST	N→H	2			3	1		5	3		10	4	
Alkaline phosphatase		2			3			5			10		
Anion gap		0			0			0			0		
Bilirubin	N→H	2			3			5			10		
BUN	N→L	4	2		3	1		6	2		13	5	
Calcium	N→L	4	3	1	3	2	1	6	6	2	13	11	4
Carbon Dioxide	N→H	4			3	1		6	1		13	2	
Chloride	N→L	4			3			6	1		13	1	
Creatinine		4			3			6			13		
Glucose	N→H	4			3	1	1	6			13	1	1
Ion Gap		2			0			1			3		
Potassium	N→H N→L	4	 1		3	1		6	 1		13	1 2	
Protein	N→L	2	1	1	3	1	1	5	3	3	10	5	5
Sodium	N→L	4	3		3	1		6	3		13	7	

Source: Table 14.3.4.1.2 on pages 208-214 and Table 14.3.4.2.2 on pages 244-249 in study report of Study EN3203-010. Table 9 on page 15 of the Response to Information Request (IR) submitted on April 1, 2019. Table 1 on page 2 of the Response to Information Request (IR) submitted on August 9, 2019.

Study EN3319-302

For the 0-12 years age group in Study EN3319-302, laboratory data are summarized for the entire age group and not for the three age subgroups because of small sample sizes for age subgroups and relatively high proportions of missing data. As shown in the table below the individual lab test comparisons were available in 9-14 of 20 patients in the 0.05 mg/kg dose group, 7-8 of 16 patients in the 0.1 mg/kg dose group, and 3-7 of 13 patients in the 0.2 mg/kg dose group, or up to 57% (28/49) patients across dose groups in the single-dose phase. In the multiple-dose phase lab test comparisons were available in 1-8 of 16 patients (up to 50%) in the 0.2 mg/kg dose group, the only dose studied. More common clinically significant laboratory shifts were reported as decreases in hematocrit (eight cases), hemoglobin (seven cases), RBC (four cases), protein (nine cases), lymphocytes (three cases), and bicarbonate (three cases) and increase in glucose (four cases) in the single-dose phase and as decreases in hematocrit, hemoglobin, albumin, and protein (two cases each) in the multiple-dose phase.

Table 31 Shift in Clinical Laboratory Tests Post Treatment, Study EN3319-302

Study EN3319-302 Lab test		**Single dose**												**Multiple dose**		
		.05mg/kg (N=20)			**0.1 mg/kg (N=16)**			**0.2mg/kg (N=13)**			**Total (N=49)**			**0.2 mg/kg (N=16)**		
		#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig	#Labs	#Shift	#Sig
Hematology																
Basophils	N→H N→L	**13**	2	1	**8**			**6**			**25**	2	1	**6**	 1	
Eosinophils	N→H N→L	**13**	1 1		**8**	1		**6**			**25**	2 1		**7**	2 1	1
Erythrocytes	N→L	**14**	5	2	**8**	5	2	**6**	2		**28**	12	4	**8**	1	1
Hematocrit	N→L	**14**	5	3	**8**	4	4	**6**	4	1	**28**	13	8	**8**	4	2
Hemoglobin	N→L	**14**	5	4	**8**	5	3	**6**	3		**28**	13	7	**8**	5	2
Leukocytes	N→H N→L	**14**	 2		**8**			**6**			**28**	 2		**7**	1	
Lymphocytes	N→L	**13**	7	1	**8**	4	2	**6**	1		**25**	12	3	**7**	2	1
Monocytes	N→H	**13**	3		**8**	2		**6**	1		**25**	6		**7**	3	
Neutrophils	N→H	**No**			**7**	3		**6**			**11**	3		**7**	2	
Chemistry																
Albumin	N→L	**0**			**7**	6	1	**6**	3		**13**	9	1	**7**	5	2
ALT	L→H N→L	**13**	1 3		**8**	 3		**6**	1		**26**	2 6		**7**	1	
AST	N→H N→L	**13**	1 1		**8**	1		**6**	2		**26**	4 1		**7**	1	1
Bicarbonate	N→H N→L	**14**	 1	 1	**8**	 1	 1	**7**	1 1	 1	**28**	1 3	 3	**7**		
Bilirubin	N→H	**13**	2	2	**8**			**6**			**26**	2	2	**7**		
Calcium	N→L	**13**	3	1	**8**	1		**6**	1		**26**	5	1	**6**	1	
Chloride	N→H N→L	**14**	1 1		**8**			**7**			**28**	1 1		**7**		
Creatinine		**14**			**8**			**6**			**27**			**7**		

Glucose	L→H N→H	**14**	1 4	4	**8**			**7**	1 1		**28**	2 5	4	**7**	1	
Lactate Dehydrogenase	L→H N→H	**12**	1 4		**7**			**4**	1 1		**22**	2 5		**7**		
Phosphate	N→H N→L H→L	**10**	1 3 1		**7**	1 3		**3**	1		**19**	2 7 1		**7**	1 2	
Potassium	N→H N→L	**12**	2 1		**8**	1	1	**7**			**26**	3 1	1	**7**		
Protein	N→L	**13**	3	3	**8**	5	5	**6**	2	1	**26**	10	9	**7**	2	2
Sodium	N→L	**14**	5		**8**	3		**7**	1		**28**	9		**7**	1	
Urea Nitrogen	N→L	**14**	5	1	**8**	2		**6**			**27**	7	1	**7**	2	

Source: Tables 4-8 on pages 6-14 of the Response to Information Request (IR) submitted on April 1, 2019. Table 3 on page 6 of the Response to IR submitted on August 9, 2019.

Conclusion on laboratory findings

No concerning trends could be identified in the database with the evaluation limited due to small sample sizes and high rates of missing data. The changes in laboratory values observed are generally expected in the population studied.

8.4.7. **Vital Signs**

Vital sign (VS) measurements are summarized in terms of the number of patients who had abnormal shifts from baseline per dose group per treatment phase in each study.

In Study EN3203-010, which included the >12-17 years age group, there were no trends to suggest dose-related findings or marked differences between the sing-dose phase and the multiple-dose phase.

Table 32 Summary of Shift in Vital Signs from Baseline, Study EN3203-010

EN3203-010	Shift from baseline	**Single Dose**				**Multiple Dose**			
		5 mg (N=13)	**10 mg (N=9)**	**15 mg (N=11)**	**Total (N=33)**	**5 mg (N=9)**	**10 mg (N=8)**	**15 mg (N=8)**	**Total (N=25)**
Diastolic Blood Pressure (mmHg)	N→L		2 (22.2%)	3 (27.3%)	5 (15.2%)	2 (22.2%)	1 (12.5%)	2 (25.0%)	5 (20.0%)
Heart Rate (beats/min)	N→H N→L	1 (7.7%) 1 (7.7%)	2 (22.2%)	1 (9.1%)	4 (12.1%) 1 (3.0%)	1 (11.1%)	1 (12.5%)		2 (8.0%)
Pulse Oximetry (%)	N→L			1 (9.1%)	1 (3.0%)			1 (12.5%)	1 (4.0%)
Respiratory Rate (breaths/min)	N→H N→L	3 (23.1%)	1 (11.1%)	1 (9.1%)	4 (12.1%) 1 (3.0%)	2 (22.2%)	1 (12.5%)	1 (12.5%)	3 (12.0%) 1 (4.0%)
Systolic Blood Pressure (mmHg)	N→H N→L H→L	1 (7.7%)	2 (22.2%) 1 (11.1%) 1 (11.1%)	1 (9.1%) 1 (9.1%) 1 (9.1%)	3 (9.1%) 3 (9.1%) 2 (6.1%)	1 (11.1%)	1 (12.5%) 3 (37.5%)	1 (12.5%)	1 (4.0%) 4 (16.0%) 1 (4.0%)
Temperature (C)	N→H L→H N→L H→L	1 (7.7%)	1 (11.1%)	2 (18.2%) 1 (9.1%) 1 (9.1%) 1 (9.1%)	2 (6.1%) 2 (6.1%) 1 (3.0%) 2 (6.1%)	2 (22.2%) 1 (11.1%)	1 (12.5%)	1 (12.5%) 1 (12.5%)	4 (16.0%) 2 (8.0%)

Source: Tables 12-13 on pages 19-20 of the Response to Information Request (IR) submitted on April 1, 2019.

In Study EN3319-302, which included the 0-12 years age group, there were no trends to suggest dose-related findings or marked differences between the sing-dose phase and the multiple-dose phase.

Table 33 Summary of Shift in Vital Signs from Baseline, Study EN3319-302

Study EN3319-302 Vital signs	Shift from baseline	Single dose				Multiple dose
		.05mg/kg (N=20)	0.1mg/kg (N=12)	0.2mg/kg (N=13)	Total (N=45)	0.2 mg/kg (N=16)
Diastolic Blood Pressure (mmHg)	N→H	2 (10.0%)	2 (16.7%)		4 (8.8%)	
	N→L		2 (16.7%)	2 (15.4%)	4 (8.8%)	2 (12.5%)
	H→L			1 (7.7%)	1 (2.2%)	
Heart Rate (beats/min)	N→H	1 (5.0%)	1 (8.3%)	2 (15.4%)	4 (8.8%)	1 (6.3%)
	L→H			1 (7.7%)	1 (2.2%)	
	N→L			1 (7.7%)	1 (2.2%)	1 (6.3%)
Oxygen Saturation (%)	N→L					2 (12.5%)
Respiratory Rate (breaths/min)	N→H	3 (15.0%)			3 (6.7%)	
	N→L	2 (10.0%)			2 (4.4%)	2 (12.5%)
	H→L		1 (8.3%)		1 (2.2%)	
Systolic Blood Pressure (mmHg)	N→H	3 (15.0%)	2 (16.7%)	2 (15.4%)	7 (15.6%)	1 (6.3%)
	N→L					1 (6.3%)
Temperature (C)	N→H			4 (30.8%)	4 (8.8%)	2 (12.5%)
	L→H	3 (15.0%)	3 (25.0%)	2 (15.4%)	8 (17.8%)	1 (6.3%)
	N→L	1 (5.0%)	1 (8.3%)		2 (4.4%)	3 (18.8%)
	H→L	1 (5.0%)	2 (16.7%)	1 (7.7%)	4 (8.8%)	1 (6.3%)

Source: Tables 10-11 on pages 17-18 of the Response to Information Request (IR) submitted on April 1, 2019.

In response to the Review Division's request of information on clinically significant shifts in VS the Applicant replied that these shifts in VS were not found to be clinically significant and/or related to study drug because none of the vital signs collected during the study rose to the level of reportability as an AE or SAE and there were no reports of drug related respiratory distress or post-operative infection.

8.4.8. **Electrocardiograms (ECGs)**

There were no ECG assessments.

8.4.9. **QT**

Not applicable.

8.4.10. **Immunogenicity**

Not applicable.

8.5. **Analysis of Submission-Specific Safety Issues**

Respiratory assessments did not identify any case of apnea and cases of mild to moderated CNS AEs leading to early dropouts were described in the Review Section 8.4.2 above.

8.5.1. [Name Safety Issue]

None.

8.6. Safety Analyses by Demographic Subgroups

The sample sizes of the pediatric age groups were too small to allow subgroup analyses by demographic characteristics.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

The adult single-dose PK study and the two pediatric studies of PK and safety were not designed to evaluate human reproduction and pregnancy. A consult review on updating pregnancy and lactation labeling has been completed by Dr. Miriam Dinatale from the Division of Pediatric and Maternal Health (refer to the review dated September 17, 2019 in DARRTS for detail).

8.8.3. Pediatrics and Assessment of Effects on Growth

The two pediatric studies were not designed to assess drug effects on growth. The individual protocols and trial conduct were described in the Review Section 6 and safety was in the Review Section 8.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Warnings and precautions about misuse, abuse, and diversion of opioids and statements describing drug abuse and dependence and drug overdose are all included in the product labeling. The Applicant recently updated the Risk Evaluation and Mitigation Strategy (REMS) Assessment 2 at 12 Months covering the reporting period of January 18, 2019 through July 18, 2019 by cross reference to the Type V Drug Master File (DMF) (b) (4) for the Shared System REMS (SSR) for the Opioid Analgesic REMS, Sequence 0041 dated September18, 2019.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Postmarketing safety of opioids including oxymorphone is monitored by the FDA through various programs such as periodic safety reports and REMS. Oxymorphone labeling had been updated to reflect safety signals identified through postmarketing surveillance, e.g., labeling statements about anaphylaxis, angioedema, and other hypersensitivity reactions were added to the Warnings and Precautions and Contraindications sections of the label for all formulations of oxymorphone in 2016.

The Office of Surveillance and Epidemiology, OSE was consulted by the Review Division regarding analysis of current drug utilization for oxymorphone-containing drugs (oral formulations) in the treatment of pain in the pediatric population. The OSE reviewer Dr. Ibrahim decided to present the pediatric utilization pattern for all opioid analgesics including oxymorphone together. Oxymorphone was not on the list of top five opioids given to pediatric patients because it has not been approved for pediatric use. Safety information related to off-label use of the product in pediatric patients is not available.

8.9.2. Expectations on Safety in the Postmarket Setting

FDA requested all Opioid Analgesic NDA Applicants to submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the approval of the REMS for opioid analgesics on September 18, 2018.

8.9.3. Additional Safety Issues from Other Disciplines

None.

8.10. Integrated Assessment of Safety

The pediatric safety database supporting the current pediatric supplement for Opana tablets consists of 119 pediatric patients who received oxymorphone treatment including 58 in the >12-17 years age group exposed to the tablet formulation and 61 in the 2-12 years age group exposed to the oral solution formulation. Thirty patients including 16 in the >12-17 years age group and 14 in the 2-12 years age group were exposed to more than one dose. The maximum exposures consisted of exposure to 8-12 doses of the 15 mg tablet by five patients in the >12-17 years age group and 8-12 doses of the 0.2 mg/kg solution by seven patients in the 2-12 years age group.

Safety findings included no cases of death, seven cases of serious AEs, and five cases of early discontinuation due to AEs. All SAEs were considered unlikely to be related to the study drug and all AE-related early dropouts were due to CNS symptoms such as sedation, tremor, somnolence, and lethargy based on analyses of case narratives.

Treatment-emergent AEs (TEAEs) pooled across studies revealed that approximately two thirds (66%) of pediatric patients experienced AEs and more AEs were reported with multiple doses than with single doses (80% versus 60%, respectively). The most commonly reported AEs (≥5%) included nausea, pyrexia, constipation, vomiting, and headache.

The most commonly reported (≥5 cases) clinically significant laboratory shifts were decreases in hematocrit, hemoglobin, RBC, protein, albumin, and calcium and increase in glucose.

The shifts in vital signs (VS) did not rise to the level of reportability as an AE or SAE.

The reported safety findings from the database were generally consistent with post-operative experiences and with the known safety profile of opioid analgesics. However, the overall data submitted raised concerns related to the safety of oxymorphone in pediatric populations because of the unexpected and nonexplainable overexposure reported in two out of 24 patients aged >12-17 years. In addition, high proportions of early discontinuation due to lack of efficacy in the >12-17 years age group raised questions about if safety has been evaluated in the efficacious dose range. Other limitations to the safety database included small sample sizes and high proportions of missing scheduled safety evaluations such as laboratory test results and vital signs measurements.

9. Advisory Committee Meeting and Other External Consultations

At the joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 26, 2019, the results of the pediatric studies of Opana were presented and discussed as an example of translating pediatric study results into labeling. The committee members expressed concerns with uncertainty about efficacious dosage based on high dropouts due to lack of efficacy and safety not yet studied for the to be identified efficacious dosage and concerns with variation in exposure as exemplified in the two patients with unexpected and nonexplainable very high levels of blood concentrations. Therefore, majority of the committee members voted for not approving pediatric labeling for Opana IR by not including PK, safety, and dosing information from pediatric clinical trials to avoid encouragement of pediatric use of the product.

Opana pediatric data were also presented to the Pediatric Review Committee (PeRC). The PeRC agrees that the PREA PMR 127-3 has been fulfilled.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

To better inform product labeling regarding the pediatric experience with the product in clinical studies and to discourage off-label use of the product in the pediatric population the Review Division (b) (4) included the pediatric labeling below in Section 8.4:

Safety and effectiveness for pediatric patients aged 0 to 17 years, have not been established.

An open-label study was conducted in 58 pediatric patients 12 years of age and older with postoperative pain using OPANA tablets. Efficacy was not demonstrated in this population treated with doses expected to be comparable to effective starting doses in adults. In addition, the pharmacokinetic results revealed that treatment with OPANA tablets resulted in substantially higher systemic exposures to oxymorphone in two out of 24 patients.

OPANA tablets are not recommended for use in the pediatric population.

The Division of Pediatric and Maternal Health (DPMH) provided recommendations on revised labeling statements for sections 5.4, 8.1, 8.2, 8.3 and 17 under Pregnancy and Lactation Labeling Rule (PLLR) based on Dr. Dinatale's consult review of nonclinical data, pharmacovigilance database and review of published literature (refer to the consult review in DARRTS dated September 19, 2019 for detail).

The Office of Prescription Drug Promotion (OPDP) also reviewed the labeling and did not have any comments.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Opana and all other opioid analgesics intended for outpatient use are part of a class-wide REMS to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

12. Postmarketing Requirements and Commitments

No additional Postmarketing Requirements or Commitments will be issued at this time.

13. Appendices

13.1. References

- CMC Review by Dr. Daneli Lopez-Perez dated July 8, 2019 in DARRTS
- Pharmacology/Toxicology Review by Dr. Elizabeth Bolan dated September 16, 2019 in DARRTS
- Clinical Pharmacology Review by Dr. David Lee dated October 1, 2019 in DARRTS
- Consult Review of Pregnancy and Lactation Labeling by Dr. Miriam Dinatale dated September 16, 2019 in DARRTS

13.2. Financial Disclosure

The financial disclosure form signed by the Applicant certified that no financial arrangement had been made with the listed clinical investigators (N=24) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Covered Clinical Study (Name and/or Number): Study EN3203-010 and EN3319-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 24		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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