Office of Clinical Pharmacology Review

NDA or BLA Number	21611 S-016
Link to EDR	\\CDSESUB1\evsprod\NDA021611\0059
Submission Date	12/21/18 (Serial # 0059); 4/1/19 (Serial #0066); 4/9/19 (Serial #0067); 5/17/19 (Serial #0071)
Submission Type	Standard Review; Prior Approval Supplement (PAS): efficacy; Efficacy supplement to fulfill PREA for PMR 127-3 in pediatric subjects 2 to 17 years old 505(b)(1); PDUFA date: 10/21/19
Brand Name	OPANA® Tablets and Oral Solution
Generic Name	Oxymorphone Hydrochloride Tablets
Dosage Form and Strength	5 and 10 mg Tablet; (b) (4)
Route of Administration	Oral
Proposed Indications and Usage	For the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate <u>Limitations of Use</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve OPANA for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]: □ Have not been tolerated, or are not expected to be tolerated, □ Have not provided adequate analgesia, or are not expected to provide adequate analgesia
Dosage Regimen	□Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals □ Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse □ Initiate treatment with 10 to 20 mg orally every four to six hours □ OPANA should be taken on an empty stomach, at least one hour prior to or two hours after eating □ Conversion to OPANA: Follow recommendations for conversion from other opioids or parenteral oxymorphone □ Do not stop OPANA abruptly in a physically dependent patient □ Mild Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression □ Renal Impairment: Initiate treatment with 5 mg and titrate

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	slowly. Monitor for signs of respiratory and central nervous system depression □ Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression □ CNS Depressants: Initiate treatment with 1/3 to 1/2 the recommended starting dose, consider using a lower dosage of the concomitant CNS depressant, and monitor closely.
Applicant	Endo Pharmaceuticals, Inc.
Associated IND	-
OCP Reviewer	David Lee, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 21611, Supplement 016, an efficacy Prior Approval Supplement (PAS) to fulfill PREA for PMR 127-3 in pediatric subjects 2 to 17 years old, for OPANA® Tablets and Oral Solution. This application was submitted as a 505(b)(1) on 12/21/18. From a clinical pharmacology perspective, the information submitted in the NDA is adequate, pending the outcome of the Labeling negotiation with the Applicant.

It is noted that, on September 26, 2019, a joint meeting of the Pediatric Advisory Committee (PAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was convened (FDA White Oak Campus, Building 31 Conference Center, the Great Room, Silver Spring, MD) 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 following question was put to discussion: 'In the studies of OPANA IR, notably higher systemic exposures were observed in 2 of the 24 patients in the PK and safety study conducted in 12 to 17 years of age (although one set of values suggests possible contamination of the sample). The patients did not experience any serious safety issues associated with these high levels. Discuss the implications a small number of patients with higher than expected drug levels when considering labeling an opioid analgesic with information from pediatric studies.' After the discussion, the Committee voted on the following question: 'Should pediatric labeling be approved for OPANA

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IR (immediate-release oxymorphone)?' The Committee voted eight 'yes,' sixteen 'no,' and one 'abstain.'

In all, the Applicant's proposed Package Insert is under discussion as well as the labeling negotiation is still ongoing currently. The Supplement NDA reviewing team will take the recommendations from the AC members into consideration in assessing the overall information submitted in this Supplement, and, **incorporate them in the labeling language**.

Review Issue	**Recommendations and Comments**
Pivotal or supportive evidence of effectiveness	3 PK/ information/studies were submitted in pediatric subjects 2 to 17 years old. 1. Study EN3203-010 (OPANA IR tablet in children aged >12 to 17 years): Based on the single-dose comparison, the observed Cmax and AUC values are slightly higher in subjects from 12 to 17 years compared to adults at the 5 mg dose level. It is possible that the higher exposures in 12 to 17 were driven by subjects with a lower body weight. 2. Study EN3319-302 (oxymorphone HCl IR oral solution* in children aged 2 to ≤12 years): A dose between 0.05 and 0.1 mg/kg, (e.g., 0.075 mg/kg [based on oxymorphone's dose proportional behavior between from 5 to 20 mg under both single- and steady-state conditions in adults (OPANA IR Prescribing Information)]), provides similar oxymorphone exposures to that of a 5 mg single dose in adults. 3. *Study EN3319-101 was conducted to evaluate the pharmacokinetics of oxymorphone oral solution formulation in adults before use in the pediatric population. The results from Study EN3319-101 indicate that oxymorphone and 6-OH-oxymorphone exposures from EN3319 5 mg (1 mg/mL solution) and OPANA 5 mg in healthy adults were bioequivalent.
General dosing instructions	The proposed indication remains the same and the Applicant is not seeking a pediatric indication, nor are there new proposals for pediatric dosing under Dosage and Administration. Therefore, the general dosing regimens as described in the OPANA's Label (N21611, 9/18/18), Highlights Of Prescribing Information, are: •Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse • Initiate treatment with 10 to 20 mg orally every four to six hours • OPANA should be taken on an empty stomach, at least one hour prior to or two hours after eating • Conversion to OPANA: Follow recommendations for

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	conversion from other opioids or parenteral oxymorphone • Do not stop OPANA abruptly in a physically dependent patient • Mild Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression • Renal Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression • Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression • CNS Depressants: Initiate treatment with 1/3 to 1/2 the recommended starting dose, consider using a lower dosage of the concomitant CNS depressant, and monitor closely.
Dosing in patient subgroups (intrinsic and extrinsic factors)	3 PK/ information/studies were submitted in this PAS efficacy supplement, to fulfill PREA PMR 127-3 in pediatric subjects 2 to 17 years old. There are no changes to OPANA dosing instructions in this supplement.
Labeling	The proposed indication remains the same, and, is stated as: "For the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate." However, the Applicant does propose to incorporate the findings from the submitted open-label pediatric studies into revised labeling under the following sections: (b) (4) • 8.4 Pediatric Use: updates include a description of the safety information derived from the pediatric studies (b) (4) Currently, the Applicant's proposed Labeling is under discussion at the time of this Review submission into DARRTS.

Bridge between the to-be-marketed and clinical trial formulations	Study EN3203-010 utilized approved OPANA (oxymorphone HCl) 5 mg tablets (N21611) in pediatric subjects >12 to 17 years old. Study EN3319-302 utilized oxymorphone HCl oral solution (1 mg/mL) in pediatric subjects 2 to ≤12 years old. This oral solution was developed to support the pediatric study in the 2 to <12 years old, who may not be able to swallow OPANA tablets. The Applicant will not market or distribute the oxymorphone HCl oral solution.
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant, Endo Pharmaceuticals, Inc., submitted an efficacy prior approval supplement (PAS) for OPANA tablets (Supplement 16) to fulfill PREA requirement PMR 127-3 in pediatric patients 2 to 17 years of age. This submission includes the final pediatric study reports; CMC data supporting oxymorphone HCL 1 mg/mL oral solution, which was used in the youngest patients; and proposed labeling changes regarding the pediatric clinical experience.

The Applicant has stated that they do not intend to market or distribute the oxymorphone HCl oral solution, 1 mg/mL. Additionally, the Applicant is not seeking a pediatric indication, nor are there new proposals for pediatric dosing under Dosage and Administration.

The proposed indication remains the same and is stated as: "*For the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate*." However, the Applicant does propose to incorporate the findings from the submitted open-label pediatric studies into revised labeling under the following sections:

(b) (4)

- 8.4 Pediatric Use: updates include a description of the safety information derived from the pediatric studies

(b) (4)

The Applicant submitted the following studies:

1. Adult relative bioavailability/BE study comparing the pediatric liquid formulation (1 mg/mL) and OPANA tablet IR formulation.

Study EN3319-101: An OL, R, SD, Two-Period, Two-Seq. Crossover; EN3319 5 mg (solution) vs. OPANA® 5 mg in Healthy Adult Subjects Under Fasted Conditions (report submitted on 3/25/11 (IND 58602, SN 0121))

2. Two Open Label safety, efficacy and pharmacokinetic (as a secondary parameter in EN3319-302) studies in pediatric subjects ages 2 ≤12 and >12 to 17.
    - Study EN3203-010: An OL, Ascending, Two-Part, Single- and Multiple-Dose Evaluation of the Safety, Pharmacokinetics, and Effectiveness of Oxymorphone for Acute Postoperative Pain in Pediatric Subjects Ages >12 to 17
    - Study EN3319-302: An OL, 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 Ages 2 ≤12

In the pediatric studies, the Applicant used the following formulations:

1. The marketed OPANA IR tablets for 12 to 17 years old
2. An oxymorphone oral solution (1 mg/mL) for 2 to 12 years old

Below is a discussion of the conduct and results of the Applicant's three studies assessing the bioavailability, bioequivalence, and, pharmacokinetics of the pediatric formulations. Oxymorphone and its major metabolite, 6-OH-oxymorphone were assayed in the pharmacokinetic (PK) studies. In animal studies, 6-OH-oxymorphone has been shown to have some analgesic bioactivity, but the in vivo levels are less than the parent, oxymorphone, in humans. Therefore, the exposure comparisons between pediatric and adult populations are based on oxymorphone exposure levels.

Study design and results

Study EN3319-101:

Study Title: An open-label, randomized, single dose, two-period, two-sequence crossover; EN3319 5 mg (solution) vs. OPANA 5 mg in Healthy Adult Subjects Under Fasted Conditions

Study Description: Adult relative bioavailability/bioequivalence study comparing the pediatric liquid formulation (1 mg/mL) and the OPANA tablet IR formulation.

Results from Study EN3319-101:
This study was conducted to evaluate the pharmacokinetics of the pediatric solution formulation in adults before use in the pediatric population. The results from Study EN3319-101 indicate that oxymorphone and 6-OH-oxymorphone exposures from EN3319 5 mg (1 mg/mL solution) and OPANA 5 mg in healthy adults are bioequivalent.

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Study EN3203-010:

Study 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 Ages greater than 12 to 17

Study Description: An open-label safety, efficacy, and pharmacokinetic (as a secondary parameter in EN3319-302) study in pediatric subjects ages greater than 12 to 17. The single-dose phase consisted of three ascending doses of oxymorphone IR, given in stepwise order based on the lower dose's ability to demonstrate safety and tolerability:

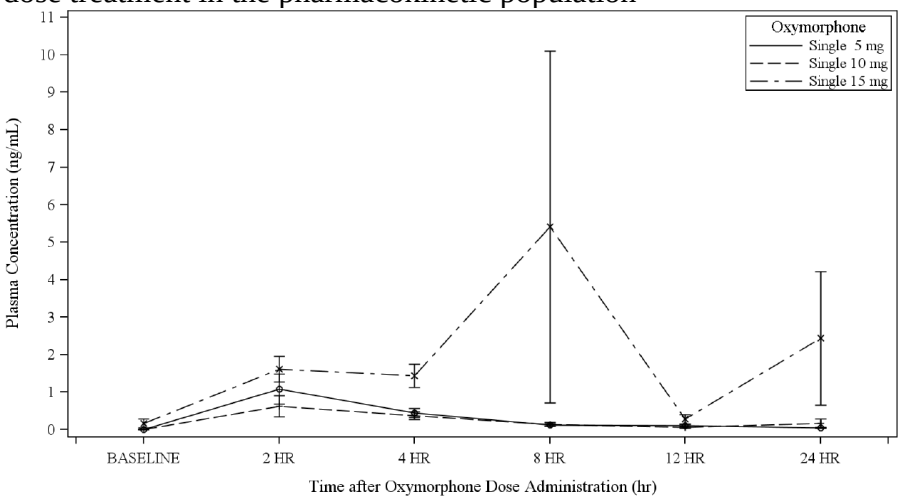
- 5 mg (equivalent to 0.1 mg/kg for a 50-kg child)
- 10 mg (equivalent to 0.2 mg/kg for a 50-kg child)
- 15 mg (0.3 mg/kg for a 50-kg child)

The multiple-dose phase also consisted of three ascending doses of oxymorphone IR, given in stepwise order based on the lower dose's ability to demonstrate safety and efficacy. The doses were given every 4 to 6 hours, but, no sooner than every 4 hours and no later than every 6 hours.

Doses used in the multiple-dose period were determined from the results of the single-dose period. The Applicant stated that during the multiple-dose phase of this study only trough levels at the beginning of each dose interval were obtained. Additionally, plasma oxymorphone and 6-OH-oxymorphone concentrations were determined at 4-hour intervals, only; therefore, PK parameters were not evaluated.

Results from Study EN3203-010:
The mean oxymorphone plasma concentration versus time profiles after administration of a single dose of OPANA IR tablets are shown in Figure 1.

Figure 1: Mean (+/- SE) plasma concentrations of oxymorphone versus time following single-dose treatment in the pharmacokinetic population



Source: Listing 16.2.5.2; Program: FPK1b.sas Output: FPK1b rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 114/317)

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The plasma pharmacokinetic parameters of a single dose of oxymorphone are shown in Table 1.

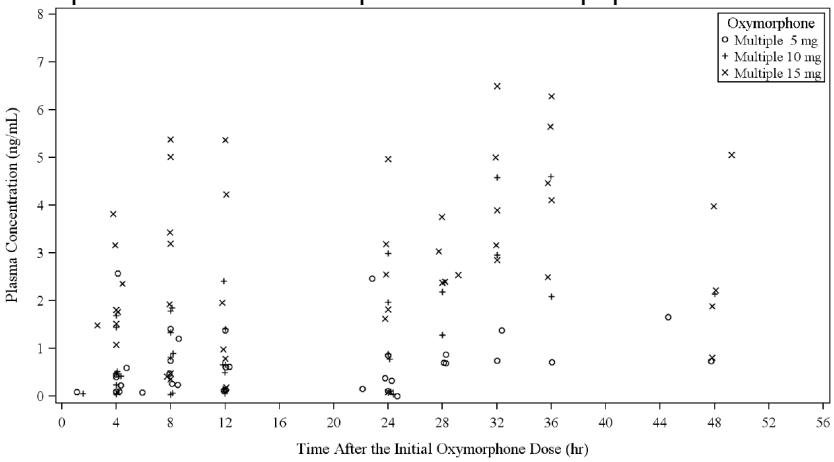
Table 1 Summary of oxymorphone plasma pharmacokinetic parameters of a single dose of oxymorphone by treatment group – pharmacokinetic population

Statistics	Oxymorphone (ng/mL)		
	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)
AUC_{0-t} (ng*hr/mL)			
n	9	6	9
Mean	6.395	3.766	67.040
SD	6.0752	2.2587	150.7979
AUC_{0-inf} (ng*hr/mL)			
n	9	3	8
Mean	7.632	10.223	109.294
SD	6.6828	6.5195	257.5421
Cmax (ng/mL)			
n	9	6	9
Mean	1.243	0.828	5.295
SD	1.2192	0.6892	10.6386
T_{max} (hour)			
n	9	6	9
Median	2.350	2.842	4.000
$t_{½}$ (hour)			
n	9	3	8
Mean	12.099	15.900	19.974
SD	9.9336	18.2533	22.4488

Data Source: Table 14.2.4 (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 48/317)

A scatter plot of plasma concentration of oxymorphone versus dose time by multiple-dose treatment are shown in Figure 2.

Figure 2 Scatter plot of plasma concentration of oxymorphone versus previous dose time by multiple dose treatment for pharmacokinetic population



Source: Listing 16.2.5.2 Program: FPK2b.sas Output: FPK2b rtf (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 116/317)

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A summary of observed mean plasma concentrations per the sampling time-points of oxymorphone by treatment (Dose) group after multiple dose are shown in Table 2.

Table 2 Summary of observed oxymorphone mean plasma concentrations per the sampling time-points of oxymorphone by treatment group after multiple dose

Timepoint	Statistics	Oxymorphone (ng/mL)		
		5 mg	10 mg	15 mg
		(N=8)	(N=8)	(N=8)
4 hours	n	8	7	8
	Mean	0.56655	0.69068	1.94886
	SD	0.832757	0.623060	1.171995
8 hours	n	6	7	8
	Mean	0.72122	0.96958	2.52175
	SD	0.493076	0.742611	2.046728
12 hours	n	6	6	7
	Mean	0.49530	0.94882	1.95010
	SD	0.493681	0.839298	2.059903
24 hours	n	7	5	7
	Mean	0.60953	1.33032	2.04354
	SD	0.861570	1.153598	1.735689
28 hours	n	3	4	5
	Mean	0.75157	1.54550	2.82080
	SD	0.105814	0.943873	0.583736
32 hours	n	2	3	5
	Mean	1.06000	3.34100	4.28140
	SD	0.452548	1.103008	1.488950
36 hours	n	1	2	5
	Mean	0.71450	3.34350	4.59860
	SD	-	1.784030	1.468756
48 hours	n	3	1	5
	Mean	0.81028	2.13700	2.78800
	SD	0.809334		1.701034

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 132/317)

Study EN3319-302:

Study Title: 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 Ages 2 ≤12.

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Study Description: An open-label safety, efficacy, and pharmacokinetic (as a secondary parameter in EN3319-302) study in pediatric subjects ages 2 to greater than or equal to 12.
Study EN3319-302 was an open-label, 2-part (single- and multiple-dose), ascending-dose, multicenter study utilizing oxymorphone HCl oral solution (1 mg/mL) in pediatric subjects aged 2 to less than or equal to 12 years with postoperative pain requiring an opioid.

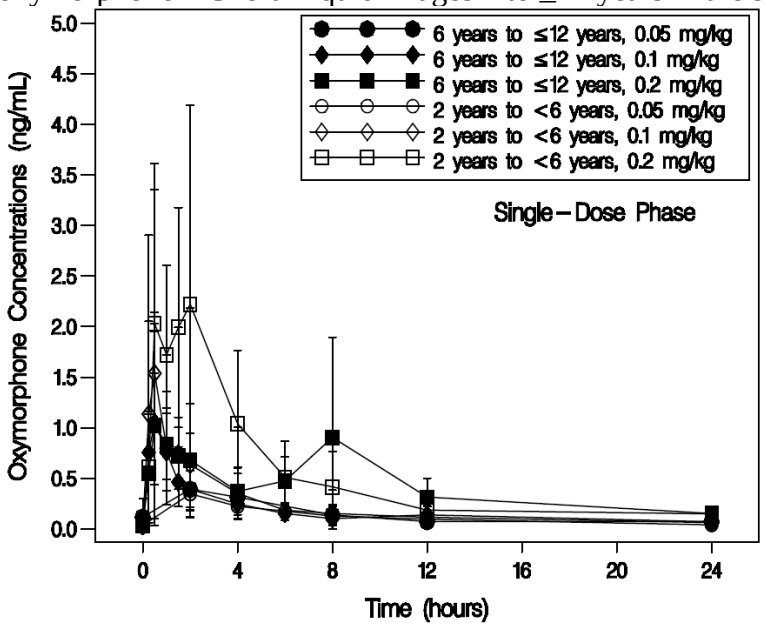
Patients in the single-dose phase, which was comprised initially of three groups of subjects including a 0 to 2 years age group, were given a single dose of oxymorphone HCl oral solution. The Applicant stated that the 0 to 2 years age group was removed due to this group of subjects being studied in another ongoing study. The final two age groups were 2 to less than 6 years and 6 to less than or equal to 12 years. Within each age group, there were three treatment cohorts comprised of three different doses of oxymorphone HCl oral solution, namely, 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg, which were administered following an ascending dose scheme.

It was noted by the Applicant that, at the end of the single-dose phase, an Independent Data Monitoring Committee recommended that a dose of 0.2 mg/kg be used in the Multiple-Dose Phase. Thus, the multiple-dose phase employed only one dose at 0.2 mg/kg. Subjects were dosed approximately every 4 to 6 hours for up to 48 hours.

Results from Study EN3319-302:

The mean oxymorphone plasma concentration versus time profiles after a single dose of oxymorphone HCl oral solution are shown in Figure 3.

Figure 3 Mean (SD) plasma oxymorphone concentrations following administration of oxymorphone HCl oral liquid in ages 2 to ≤12 years in the single-dose phase



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 1]
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 53/642)

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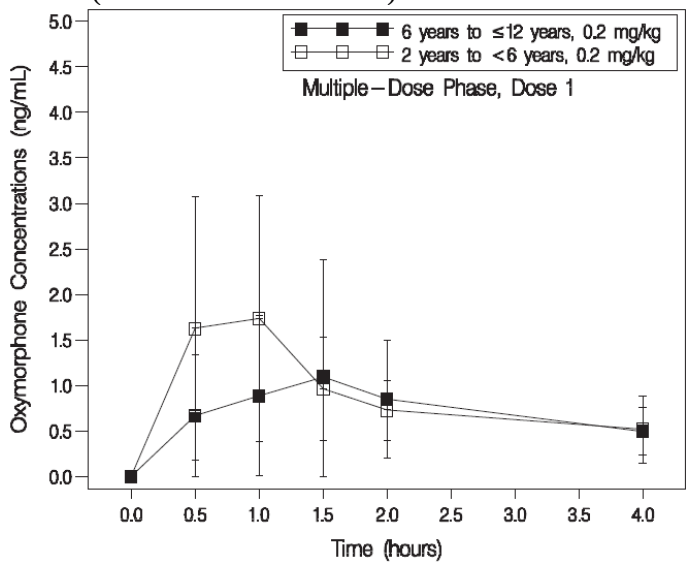
The mean oxymorphone plasma concentration versus time profiles after Dose 1 in the multiple-dose phase after oxymorphone HCl oral solution administration are shown in Figure 4.

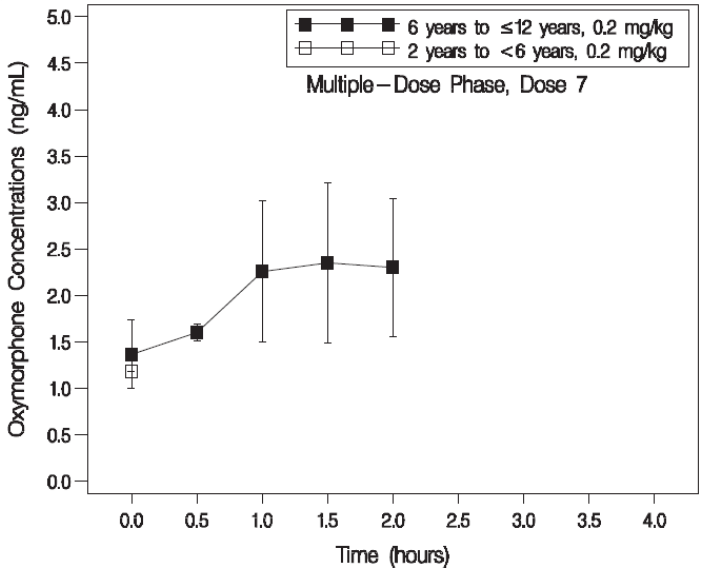
Figure 4 Mean (SD) plasma oxymorphone concentrations following single-dose administration of oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from Dose 1 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 54/642)

The mean oxymorphone plasma concentration versus time profiles after Dose 7 in the multiple-dose phase after oxymorphone HCl oral solution administration are shown in Figure 5.

Figure 5 Mean (SD) plasma oxymorphone concentrations following single-dose administration of oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from dose 7 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 55/642)

Summary oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to less than or equal to 12 years in the single-dose phase are shown in Table 3.

Table 3 Summary oxymorphone pharmacokinetic parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase

	Cmax (ng/mL)	Tmax* (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	T1/2 (h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	0.415	2.95	2.56	.	.
SD	0.211	1.66	2	0.0516	0.232
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	2	2
Mean	0.33	2.05	1.69	3.22	5.01
SD	0.217	1.03	0.943	1.56	1.4
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	1.14	1.04	3.01	3.01	7.5
SD	0.847	1.3	0.766	0.946	7.33
0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	3	3
Mean	1.76	1.45	3.99	3.69	4.38
SD	1.62	1.39	2.09	3.12	2.9
0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	3	3
Mean	1.33	1	5.32	6.92	5.13
SD	0.772	3.17	4.53	4.02	3.16
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Mean	3.16	1.26	9.37	14.3	4.39
SD	1.65	1.38	5.81	5.01	1.16

Source: Supportive Tables ST-4.1 and ST-4.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 62-64/642)
*Tmax: median

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Summary oxymorphone PK parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to less than or equal to 12 years in the multiple-dose phase from Dose 1 and Dose 7 are presented in Table 4.

Table 4 Summary oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the multiple-dose phase from Dose 1 and Dose 7

	Cmax (ng/mL)	Tmax* (h)	AUC0-t (h*ng/mL)	AUC0-inf (h*ng/mL)	T1/2 (h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Mean	1.46	1.55	3.49	4.01	2.18
SD	1.16	0.599	3.22	1.43	0.459
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Mean	2.58	0.867	3.88	4.53	1.17
SD	1.24	0.622	1.45	2.21	0.632
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	0	0
Mean	2.66	1.5	4.24	.	.
SD	0.805	1.1	0.9	.	.
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Mean	.	.	.	.	.
SD	.	.	.	.	.

Source: Supportive Tables ST-4.9 to ST-4.12 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate. (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.66-67/642)
*Tmax: median

Clinical Pharmacology Discussion

The exposure comparisons between pediatric and adult populations are based on oxymorphone exposure levels. Table 5 compares single-dose oxymorphone parameters between pediatrics and adults. As a reference, single-dose 6-OH-oxymorphone parameters between pediatrics and adults are also summarized in Table 6.

Table 5 Comparison of oxymorphone pharmacokinetic parameters after a single-dose

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Pop.**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	**Adults**	**5 mg**	**0.69**	**0.34**	**0.22**	**1.88**	**3.94**	**1.67**	**1.67**	**8.83**	**4.34**	**1.86**	**2.01**	**9.21**
EN3203-010	>12 to 17 y Ped	5 mg	1.24	1.22	0.08	4.00	6.40	6.08	1.18	20.96	7.63	6.68	1.60	22.26
		10 mg	0.83	0.69	0.04	1.96	3.77	2.26	0.12	6.47	10.22	6.525	6.16	17.74
		15 mg	5.30	10.64	0.05	33.55	67.04	150.80	3.30	467.26	109.29	257.54	3.89	746.34
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.42	0.21	0.16	0.73	2.56	2.00	1.25	6.56	2.42	0.052	2.39	2.46
		0.10 mg/kg	1.14	0.85	0.49	2.81	3.01	0.77	2.22	4.35	3.01	0.95	2.34	3.68
		0.20 mg/kg	1.33	0.77	0.46	2.43	5.32	4.53	0.14	12.90	6.92	4.02	3.69	11.40
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.33	0.22	0.11	0.62	1.69	0.94	0.76	3.69	3.22	1.56	2.12	4.32
		0.10 mg/kg	1.76	1.62	0.42	4.52	3.99	2.09	1.63	7.01	3.69	3.12	1.83	7.29
		0.20 mg/kg	3.16	1.65	1.18	5.60	9.37	5.81	2.69	17.30	14.30	5.01	10.80	17.90

(Source: Information Request response, m1\us\response-info-req.pdf, 26/179; 4/1/19; Submission #0066)

Table 6 Comparison of 6-OH-Oxymorphone pharmacokinetic parameters after a single-dose

			C_{max} (ng/mL)				AUC_{0-t} (ng h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Pop.**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	Adults	5 mg	0.76	0.29	0.32	1.36	4.85	2 31	1.34	11.67	6.59	2.50	3.17	11.05
EN3203-010	>12 to 17 y Ped	5 mg	0.31	0.29	0.05	0.96	1.54	1 88	0.28	5.27	4.99	7.57	0.58	18.24
		10 mg	0.49	0.29	0.16	1.02	3.04	1 16	1.38	4.42	8.69	10.24	3.45	26.99
		15 mg	0.94	0.52	0.30	1.87	7.35	3 33	2.34	12.14	12.80	8.84	4.15	34.41
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.10	0.06	0.00	0.16	0.46	0.40	0.00	1.09	1.83	NA	1.83	1.83
		0.10 mg/kg	0.38	0.18	0.18	0.62	1.22	0.76	0.44	2.57	0.54	NA	0.54	0.54
		0.20 mg/kg	0.60	0.51	0.13	1.51	2.64	2.52	0.14	7.45	7.58	5.12	3.95	11.20
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.10	0.073	0.04	0.25	0.47	0.47	0.04	1.25	1.11	NA	1.11	1.11
		0.10 mg/kg	0.44	0.42	0.17	1.27	1.27	0.64	0.60	2.40	1.76	0.76	0.94	2.78
		0.20 mg/kg	0.59	0.18	0.35	0.80	2.26	1.07	0.33	3.58	2.76	0.40	2.47	3.04

(Source: Information Request response, m1\us\response-info-req.pdf, 26/179; 4/1/19; Submission #0066)

Reference ID: 4499855

No multiple-dose PK parameter values for oxymorphone or 6-OH-Oxymorphone were generated. Of the three studies submitted in this supplement, multiple-dose PK parameter values were only calculated in Study EN3319-302 after Dose 1 and Dose 7; however, there were too few subjects remaining in the study at the time of Dose 7 to accurately calculate multiple-dose PK parameter values.

Based on the single-dose comparison, the observed C_{max} and AUC values are higher in subjects from 12 to 17 years compared to adults at the 5 mg dose level. It is possible that the higher exposures in 12 to 17 were driven by subjects with a lower body weight.

Among the total of 24 subjects studied (n=9 for 5 mg, n=6 for 10 mg, and, n=9 for 15 mg), two subjects (EN3203-010-(b) (6) (5 mg dose) and EN3203-010-(b) (6) (15 mg dose)) had substantially higher oxymorphone exposure levels. The Applicant investigated these subjects and could find no obvious reasons for the higher exposures. Because the oxymorphone exposure levels for these two subjects are many-fold higher than the others, these two subjects may be considered outliers. Therefore, subjects EN3203-010-(b) (6) (5 mg dose) and EN3203-010-(b) (6)(15 mg dose) were excluded in the overall assessment.

Additionally, in order to compare with 2 to 12-year-old subjects, the dose column in Table 5 was revised to dose/kg and is presented in Table 7. Note subjects EN3203-010(b) (6) (5 mg dose) and EN3203-010-(b) (6) (15 mg dose) in 12 to 17 were excluded from the PK parameter calculations in Table 7, while they were not excluded from those in Table 5.

Reference ID: 4499855

Table 7 Comparison of oxymorphone pharmacokinetic parameters after a single-dose presented as dose/kg body weight

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Population**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	**Adults**	**5 mg**	**0.69**	**0.34**	**0.22**	**1.88**	**3.94**	**1.67**	**1.67**	**8.83**	**4.34**	**1.86**	**2.01**	**9.21**
EN3203-010	>12 to 17 y Ped	**0.08 mg/kg***	**0.90**	0.69	0.08	1.84	**4.57**	2.84	1.18	9.74	**5.80**	4.08	1.60	14.44
		0.16 mg/kg*	**0.83**	0.69	0.04	1.96	**3.77**	2.26	0.12	6.47	10.22#	6.52#	6.16#	17.74#
		0.23 mg/kg*	1.76	1.02	0.49	3.64	17.01	15.68	3.30	52.21	18.29	9.10	3.89	28.60
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.42	0.21	0.16	0.73	2.56	2.00	1.25	6.56	2.42	0.052	2.39	2.46
		0.10 mg/kg	1.14	0.85	0.49	2.81	3.01	0.77	2.22	4.35	3.01	0.95	2.34	3.68
		0.20 mg/kg	1.33	0.77	0.46	2.43	5.32	4.53	0.14	12.90	6.92	4.02	3.69	11.40
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.33	0.22	0.11	0.62	1.69	0.94	0.76	3.69	3.22	1.56	2.12	4.32
		0.10 mg/kg	1.76	1.62	0.42	4.52	3.99	2.09	1.63	7.01	3.69	3.12	1.83	7.29
		0.20 mg/kg	3.16	1.65	1.18	5.60	9.37	5.81	2.69	17.30	14.30	5.01	10.80	17.90

Source: Reviewer's assessment
*Dose: average of dose by BW; 5 mg = ~0.08 mg/kg; 10 mg = ~0.16 mg/kg; 15 mg = ~0.23 mg/kg; Subjects EN3203-010-(b) (6) (5 mg dose) and EN3203-010 (b) (6) (15 mg dose) excluded.
#N=3

In summary, based on Table 7, it is reasonable to conclude that a 5 mg single dose in 12 to 17-year-old subjects will provide similar oxymorphone exposure to that of a 5 mg single dose in adults. Similarly, in 2 to less than 6 and 6 to less than or equal to 12 year old subjects, a dose between 0.05 and 0.1 mg/kg, (e.g., 0.075 mg/kg [based on oxymorphone's dose proportional behavior from 5 to 20 mg under both single- and steady-state conditions in adults (OPANA IR Prescribing Information)]), provides similar oxymorphone exposures to that of a 5 mg single dose in adults. Lastly, a cross study/information comparison from the submitted information suggests that the half-life of oxymorphone in the 12 to 17 age group is longer (observed half-life from Study EN3203-010: range 12 - 20 hours in 12-17 years old) and 2 to less than 12 years old is shorter (observed half-life from Study EN3319-302: range 4.4- 7.5 hours in 2 to less than 12 years old) than adults (observed half-life from OPANA IR Prescribing Information: range 7.25 to 9.43 hours in adults).

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2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication?

There are no changes in the indications for OPANA and is stated as: "*For the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate*."

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The general dosing regimens as described in the OPANA's Label (N21611, 9/18/18), Highlights Of Prescribing Information, are:

- •Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals
- • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse
- • Initiate treatment with 10 to 20 mg orally every four to six hours
- • OPANA should be taken on an empty stomach, at least one hour prior to or two hours after eating
- • Conversion to OPANA: Follow recommendations for conversion from other opioids or parenteral oxymorphone
- • Do not stop OPANA abruptly in a physically dependent patient
- • Mild Hepatic Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression
- • Renal Impairment: Initiate treatment with 5 mg and titrate slowly. Monitor for signs of respiratory and central nervous system depression
- • Geriatric Patients: Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression
- • CNS Depressants: Initiate treatment with 1/3 to 1/2 the recommended starting dose, consider using a lower dosage of the concomitant CNS depressant, and monitor closely.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

The following changes are proposed by the Applicant.

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Proposed	Comments
(b) (4) [redacted]	Overall comment: Currently, the Applicant's proposed Labeling is under discussion at the time of submission in DARRTS. (b) (4) [redacted]
8.4 Pediatric Use	8.4 - the reader is deferred

[redacted] (b) (4)	to clinical review
The safety and effectiveness of OPANA in ~~pediatric patients~~ [redacted] (b) (4) have not been established.	

[redacted] (b) (4)

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substances, oxymorphone?

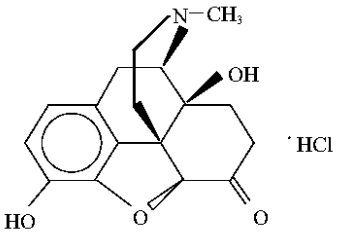
As stated above, the Applicant submitted 3 studies in this supplement. Study EN3203-010 utilized approved OPANA (oxymorphone HCl) 5 mg tablets (N21611) in pediatric subjects >12 to 17 years old.

Study EN3319-302 utilized oxymorphone HCl oral solution* (1 mg/mL) in pediatric subjects 2 to ≤12 years old. This oral solution was developed to support the pediatric study in the 2 to <12 years old, who may not be able to swallow OPANA tablets. The Applicant will not market or distribute the oxymorphone HCl oral solution.

*NOTE: Study EN3319-101 was conducted to evaluate the pharmacokinetics of oxymorphone oral solution formulation in adults before use in the pediatric population. The results from Study EN3319-101 indicate that oxymorphone and 6-OH-oxymorphone exposures from EN3319 5 mg (1 mg/mL solution) and OPANA 5 mg in healthy adults were bioequivalent.

The drug substance used in Oxymorphone HCl Oral Solution is the same as the drug substance used for commercial production of OPANA tablets. The following information was obtained from OPANA (oxymorphone hydrochloride) Tablets Label (N21611 Label; 09/2018):

> OPANA (oxymorphone hydrochloride) tablet is an opioid agonist available in 5 mg and 10 mg tablet strengths for oral administration. The chemical name for oxymorphone hydrochloride is 4, 5α-epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 337.80. The molecular formula is C17H19NO4. HCl and it has the following chemical structure.



Oxymorphone hydrochloride is white to off white odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water.

The inactive ingredients in OPANA include: lactose monohydrate, magnesium stearate, and pregelatinized starch. In addition, the 5 mg tablets contain FD&C blue No. 2 aluminum lake. The 10 mg tablets contain D&C red No. 30 aluminum lake.

3.1.2 Oxymorphone HCl oral solution formulation

The Applicant stated that oxymorphone HCl Oral Solution (1 mg/mL) is a (b) (4) solution. The composition is summarized in Table 8.

Table 8 Composition of Oxymorphone HCl Oral Solution, 1 mg/mL

Ingredients	Function	Amount (mg/mL)	Quality Standard
Oxymorphone HCl	Active	1.00	USP
(b) (4)			

NF=National Formulary; USP=United States Pharmacopeia
(Source: complete report available at \m2\23-qos\quality-overall-summary; p. 13/21)

*3.1.4 What is **proposed** route of administration for OPANA?*

OPANA and oxymorphone HCl oral solution are administered via the oral route.

3.2 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information from Study EN3319-101 provide pivotal or supportive evidence?

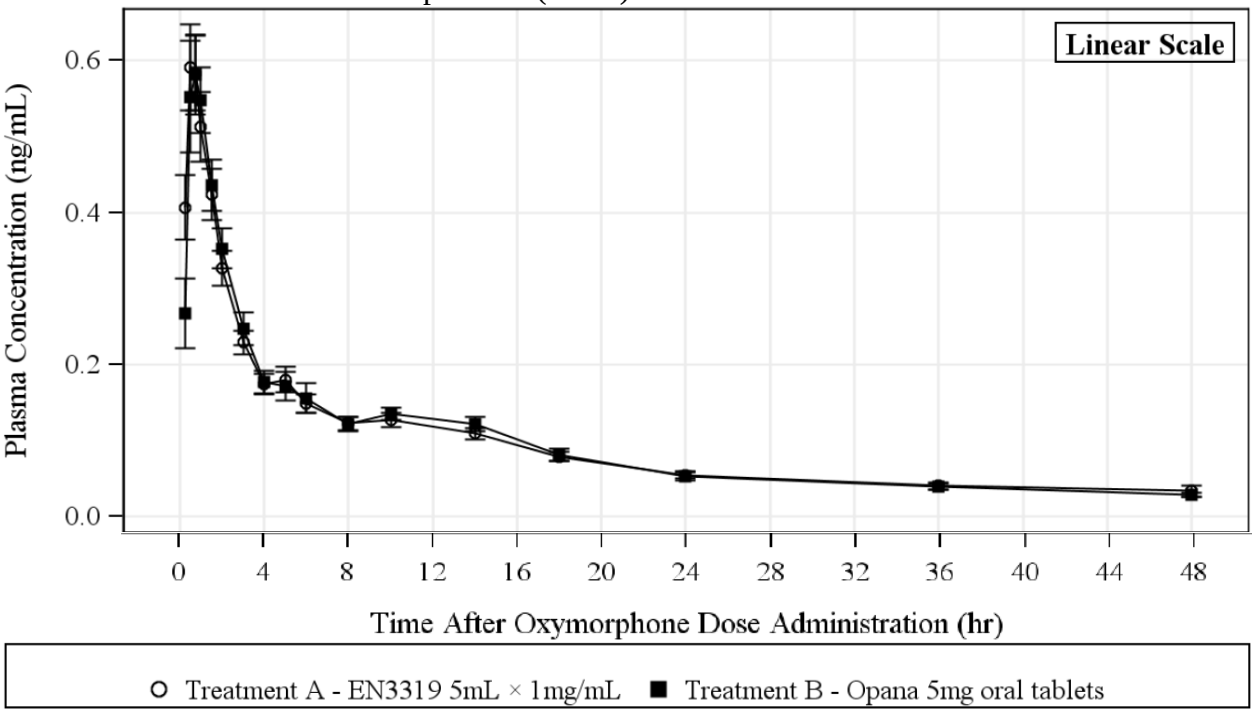
Study EN3319-101

Study EN3319-101 was an open label, randomized, single dose, two-period, two-sequence crossover study comparing EN3319 5 mg (oxymorphone HCl oral 1 mg/mL solution) and OPANA® 5 mg in Healthy Adult Subjects Under Fasted Conditions. This study was conducted prior to Study EN3319-302, which pediatric subjects ages between 2 to less than 12 years old were enrolled with liquid formulation (oxymorphone HCl oral 1 mg/mL).

The results from Study EN3319-101 suggested that oxymorphone and its metabolite, 6-OH-oxymorphone, exposures from EN3319 5 mg (oxymorphone HCl oral 1 mg/mL solution) and OPANA® 5 mg in healthy adults were bioequivalent.

The mean oxymorphone and 6-OH-oxymorphone plasma concentration versus time profiles comparing EN3319 5 mg (oxymorphone HCl oral 1 mg/mL solution) and OPANA® 5 mg are shown in Figures 6 and 7, respectively.

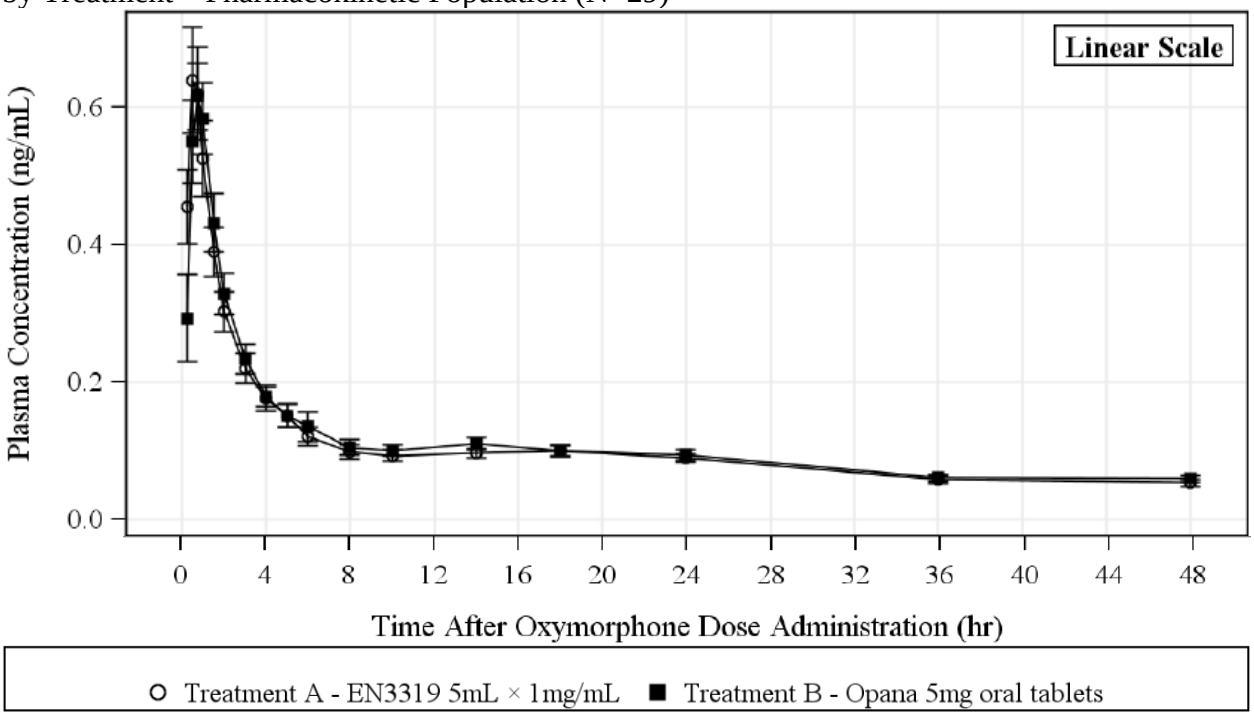
Figure 6 Mean (±SE) Plasma Concentration of Oxymorphone (ng/mL) Versus Time by Treatment – Pharmacokinetic Population (N=29)



Data Source: Figure 14.2.2
(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 35/245)

Reference ID: 4499855

Figure 7 Mean (±SE) Plasma Concentration of 6-Hydroxy-oxymorphone (ng/mL) Versus Time by Treatment – Pharmacokinetic Population (N=29)



Data Source: Figure 14.2.2
(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 40/245)

The PK parameters of oxymorphone and 6-OH-oxymorphone comparing EN3319 5 mg (1 mg/mL solution) and OPANA® 5 mg are presented in Tables, 9 and 10, respectively.

Table 9 Summary of Plasma Pharmacokinetic Parameters of Oxymorphone by Treatment – Pharmacokinetic Population

Category	**EN3319 (N=29)**	**OPANA Tablet(N=2)9**
AUC_{0-t} (ng·h/mL)		
N	29	29
Mean (SD)	3.742 (1.4073)	3.945 (1.6712)
CV (%)	37.6094	42.3586
AUC_{0-inf} (ng·h/mL)		
N	19	21
Mean (SD)	4.855 (1.4856)	4.338 (1.8591)
CV (%)	30.5973	42.8576
C_{max} (ng/mL)		
N	29	29
Mean (SD)	0.6699 (0.28186)	0.6932 (0.33706)
CV (%)	42.07279	48.62594
T_{max} (hours)		
N	29	29
Median	0.75	0.75
Min, Max	0.3, 5.0	0.3, 6.0
λ_z (1/h)		
N	19	21
Mean (SD)	0.0797 (0.03025)	0.0956 (0.03240)
CV (%)	37.93636	33.89050
$t_{1/2}$ (hours)		
N	19	21
Mean (SD)	10.06 (3.943)	8.12 (2.952)
CV (%)	39.196	36.350

Data Source: Table 14.2.3.1
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: AUC0-inf, λz, and t½ for a period are missing if plasma concentration data were not suitable for λz estimation.
N=Number of subjects; n=Number of observations; SD=Standard deviation; CV=Coefficient of variation
(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 35/245)

Reference ID: 4499855

Table 10 Plasma Pharmacokinetic Parameters of 6-Hydroxy-oxymorphone by Treatment

Category	**EN3319 (N=29)**	**OPANA tablet (N=29)**
AUC_{0-t} (ng·h/mL)		
N	29	29
Mean (SD)	4.554 (2.2900)	4.847 (2.3103)
CV (%)	50.2822	47.6601
AUC_{0-inf} (ng·h/mL)		
N	13	15
Mean (SD)	6.246 (1.7754)	6.585 (2.5028)
CV (%)	28.4237	38.0092
C_{max} (ng/mL)		
N	29	29
Mean (SD)	0.7096 (0.39076)	0.7547 (0.29069)
CV (%)	55.06811	38.51526
T_{max} (hours)		
N	29	29
Median	0.50	0.75
Min, Max	0.3, 1.5	0.3, 1.5
λ_z (1/h)		
N	13	15
Mean (SD)	0.0357 (0.00989)	0.0387 (0.01271)
CV (%)	27.70116	32.83724
$t_{1/2}$ (hours)		
N	13	15
Mean (SD)	21.03 (6.597)	19.61 (5.824)
CV (%)	31.365	29.705

Data Source: Table 14.2.3.2
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: AUC0-inf, λz, and t½ for a period are missing if plasma concentration data were not suitable for λz estimation.
N=Number of subjects; n=Number of observations; SD=Standard deviation; CV=Coefficient of variation
(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 41/245)

The 90% confidence intervals for AUC and C_{max} were all contained within 0.80 and 1.25 for both for oxymorphone and its metabolite, 6-Hydroxy-oxymorphone (Tables 11 and 12, respectively).

Reference ID: 4499855

Table 11 Analysis (90% CI: confidence intervals) of Plasma Pharmacokinetic Parameters of Oxymorphone – Pharmacokinetic Population

Parameter (unit)	Treatment[a]	n	LS Means[b]	Difference of LS Means (A-B)	Geometric LS Means	Ratio of Geometric LS Means (A/B)	90% CI of the Ratio (A/B)	
							Lower	Upper
AUC_{0-t} (ng·h/mL)	A	29	1.2463	--	3.4776	0.9598	0.9224	0.9987
	B	29	1.2874		3.6234			
AUC_{0-inf} (ng·h/mL)	A	19	1.4396	--	4.2190	1.0483	0.9753	1.1268
	B	21	1.3924		4.0244			
C_{max} (ng/mL)	A	29	-0.5025	--	0.6050	0.9695	0.8723	1.0776
	B	29	-0.4715		0.6241			
λ_z (1/h)	A	19	0.07869	-0.015439	--	--	--	--
	B	21	0.09413					

Data Source: Table 14.2.5.1

a A = EN3319: Oxymorphone HCL Oral Solution 5 mL × 1 mg/mL; B = OPANA: Oxymorphone HCL Oral 5 mg tablets

b LS means for AUC0-t, AUC0-inf, and Cmax are on the logarithm scale; LS means for λz is on the original scale.

Note: A linear mixed effects model was performed on λz and the natural logarithms of AUC0-t, AUC0-inf, and Cmax. The model included seq., period and treatment as fixed effects and subject nested within seq. as a random factor. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale. AUC0-inf and λz for a period are missing if plasma concentration data were not suitable for λz estimation.

n=observations per treatment. Subjects who completed the study and were PK evaluable throughout will have 2 observations per treatment.

(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 38/245)

Table 12 Analysis (90% CI: confidence intervals) of Plasma Pharmacokinetic Parameters for 6-Hydroxy-oxymorphone – Pharmacokinetic Population

Parameter (unit)	Treatment[a]	n	LS Means[b]	Difference of LS Means (A-B)	Geometric LS Means	Ratio of Geometric LS Means (A/B)	90% CI of the Ratio (A/B)	
							Lower	Upper
AUC_{0-t} (ng·h/mL)	A	29	1.3827	--	3.9856	0.9205	0.8661	0.9784
	B	29	1.4655		4.3296			
AUC_{0-inf} (ng·h/mL)	A	13	1.7798	--	5.9284	0.9375	0.8128	1.0812
	B	15	1.8443		6.3237			
C_{max} (ng/mL)	A	29	-0.4611	--	0.6306	0.9017	0.8182	0.9937
	B	29	-0.3576		0.6993			

Data Source: Table 14.2.5.2

a A = EN3319: Oxymorphone HCL Oral Solution 5 mL × 1 mg/mL; B = OPANA: Oxymorphone HCL Oral 5 mg tablets

b LS means for AUC0-t, AUC0-inf, and Cmax are on the logarithm scale; LS means for λz is on the original scale.

Note: A linear mixed effects model was performed on λz and the natural logarithms of AUC0-t, AUC0-inf, and Cmax. The model included seq., period and treatment as fixed effects and subject nested within seq. as a random factor. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale. AUC0-inf and λz for a period are missing if plasma concentration data were not suitable for λz estimation.

n=observations per treatment. Subjects who completed the study and were PK evaluable throughout will have 2 observations per treatment.

(Source: complete report available at \m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\en3319-101; p. 42/245)

Reference ID: 4499855

3.3.2 To what extent does the available clinical pharmacology information from Study EN3319-010 provide pivotal or supportive evidence?

Study EN3203-010 was an open-label, 2-part (single- and multiple-dose), ascending-dose, multicenter study using oxymorphone IR tablets in >12 to 17-year-old subjects with postoperative pain requiring an opioid.

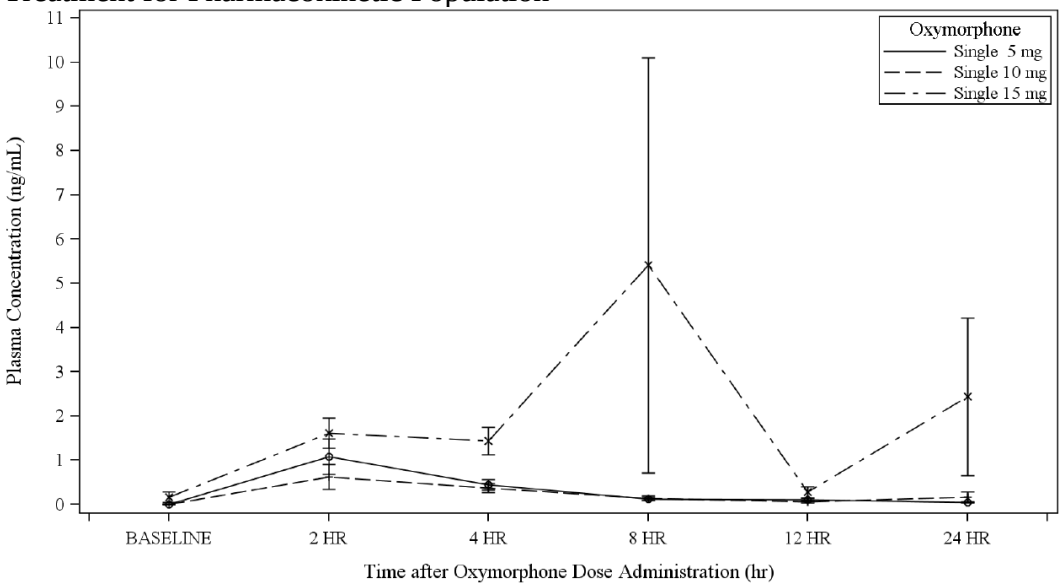
The single-dose phase comprised of 3 doses of oxymorphone IR in an ascending manner (in stepwise order, based on the previous groups' demonstrated safety and tolerability): 5 mg (equivalent to 0.1 mg/kg for a 50-kg child), 10 mg (equivalent to 0.2 mg/kg for a 50-kg child), and 15 mg (0.3 mg/kg for a 50-kg child).

The multiple-dose (every 4 to 6 hours, but, no sooner than every 4 hours and no later than every 6 hours) phase also comprised of 3 doses of oxymorphone IR in an ascending manner (in stepwise order, based on previous groups' demonstrated safety/tolerability and effectiveness).

Doses used in the multiple-dose period were determined from the results of the single-dose period. The Applicant stated that during the multiple-dose phase of this study only trough levels at the beginning of each dose interval were obtained. Additionally, plasma oxymorphone and 6-OH-oxymorphone concentrations were determined at 4-hour intervals, only; therefore, pharmacokinetic parameters were not evaluated. (clinical-overview.pdf; p.10/24)

The mean oxymorphone and 6-OH-oxymorphone plasma concentration versus time profiles after single dose OPANA IR tablets are shown in Figures 8 and 9, respectively.

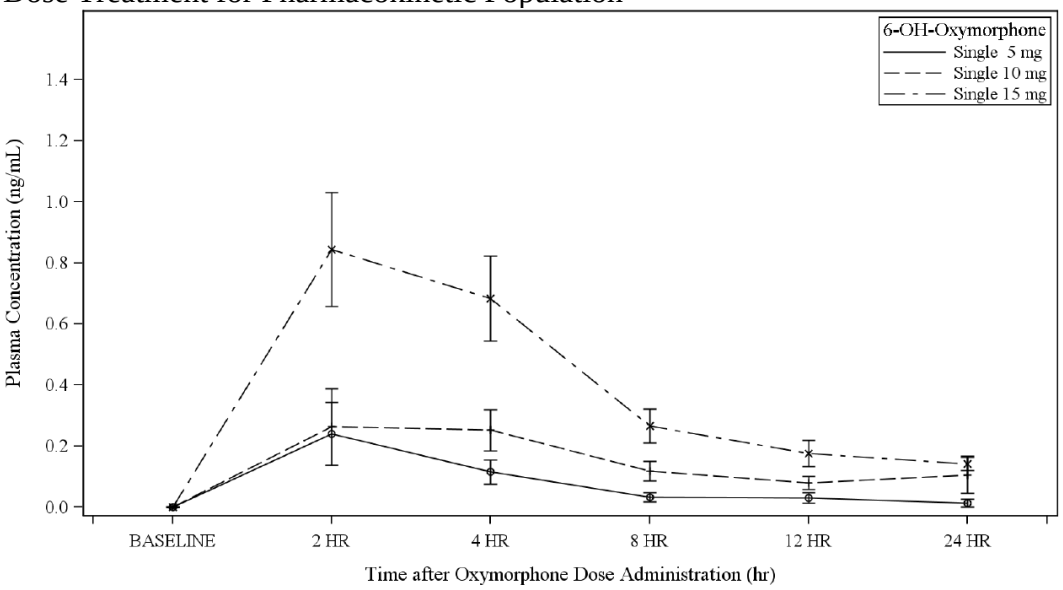
Figure 8 Mean (+/- SE) Plasma Concentration of Oxymorphone Versus Time by single dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK1b.sas Output: FPK1b rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 114/317)

Reference ID: 4499855

Figure 9 Mean (+/- SE) Plasma Concentration of 6-OH-Oxymorphone Versus Time by Single Dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK1a.sas Output: FPK1a rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 113/317)

The plasma pharmacokinetic parameters of a single dose of oxymorphone and 6-OH-oxymorphone are shown in Table 13.

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Table 13 Summary of Plasma Pharmacokinetic Parameters of Single Dose of Oxymorphone by Treatment Group – PK Population (note: all subjects)

Statistics	Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)
AUC_{0-t} (ng*hr/mL)						
n	9	6	9	8	6	9
Mean	6.395	3.766	67.040	1.544	3.040	7.354
SD	6.0752	2.2587	150.7979	1.8794	1.1625	3.3255
SE	2.0251	0.9221	50.2660	0.6645	0.4746	1.1085
CV(%)	94.998	59.984	224.937	121.739	38.233	45.219
Geometric Mean	4.580	2.337	18.638	0.864	2.836	6.559
Minimum	1.18	0.12	3.30	0.28	1.38	2.34
Maximum	20.96	6.47	467.26	5.27	4.42	12.14
AUC_{0-inf} (ng*hr/mL)						
n	9	3	8	5	5	9
Mean	7.632	10.223	109.294	4.987	8.692	12.795
SD	6.6828	6.5195	257.5421	7.5732	10.2430	8.8385
SE	2.2276	3.7641	91.0549	3.3868	4.5808	2.9462
CV(%)	87.565	63.773	235.642	151.844	117.837	69.077
Geometric Mean	5.578	9.043	25.001	2.019	5.954	10.832
Minimum	1.60	6.16	3.89	0.58	3.45	4.15
Maximum	22.26	17.74	746.34	18.24	26.99	34.41
Cmax (ng/mL)						
n	9	6	9	8	6	9
Mean	1.243	0.828	5.295	0.314	0.487	0.940
SD	1.2192	0.6892	10.6386	0.3276	0.2853	0.5212
SE	0.4064	0.2814	3.5462	0.1158	0.1165	0.1737
CV(%)	98.048	83.255	200.934	104.344	58.558	55.452
Geometric Mean	0.767	0.499	2.117	0.204	0.424	0.803
Minimum	0.08	0.04	0.49	0.05	0.16	0.30
Maximum	4.00	1.96	33.55	0.96	1.02	1.87
T_{max} (hour)						
n	9	6	9	8	6	9
Mean	4.898	3.681	6.193	3.885	4.631	3.785
SD	3.9645	2.4102	6.3784	2.7228	3.7051	3.2552
SE	1.3215	0.9840	2.1261	0.9626	1.5126	1.0851
CV(%)	80.939	65.485	103.000	70.077	80.014	85.998
Minimum	2.00	2.00	2.00	2.00	2.00	2.00
Median	2.350	2.842	4.000	2.250	3.633	2.350
Maximum	13.00	8.32	21.97	8.33	12.00	12.17
λ						

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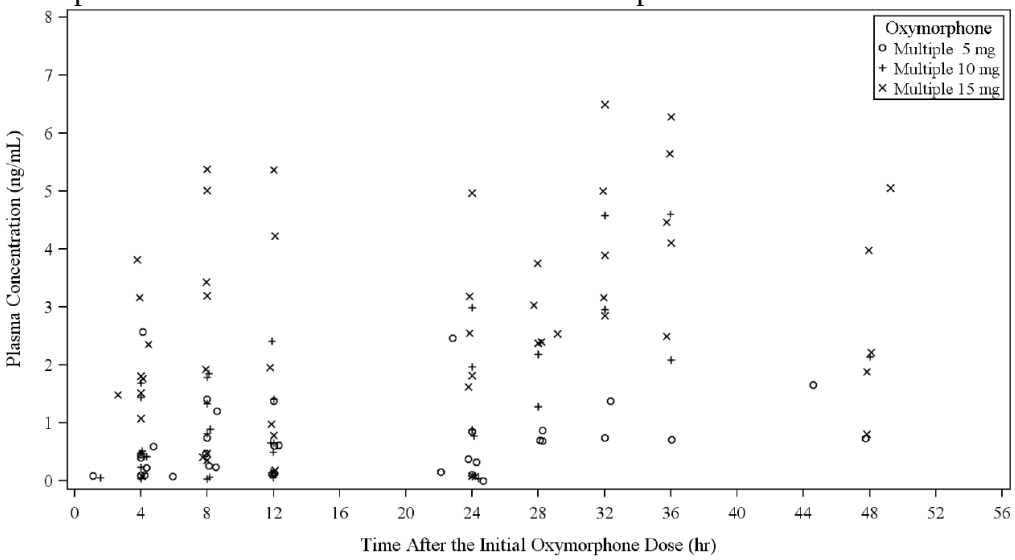
n	9	3	8	5	5	9
Mean	0.209	0.214	0.073	0.281	0.101	0.042
SD	0.2552	0.2962	0.0549	0.2072	0.0965	0.0234
SE	0.0851	0.1710	0.0194	0.0927	0.0431	0.0078
CV(%)	122.107	138.250	75.212	73.688	95.455	55.730
Minimum	0.02	0.02	0.01	0.01	0.01	0.01
Maximum	0.71	0.56	0.16	0.52	0.25	0.09
$t_{1/2}$ (hour)						
n	9	3	8	5	5	9
Mean	12.099	15.900	19.974	19.215	23.635	22.520
SD	9.9336	18.2533	22.4488	37.3737	33.6381	15.3063
SE	3.3112	10.5385	7.9368	16.7140	15.0434	5.1021
CV(%)	82.102	114.803	112.390	194.501	142.321	67.967
Minimum	0.98	1.25	4.29	1.33	2.82	7.58
Maximum	28.06	36.35	72.13	86.02	83.11	58.48

Data Source: Table 14.2.4
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 48/317)

The multiple-dose phase determined plasma oxymorphone and 6-OH-oxymorphone concentrations only at 4-hour intervals; therefore, pharmacokinetic parameters were not evaluated.

A scatter plots of plasma concentration of oxymorphone and 6-OH-oxymorphone versus dose time by multiple-dose treatment are shown in Figures 10 and 11, respectively.

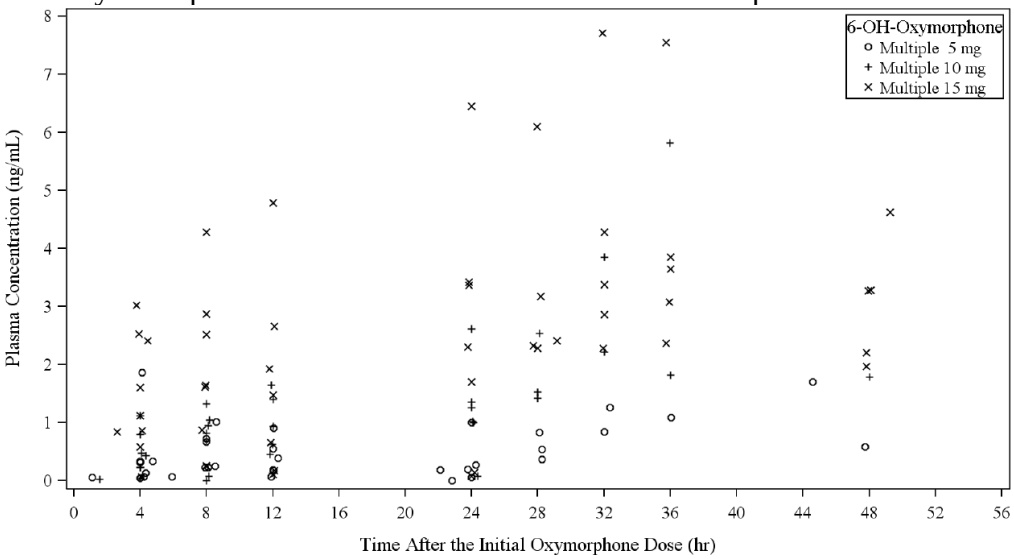
Figure 10 Scatter Plot of Plasma Concentration of Oxymorphone Versus Previous Dose Time by Multiple Dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK2b.sas Output: FPK2b rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 116/317)

Reference ID: 4499855

Figure 11 Scatter Plot of Plasma Concentration of 6-OH-Oxymorphone Versus Previous Dose Time by Multiple Dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK2a.sas Output: FPK2a rtf
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 115/317)

Summary of observed mean plasma concentrations per the sampling time-points of oxymorphone and 6-OH-Oxymorphone by treatment (Dose) group after multiple dose are shown in Table 14.

Table 14 Summary of observed mean plasma concentrations per the sampling time-points of oxymorphone and 6-OH-Oxymorphone by treatment group after multiple dose (note: all subjects)

Timepoint	Statistics	Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
		5 mg	10 mg	15 mg	5 mg	10 mg	15 mg
		(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)
4 hours	n	8	7	8	8	7	8
	Mean	0.56655	0.69068	1.94886	0.39606	0.47354	1.52452
	SD	0.832757	0.623060	1.171995	0.606024	0.373681	1.046110
8 hours	n	6	7	8	6	7	8
	Mean	0.72122	0.96958	2.52175	0.51748	0.69927	1.78771
	SD	0.493076	0.742611	2.046728	0.332790	0.492023	1.387034
12 hours	n	6	6	7	6	6	7
	Mean	0.49530	0.94882	1.95010	0.37808	0.86602	1.68254
	SD	0.493681	0.839298	2.059903	0.309694	0.577783	1.659166
24 hours	n	7	5	7	6	6	7

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	Mean	0.60953	1.33032	2.04354	0.28447	1.22062	2.49299
	SD	0.861570	1.153598	1.735689	0.364193	0.818600	2.210344
28 hours	n	3	4	5	3	4	5
	Mean	0.75157	1.54550	2.82080	0.57850	1.50850	3.25560
	SD	0.105814	0.943873	0.583736	0.232924	0.813931	1.629427
32 hours	n	2	3	5	2	3	5
	Mean	1.06000	3.34100	4.28140	1.05080	2.63200	4.10240
	SD	0.452548	1.103008	1.488950	0.295853	1.073817	2.144174
36 hours	n	1	2	5	1	2	5
	Mean	0.71450	3.34350	4.59860	1.08500	3.81700	4.09700
	SD	-	1.784030	1.468756	-	2.825599	2.014804
48 hours	n	3	1	5	3	1	5
	Mean	0.81028	2.13700	2.78800	0.78122	1.78900	3.07200
	SD	0.809334		1.701034	0.840605		1.056546

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3203-010; p. 132/317)

3.3.3 To what extent does the available clinical pharmacology information from Study EN3319-302 provide pivotal or supportive evidence?

Study EN3319-302 was an open-label, 2-part (single- and multiple-dose), ascending-dose, multicenter study utilizing oxymorphone HCl oral solution (1 mg/mL) in pediatric subjects aged 2 to ≤12 years with postoperative pain requiring an opioid.

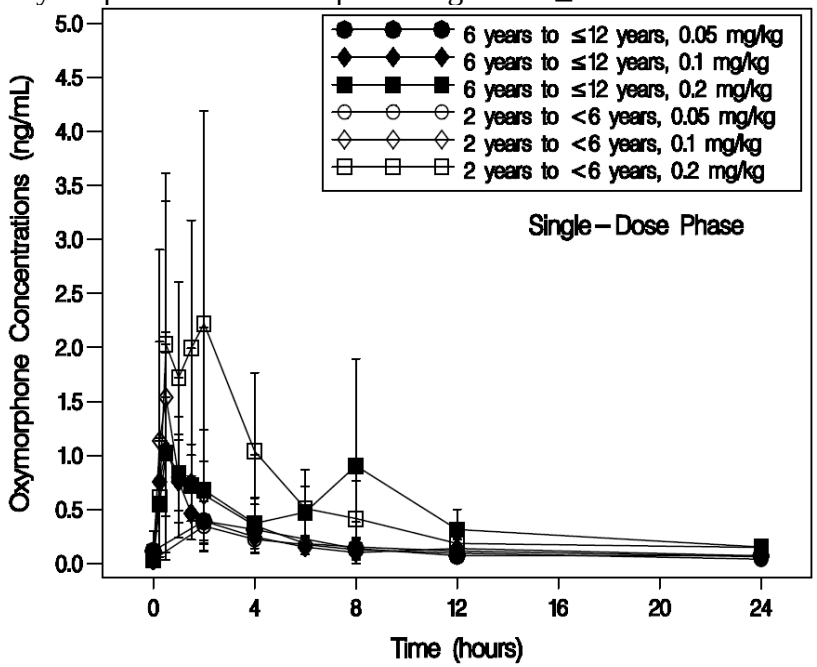
The single phase comprised initially of 3 groups of subjects (0 to 2 years, 2 to ≤12 years and 1 to < 6 years) were given a single dose of oxymorphone HCl oral solution. The Applicant stated that the 0 to 2 years age group was discontinued (Amendment 02), due to this group of subjects being studied in another ongoing study. The final two age groups were 2 to <6 years and 6 to ≤12 years. Within each age group, there were 3 treatment cohorts comprised of 3 different doses of oxymorphone HCl oral solution, namely, 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg, which were administered following an ascending dose scheme.

It was noted by the Applicant that at the end of the single-dose phase, an Independent Data Monitoring Committee recommended that a dose of 0.2 mg/kg be used in the Multiple-Dose Phase. Thus, the multiple-dose phase employed only one dose at 0.2 mg/kg. Subjects were dosed approximately every 4 to 6 hours for up to 48 hours.

The mean oxymorphone and 6-OH-oxymorphone plasma concentration versus time profiles after single dose oxymorphone HCl oral solution are shown in Figures 12 and 13, respectively.

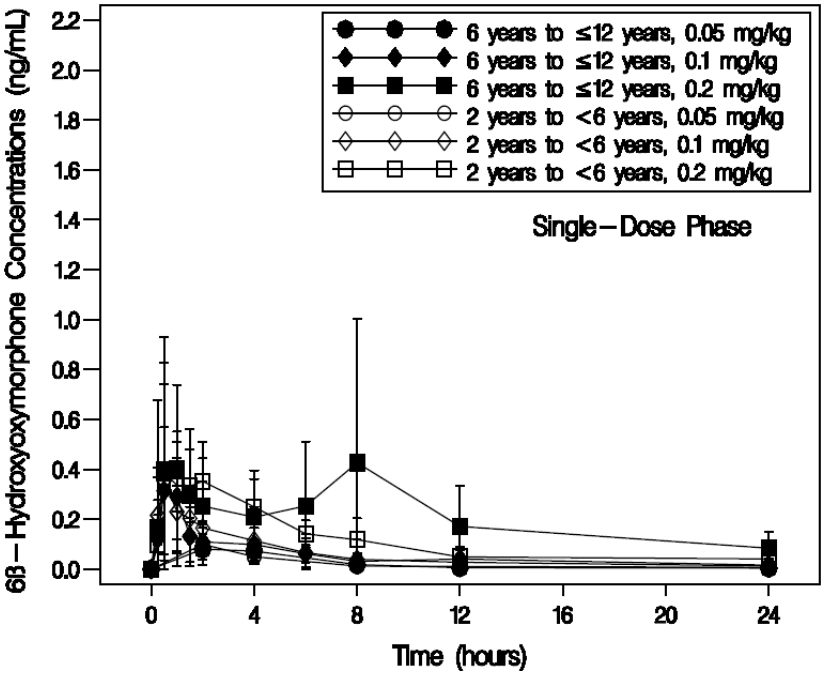
Reference ID: 4499855

Figure 12 Mean (SD) Plasma Oxymorphone Concentrations Following Administration of Oxymorphone HCl oral liquid in Ages 2 to ≤12 Years in the Single-Dose Phase



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 1]
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 53/642)

Figure 13 Mean (SD) Plasma 6β-Hydroxyoxymorphone Concentrations Following Administration of Oxymorphone HCl oral liquid in Ages 2 to ≤12 Years in the Single-Dose Phase

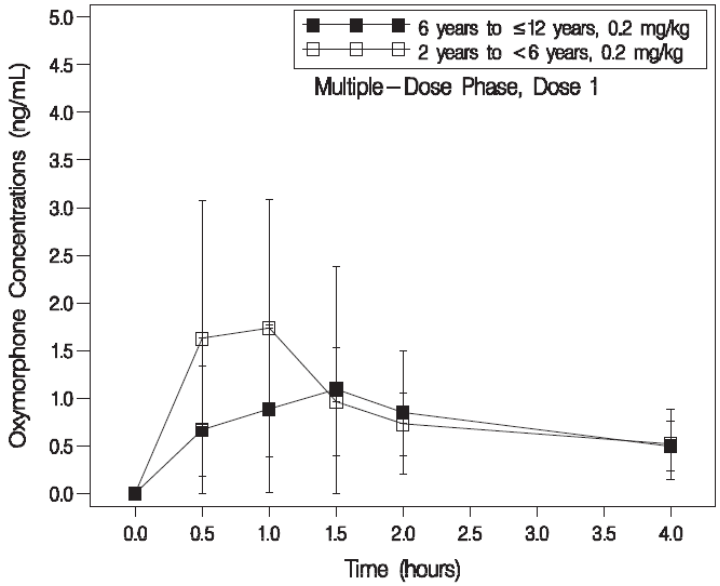


Data Source: Study EN3319-302 PK Report [Figure 1]
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 53/642)

Reference ID: 4499855

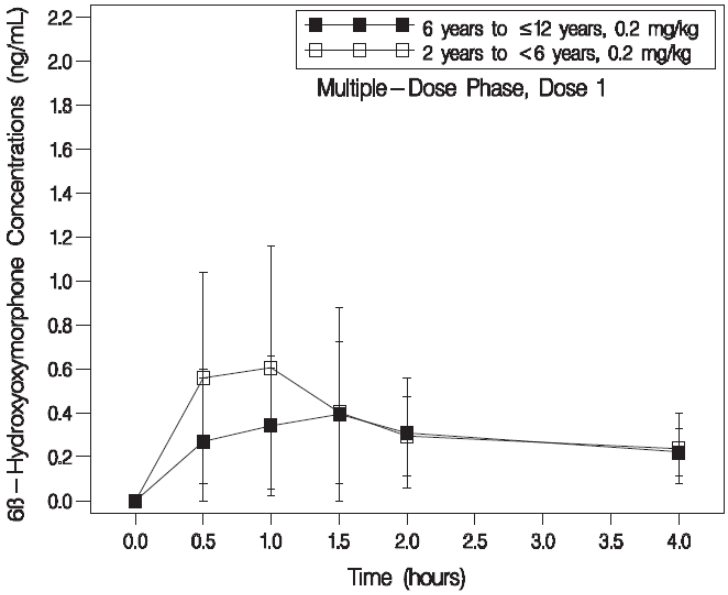
The mean oxymorphone and 6-OH-oxymorphone plasma concentration versus time profiles after Dose 1 in the multiple dose phase after oxymorphone HCl oral solution administration are shown in Figures 14 and 15, respectively.

Figure 14 Mean (SD) Plasma Oxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 54/642)

Figure 15 Mean (SD) Plasma 6β-Hydroxyoxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 (linear-linear coordinates)

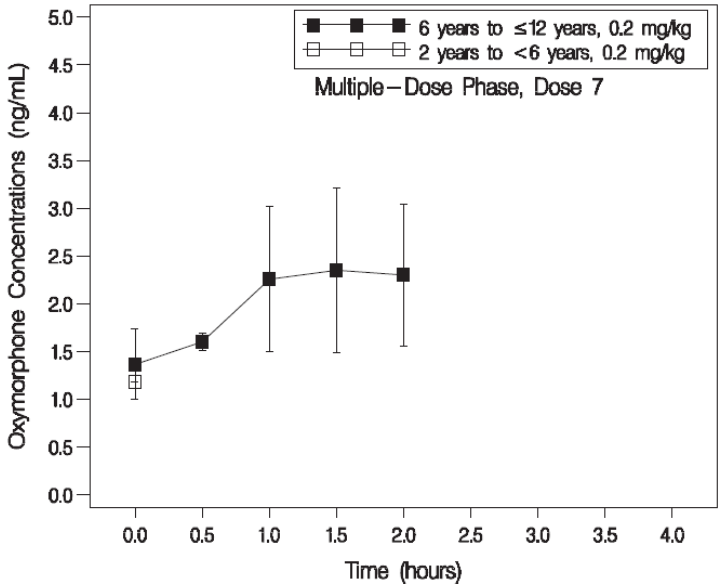


(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 54/642)

Reference ID: 4499855

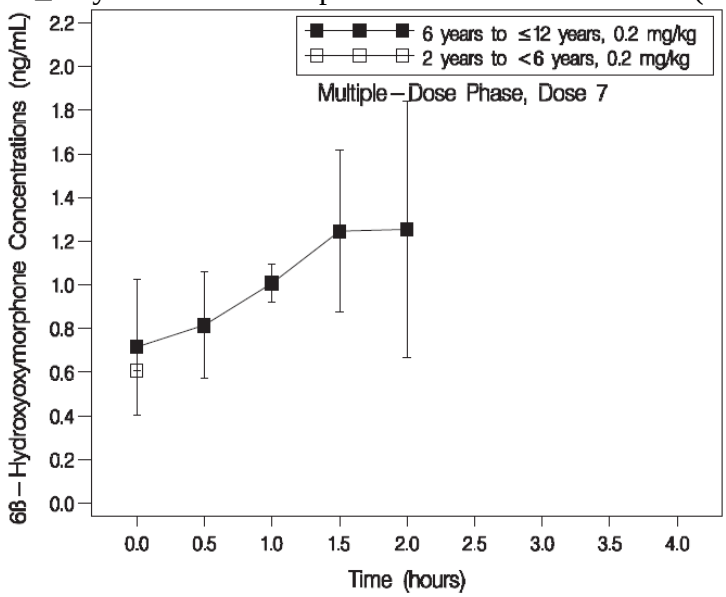
The mean oxymorphone and 6-OH-oxymorphone plasma concentration versus time profiles after Dose 7 in the multiple dose phase after oxymorphone HCl oral solution administration are shown in Figures 16 and 17. respectively.

Figure 16 Mean (SD) Plasma Oxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 7 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 55/642)

Figure 17 Mean (SD) Plasma 6β-Hydroxyoxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 7 (linear-linear coordinates)



(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 55/642)

Reference ID: 4499855

Summary oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase are shown in Table 15.

Table 15 Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.2 mg/kg Oxymorphone HCl Oral Liquid in Children Aged 2 years to ≤12 years in the Single-Dose Phase

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	0.415	2.7 Median- 2.95	2.56	.	.
SD	0.211	1.66	2	0.0516	0.232
CV(%)	51	61.7	78	2.1	8.1
Minimum	0.157	0	1.25	2.39	2.7
Maximum	0.727	4.25	6.56	2.46	3.03
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	2	2
Mean	0.33	2.64 Median-2.05	1.69	3.22	5.01
SD	0.217	1.03	0.943	1.56	1.4
CV(%)	65.9	39.1	55.7	48.3	27.9
Minimum	0.106	2	0.759	2.12	4.02
Maximum	0.622	4.28	3.69	4.32	6
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Mean	1.14	1.38 Median- 1.04	3.01	3.01	7.5
SD	0.847	1.3	0.766	0.946	7.33
CV(%)	74.3	94.6	25.5	31.4	97.8
Minimum	0.494	0.5	2.22	2.34	2.32
Maximum	2.81	3.98	4.35	3.68	12.7
0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	3	3
Mean	1.76	1.45 Median-1.45	3.99	3.69	4.38
SD	1.62	1.39	2.09	3.12	2.9
CV(%)	91.7	95.9	52.4	84.7	66.2
Minimum	0.417	0.5	1.63	1.83	1.09

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Maximum	4.52	3.98	7.01	7.29	6.57
0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	3	3
Mean	1.33	2.49 Median- 1	5.32	6.92	5.13
SD	0.772	3.17	4.53	4.02	3.16
CV(%)	58.1	127.1	85.1	58	61.5
Minimum	0.455	0.283	0.137	3.69	1.9
Maximum	2.43	8	12.9	11.4	8.21
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Mean	3.16	1.59 Median- 1.26	9.37	14.3	4.39
SD	1.65	1.38	5.81	5.01	1.16
CV(%)	52.4	87.3	62.1	35	26.4
Minimum	1.18	0.483	2.69	10.8	3.57
Maximum	5.6	4	17.3	17.9	5.21

Source: Supportive Tables ST-4.1 and ST-4.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 62-64/642)

Summary oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7 are presented in Table 16.

Table 16 Summary Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Mean	1.46	1.37 Median- 1.55	3.49	4.01	2.18
SD	1.16	0.599	3.22	1.43	0.459
CV(%)	79.9	43.8	92.2	35.7	21
Minimum	0.068	0.433	0.0548	2.75	1.8
Maximum	4.23	2.05	11	5.56	2.69
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Mean	2.58	0.967 Median- 0.867	3.88	4.53	1.17
SD	1.24	0.622	1.45	2.21	0.632
CV(%)	48.2	64.3	37.4	48.8	54
Minimum	1.14	0.467	2.81	2.99	0.687
Maximum	3.9	2	6.25	7.06	1.88
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	0	0
Mean	2.66	1.21 Median- 1.5	4.24	.	.
SD	0.805	1.1	0.9	.	.
CV(%)	30.2	90.5	21.2	.	.
Minimum	1.74	0	3.27	.	.
Maximum	3.22	2.13	5.05	.	.
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Mean	.	.	.	.	.
SD	.	.	.	.	.
CV(%)	.	.	.	.	.
Minimum	.	.	.	.	.
Maximum	.	.	.	.	.

Source: Supportive Tables ST-4.9 to ST-4.12 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate. (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.66-67/642)

Reference ID: 4499855

Summary 6-OH-Oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase are shown in Table 17.

Table 17 Summary 6-OH-oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Single-Dose Phase

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	5	6	1	1
Mean	0.104	2.86 Median-2.02	0.459	1.83	20.5
SD	0.0555	1.17	0.396	.	.
CV(%)	53.4	41	86.3	.	.
Minimum	0	2	0	1.83	20.5
Maximum	0.155	4.25	1.09	1.83	20.5
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	1	1
Mean	0.1	2.91 Median-2.05	0.467	1.11	4.48
SD	0.073	1.11	0.473	.	.
CV(%)	72.7	38.1	101.4	.	.
Minimum	0.0425	2	0.0425	1.11	4.48
Maximum	0.248	4.28	1.25	1.11	4.48
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	1	1
Mean	0.384	1.38 Median-1.04	1.22	0.535	2.31
SD	0.177	1.3	0.761	.	.
CV(%)	46.3	94.6	62.2	.	.
Minimum	0.183	0.5	0.444	0.535	2.31
Maximum	0.62	3.98	2.57	0.535	2.31
0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	4	4
Mean	0.437	1.86 Median-1.07	1.27	1.76	8.67
SD	0.419	1.69	0.637	0.762	8.06
CV(%)	95.7	90.8	50.3	43.4	92.9
Minimum	0.171	0.5	0.598	0.944	1.28
Maximum	1.27	4.07	2.4	2.78	18.6

0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	2	2
Mean	0.603	3.08 Median-1.45	2.64	7.58	18.7
SD	0.513	3.42	2.52	5.12	22.5
CV(%)	85	110.8	95.2	67.6	120.6
Minimum	0.131	0.5	0.138	3.95	2.75
Maximum	1.51	8.05	7.45	11.2	34.6
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Mean	0.587	1.93 Median-1.29	2.26	2.76	5.18
SD	0.182	1.71	1.07	0.399	2.55
CV(%)	31.1	88.6	47.5	14.5	49.3
Minimum	0.353	0.483	0.33	2.47	3.37
Maximum	0.797	4.02	3.58	3.04	6.98

Source: Supportive Tables ST-5.1 and ST-5.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.71-73/642)

Summary 6-OH-Oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7 are presented in Table 18.

Table 18 Summary 6-OH-Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Mean	0.547	1.67 median-1.58	1.35	2.15	3.61
SD	0.472	1.01	1.27	0.769	1.67
CV(%)	86.2	60.5	93.8	35.7	46.2
Minimum	0.0204	0.433	0.0068	1.32	1.82
Maximum	1.59	4.02	4.23	2.84	5.12
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Mean	0.829	1.37 Median-0.867	1.61	1.79	1.42
SD	0.541	1.5	1.19	1.73	0.73
CV(%)	65.2	109.6	74.2	96.7	51.6
Minimum	0.24	0.467	0.396	0.455	0.788
Maximum	1.5	4.03	3.09	3.74	2.22
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	1	1
Mean	1.41	1.36 Median-1.5	2.25	7.66	4.9
SD	0.473	0.85	0.547	.	.
CV(%)	33.7	62.5	24.3	.	.
Minimum	0.988	0.45	1.84	7.66	4.9
Maximum	1.92	2.13	2.87	7.66	4.9
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Mean	.	.	.	.	.
SD	.	.	.	.	.
CV(%)	.	.	.	.	.
Minimum	.	.	.	.	.
Maximum	.	.	.	.	.

Source: Supportive Tables ST-5.9 to ST-5.12 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.75-76/642)

Reference ID: 4499855

3.3.4 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and safety.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Study EN3319-101

The analytical analysis was conducted at [redacted] (b) (4) to determine the plasma concentrations of oxymorphone and 6-β-hydroxyoxymorphone, using API 4000 LC/MS/MS system. The analytes were quantitated using a solid phase extraction procedure. Linear regression, with 1/x2 weighting, performed in Watson LIMS version 6.4.0.02™ for Windows, was used to obtain the best fit of the data for the calibration curves. The lower limit of quantitation (LLOQ) was 0.02500/0.02500 ng/mL and the upper limit of quantitation (ULOQ) was 10.00/10.00 ng/mL for oxymorphone/6-β-hydroxyoxymorphone.
Nine (9) calibration curve standards were used: 0.02500/0.02500, 0.05000/0.05000, 0.1000/0.1000, 0.4000/0.4000, 1.000/1.000, 2.000/2.000, 5.000/5.000, 8.000/8.000 and 10.00/10.00 ng/mL for oxymorphone/6-β-hydroxyoxymorphone. QC concentrations were 0.07500/0.07500, 0.7500/0.7500, 7.500/7.500 ng/mL of oxymorphone/6-β-hydroxyoxymorphone were assayed. Table 19 represents a summary of the analytical assay for Study EN3319-101.

Table 19 Summary of analytical assay for Study EN3319-101

Parameter	
Analytical Report	0911166.00
Oxymorphone standard curve (observed % CV)	3.3 - 6.2
6β-hydroxyoxymorphone standard curve (observed % CV)	2.0 - 6.2
Oxymorphone Interday Precision (% CV)	0.0750 ng/mL: 9.7% 0.7500 ng/mL: 6.4% 7.500 ng/mL: 8.6%
Oxymorphone Interday Accuracy (% Bias)	0.0750 ng/mL: 2.2% 0.7500 ng/mL: -1.2% 7.500 ng/mL: 1.0%
6β-hydroxyoxymorphone Interday Precision (% CV)	0.0750 ng/mL: 7.8% 0.7500 ng/mL: 5.8% 7.500 ng/mL: 5.2%
6β-hydroxyoxymorphone Interday Accuracy (% Bias)	0.0750 ng/mL: -1.3% 0.7500 ng/mL: 0.3% 7.500 ng/mL: -4.8%

Reference ID: 4499855

Duration from Time Sample Was First Drawn to Date of Last Sample Analysis (Including ISR)	Date of 1st sample:24-Sep-2009 Last assays: 13-Nov-2009 Samples stored ≤81 days
Actual Sample Storage Temperature	-70°C±20°C

Source: m2\27-clin-sum\summary-biopharm.pdf; p. 14/40

Table 20 represents a summary of the analytical assay for Study EN3319-010.

Table 20 Summary of analytical assay for Study EN3319-010

Parameter	
Analytical Report	0911166.00
Oxymorphone standard curve (observed % CV)	3.9 - 7.5
6β-hydroxyoxymorphone standard curve (observed % CV)	2.9 - 6.8
Oxymorphone Interday Precision (% CV)	0.0750 ng/mL: **128.2**% 0.7500 ng/mL: 6.3% 7.500 ng/mL: 10.6%
Oxymorphone Interday Accuracy (% Bias)	0.0750 ng/mL: 27.7% 0.7500 ng/mL: -2.4% 7.500 ng/mL: 12.3%
6β-hydroxyoxymorphone Interday Precision (% CV)	0.0750 ng/mL: 8.9% 0.7500 ng/mL: 5.8% 7.500 ng/mL: 6.1%
6β-hydroxyoxymorphone Interday Accuracy (% Bias)	0.0750 ng/mL: 2.2% 0.7500 ng/mL: -0.1% 7.500 ng/mL: 4.6%
Duration from Time Sample Was First Drawn to Date of Last Sample Analysis (Including ISR)	Date of 1st sample: 26-Feb-2009 Last assays: 17-Jun-2011
Actual Sample Storage Temperature	-70°C

Source: m2\27-clin-sum\summary-biopharm.pdf; p. 15/40

Reference ID: 4499855

Table 21 represents a summary of the analytical assay for Study EN3319-302.

Table 21 Summary of analytical assay for Study EN3319-302

Parameter	
Analytical Report	3006204
Oxymorphone standard curve (observed % CV) NOTE: 0.02500, 0.05000, 0.125, 0.5000, 2.5000, 6.2500, 13.5000and 15.00ng/mL	2.1 - 8.2
6β-hydroxyoxymorphone standard curve (observed % CV) NOTE: 0.0200, 0.0400, 0.100, 0.400, 2.00, 5.00, 10.8, 12.0 ng/mL	1.4 - 5.3
Oxymorphone Interday Precision (% CV)	0.0750 ng/mL: 5.6% 0.750 ng/mL: 7.1% 1.50 ng/mL: 6.3% 4.80 ng/mL: 6.2% 12.0 ng/mL: 8.6%
Oxymorphone Interday Accuracy (% Bias)	0.0750 ng/mL: -2.3% 0.750 ng/mL: 2.7% 1.50 ng/mL: 1.3% 4.80 ng/mL: 6.5% 12.0 ng/mL: 5.0%
6β-hydroxyoxymorphone Interday Precision (% CV)	0.0600 ng/mL: 6.0% 0.600 ng/mL: 1.9% 1.20 ng/mL: 3.1% 3.84 ng/mL: 3.4% 9.60 ng/mL: 5.0%
6β-hydroxyoxymorphone Interday Accuracy (% Bias)	0.0600 ng/mL: 2.7% 0.600 ng/mL: 4.2% 1.20 ng/mL: 1.7% 3.84 ng/mL: 2.6% 9.60 ng/mL: -1.0%
Duration from Time Sample Was First Drawn to Date of Last Sample Analysis (Including ISR)	Date of 1st sample: 02-Oct-2012 Last assays: 27-Oct-2017 Samples stored ≤632 days
Actual Sample Storage Temperature	-70°C

Source: m2\27-clin-sum\summary-biopharm.pdf; p. 16/40

Validation Report NUMBER: V0905013.00 [(ANALYSIS OF OXYMORPHONE AND 6-β-HYDROXYOXYMORPHONE IN HUMAN PLASMA USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY WITH TANDEM MASS SPECTROMETRY (LC-MS/MS) Bioanalytical Method AP LC/MS/MS 374.100]

Reference ID: 4499855

The analytical method was validated in the range 0.02500/0.02500, 0.05000/0.05000, 0.1000/0.1000, 0.4000/0.4000, 1.000/1.000, 2.000/2.000, 5.000/5.000, 8.000/8.000 and 10.00/10.00 for oxymorphone/6-β-hydroxyoxymorphone. The analytes were quantitated using a solid phase extraction procedure, followed by injection onto an LC/MS/MS system. Linear regression, with 1/x2 weighting, was used to obtain the best fit of the data for the calibration curves. Quality control samples were 0.07500/0.07500, 0.7500/0.7500 and 7.500/7.500 ng/mL for oxymorphone/6-β-hydroxyoxymorphone. In addition, the stability of oxymorphone and 6-β-hydroxyoxymorphone in plasma during freeze-thaw cycles and at room temperature, extracted samples in the refrigerator and on bench top and long-term freezer stability at -70°C ±20°C was also studied.

The observed %CV for oxymorphone and 6-β-hydroxyoxymorphone standard curves range from 2.1 - 6.3 and 2.0 – 7.2%, respectively. The lower limit of quantification is 0.02500/0.02500 ng/mL for oxymorphone and 6-β-hydroxyoxymorphone, respectively.

The intra-day precision (%CV) of oxymorphone QC samples was within the range of 1.8 to 6.4% and the intra-day accuracy (%Bias) was within the range of -5.6 to 8.8%. The intra-day precision of 6-β-hydroxyoxymorphone QC samples was within the range of 1.5 to 5.8% and the intra-day accuracy (%Bias) was within the range of -2.3 to 4.6%. The inter-day precision of oxymorphone QC samples was within the range of 2.1 to 7.5% and the inter-day accuracy was within the range of -4.2 to -0.3%. For the 6-β-hydroxyoxymorphone QC samples, the inter-day precision was within the range of 1.9 to 4.3% and the accuracy ranged from -1.9 to 2.9%. For the room temperature stock solution stability (6-h sample compared to fresh stock solutions), the percent bias for oxymorphone was -1.1%. The percent bias for 6-β-hydroxyoxymorphone was 0.3%. For the refrigerated stock solution stability (4°C ±6°C for 21 days compared to fresh stock solutions), the percent bias for the refrigerated stock solution was -0.7% and 0.4% for oxymorphone and 6-β-hydroxyoxymorphone, respectively. For the freeze-thaw stability, the precision (%CV) and accuracy (%Bias) for all six (6) freeze-thaw cycles for oxymorphone compared to the nominal values was within 0.9 to 11.4% and -10.3 to 2.9%, respectively. The precision (%CV) and accuracy (%Bias) for the six (6) freeze-thaw cycles compared to the nominal values for 6-β-hydroxyoxymorphone was within 0.9 to 8.9% and -9.1 to 5.9%, respectively.

4.2 Information Requests

Timelines of Information Requests

1. Prior to the first team meeting, the cursory review of the submission identified that the information was needed regarding the comparison of oxymorphone Cmax and AUC values between the adult and pediatric populations. The following Information Request (IR) was sent to the Applicant to address this concern (DARRTS date 2/28/19):

Reference ID: 4499855

"#6. Observed pharmacokinetic (PK) parameters, and not dose-normalized PK parameters, are used for the purposes of demonstrating comparable systemic exposures between pediatric populations and adults as the basis for extrapolating efficacy. In addition to the already provided comparison tables of dose-normalized PK parameters (i.e., Cmax, AUC0-t, AUC0-inf) between pediatric patients and adults, provide comparison tables between pediatric and adult populations based on the observed PK parameters (i.e., without dose normalization). Refer to the example PK comparison table below and provide PK results for both single- and multiple-dose oxymorphone and 6β-hydroxyoxymorphone, as appropriate. In addition, propose a dosing regimen in each pediatric age group that will result in comparable PK exposure to the approved labeled dosing regimen in adults based on the analysis of observed PK parameters without dose-normalization."

Table Comparison of oxymorphone PK parameters after a single dose…pediatric and adult populations

Study	Pop.	Dose	Cmax (ng/mL)				AUC0-t (ng h/mL)				AUC0-inf			
			Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
-101	Adults	5 mg												
-010	>12 to 17 y Ped	5 mg												
		10 mg												
		15 mg												
-302	6 to <12 y Ped	0.05 mg/kg												
		0.1 mg/kg												
		0.2 mg/kg												
	2 to <6 y Ped	0.05 mg/kg												
		0.1 mg/kg												
		0.2 mg/kg												

Applicant's response dated 4/1/19 (Serial #0066):

The Applicant submitted single-dose PK parameter values that were not dose-normalized from Studies EN3319-101, EN3203-010, and, EN3319-302 for oxymorphone and 6ß-hydroxyoxymorphone (Table 18 and Table 19, respectively). The Applicant did not provide tables of multiple-dose PK parameter values for oxymorphone and 6β-hydroxyoxymorphone. The Applicant stated that "Of the 3 studies submitted in this supplement, multiple-dose PK parameter values were only calculated in Study EN3319-302 after Dose 1 and Dose 7. There were too few subjects remaining in the study at the time of Dose 7 to accurately calculate multiple-dose PK parameter values."

Reference ID: 4499855

Table 18: Comparison of Oxymorphone PK Parameters after a Single-Dose (note: all subjects-DL)

			C_{max} (ng/mL)				AUC_{0-t} (ng.h/mL)				AUC_{0-inf} (ng.h/mL)			
Study	**Pop.**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	Adults	5 mg	0.693	0.3371	0.221	1.883	3.945	1.6712	1.670	8.830	4.338	1.8591	2.010	9.210
EN3203-010	>12 to 17 y Ped	5 mg	1.243	1.2192	0.080	4.000	6.395	6.0752	1.180	20.960	7.632	6.6828	1.600	22.260
		10 mg	0.828	0.6892	0.040	1.960	3.766	2.2587	0.120	6.470	10.223	6.5195	6.160	17.740
		15 mg	5.295	10.6386	0.050	33.550	67.040	150.7979	3.300	467.260	109.294	257.5421	3.890	746.340
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.415	0.211	0.157	0.727	2.560	2	1.250	6.560	2.425	0.0516	2.390	2.460
		0.10 mg/kg	1.140	0.847	0.494	2.810	3.010	0.766	2.220	4.350	3.010	0.946	2.340	3.680
		0.20 mg/kg	1.330	0.772	0.455	2.430	5.320	4.53	0.137	12.900	6.920	4.02	3.690	11.400
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.330	0.217	0.106	0.622	1.690	0.943	0.759	3.690	3.220	1.56	2.120	4.320
		0.10 mg/kg	1.760	1.62	0.417	4.520	3.990	2.09	1.630	7.010	3.690	3.12	1.830	7.290
		0.20 mg/kg	3.160	1.65	1.180	5.600	9.370	5.81	2.690	17.300	14.300	5.01	10.800	17.900

Reference ID: 4499855

Table 19: Comparison of 6β-hydroxyoxymorphone PK Parameters after a Single-Dose (note: all subjects-DL)

			C_{max} (ng/mL)				AUC_{0-t} (ng h/mL)				AUC_{0-inf} (ng h/mL)			
Study	**Pop.**	**Dose**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
EN3203-101	Adults	5 mg	0.755	0.2907	0.317	1.358	4.847	2.3103	1.340	11.670	6.585	2.5028	3.170	11.050
EN3203-010	>12 to 17 y Ped	5 mg	0.314	0.2853	0.050	0.960	1.544	1.8794	0.280	5.270	4.987	7.5732	0.580	18.240
		10 mg	0.487	0.2853	0.160	1.020	3.040	1.1625	1.380	4.420	8.692	10.243	3.450	26.990
		15 mg	0.940	0.5212	0.300	1.870	7.354	3.3255	2.340	12.140	12.795	8.8385	4.150	34.410
EN3319-302	6 to ≤12 y Ped	0.05 mg/kg	0.104	0.0555	0.000	0.155	0.459	0.396	0.000	1.090	1.830	NA	1.830	1.830
		0.10 mg/kg	0.384	0.177	0.183	0.620	1.220	0.761	0.444	2.570	0.535	NA	0.535	0.535
		0.20 mg/kg	0.603	0.513	0.131	1.510	2.640	2.52	0.138	7.450	7.580	5.12	3.950	11.200
EN3319-302	2 to <6 y Ped	0.05 mg/kg	0.100	0.073	0.043	0.248	0.467	0.473	0.043	1.250	1.110	NA	1.110	1.110
		0.10 mg/kg	0.437	0.419	0.171	1.270	1.270	0.637	0.598	2.400	1.760	0.762	0.944	2.780
		0.20 mg/kg	0.587	0.182	0.353	0.797	2.260	1.07	0.330	3.580	2.760	0.399	2.470	3.040

The following statements were submitted by the Applicant:

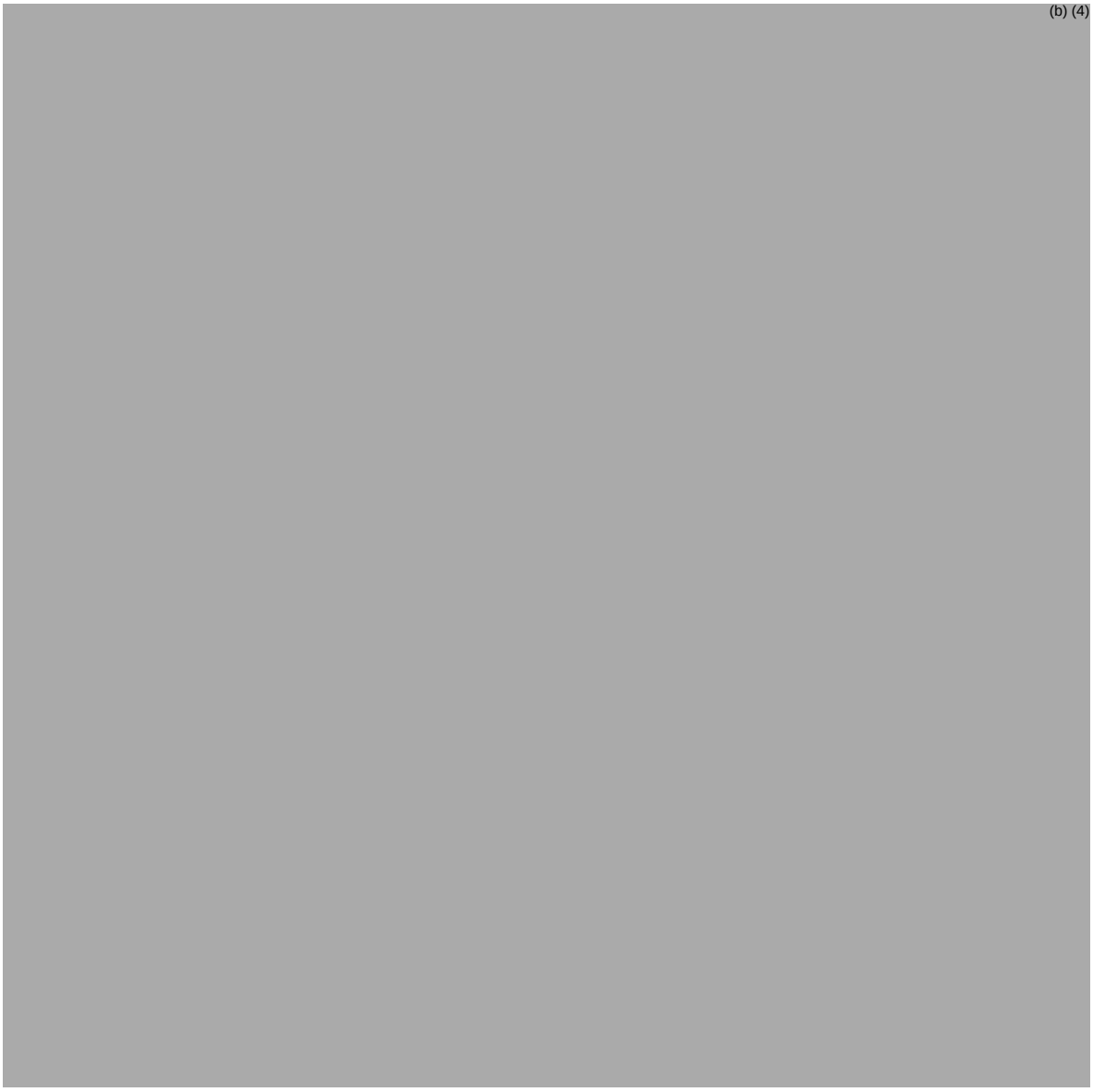
"The OPANA Prescribing Information recommends an initial dose in adults of 10 to 20 mg every 4 to 6 hours as needed for pain (OPANA Prescribing Information). At steady-state, this dosing regimen is expected to result in mean oxymorphone Cmax parameter values that range from 3.5-7.3 ng/mL and AUC parameter values that range from 10.2-21.1 ng·h/mL (OPANA Prescribing Information, and Table 20).

(b) (4)

As noted, multiple dose PK parameter values for oxymorphone were not generated in these studies; therefore, steady-state Cmax and AUC values were estimated from the single-dose PK parameter values. Based on pharmacokinetic principles, the AUC0-inf following a single dose will equal the steady-state AUC for that dose within any fixed dosing interval, (AUCτ), i.e., AUC0-inf = AUCτ. During multiple dosing at a fixed dosing rate, drugs will accumulate in the

body until steady-state is reached at which time no further accumulation will occur. The degree of accumulation is determined by the rate the drug is given relative to the half-life of the drug. The extent of accumulation from that of the initial dose can be quantitated as $1/(1-e^{-k\tau})$, where k= elimination rate constant, and is equal to 0.693/t1/2 and τ is the dose interval Rowland M and Tozer T 1995).

The mean half-life of oxymorphone across the three dose levels of 0.05, 0.1, and 0.2 mg/kg was approximately 5 hours (k= 0.1386 hr-1) for both the 2 to <6 and the 6 to <12-year-old age groups (Table 6 of EN3319-302 PK report). Therefore, administering oxymorphone every 5 h to pediatric patients ages 2 to <12-year-old, the Cmax for oxymorphone at steady-state is estimated to increase by approximately 100% from that following the first dose. For the >12 to 17-year-old age groups, we have assumed an oxymorphone t½ of 8 hours, which is similar to that in adults. Using the same approach that was used in the 2-<12-year-old age group, we estimate that the Cmax at steady-state will be approximately 150% higher than that after a single dose.



(b) (4)

Table 20: Mean (±SD) OPANA Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{1/2}$ (hr)
Single Dose	5 mg	1.10±0.55	4.48±2.07	7.25±4.40
	10 mg	1.93±0.75	9.10±3.40	7.78±3.58
	20 mg	4.39±1.72	20.07±5.80	9.43±3.36
Multiple Dose[a]	5 mg	1.73±0.62	4.63±1.49	NA
	10 mg	3.51±0.91	10.19±3.34	NA
	20 mg	7.33±2.93	21.10±7.59	NA

Source: OPANA IR Prescribing Information, Table 3
a Results after 5 days of every 6 hours dosing.
NA=Not applicable

A summary of the PK parameters of exposure (Cmax and AUC) of the proposed starting dose regimens (b) (4) is shown in Table 21.

Table 21: Summary of the Mean Cmax and AUC Parameters for the Initial Recommended Dosing Regimen of Oxymorphone (b) (4)

Age Group	Recommended Oral Oxymorphone Initial Dosing Regimen	Oxymorphone Steady-State PK Parameter Values	
		C_{max} (ng/mL)	AUC (ng·h/mL)
Adults	10-20 mg every 4-6 h	3.5-7.3 [a]	10.2-21.1[a]

(b) (4)

Source: OPANA IR Prescribing Information and Table 18
a OPANA IR Prescribing Information. Values are mean values for the 10 mg and 20 mg doses given every 6 h to adults

(b) (4)

6-β hydroxyoxymorphone Exposures

As requested by the Agency, the pharmacokinetic parameter values are presented in Table 19. Although 6-β hydroxyoxymorphone is believed to have analgesic activity (Smith HS, 2009), it is considered a minor metabolite of OPANA IR, representing less than 3% of the recovered dose in the urine of humans administered oxymorphone (Cone EJ, et al 1983). As a result, Endo does not believe the pharmacokinetics of this metabolite should contribute to the dosing recommendation in pediatric subjects."

2. After the receipt of the response a further IR was deemed necessary and the following IR was sent to the Applicant (dated 4/3/19):

"We acknowledge your submission on 4/1/19 to address Division's IR regarding observed PK parameters. Based on your submission, the observed Cmax and AUC values are higher in subjects from 12 to 17 years compared to adults at 5 mg dose level. It is possible that the higher exposure in 12 to 17 is driven by the subjects with lower body weight.

Provide individual PK parameters for oxymorphone and 6ß-hydroxyoxymorphone in the age group of 12 to 17 after single dose administration, and multiple dose administration (if applicable).

For each subject, include subject ID, administered dose (5, 10 or 15 mg), body weight, dose by body weight (mg/kg), and observed PK parameters (e.g. Cmax, AUC0-t, AUC 0-inf)."

Individual subject pharmacokinetic parameters for 12-17 years old Study EN3203-010

Subject ID	Dose (mg)	Body Weight (kg)	Dose by Body Weight (mg/kg)	Cmax	AUC0-t	AUC0-inf
	5					
	.					
	.					
	10					
	.					
	.					
	15					
	.					
	.					

Applicant's response dated 4/9/19 (Serial #0067):

The Applicant submitted the individual PK parameters and body weight information for the 12 to 17-year old subjects in study EN3203-010 (Tables 1 and 2 for oxymorphone and 6ß-hydroxyoxymorphone, respectively). The Applicant stated that "PK parameters are only available for the single dose cohort in this study."

Reference ID: 4499855

Table 1: Individual Oxymorphone PK Parameters in the Age Group of 12 to 17 Subjects after a Single Dose (note: all subjects-DL)

Subject ID	Dose (mg)	Body Weight (kg)	Dose by Body Weight (mg/kg)	C_{max}	AUC_{0-t}	AUC_{0-inf}
EN3203-010 (b) (6)	5	58.4	0.08562	4.00	20.96	22.262122
EN3203-010	5	66.7	0.07496	0.52	3.61	4.6704245
EN3203-010	5	65	0.07692	0.65	2.00	2.0760854
EN3203-010	5	80.5	0.06211	0.08	1.18	1.597359
EN3203-010	5	93.1	0.05371	0.35	2.96	3.5902727
EN3203-010	5	33.9	0.14749	1.84	6.92	6.9949329
EN3203-010	5	66.4	0.0753	0.52	4.04	5.6234958
EN3203-010	5	63.8	0.07837	1.41	6.14	7.4308224
EN3203-010	5	61.9	0.08078	1.83	9.74	14.441455
EN3203-010	10	79.4	0.12594	0.64	3.35	n/a
EN3203-010	10	74.8	0.13369	0.04	0.12	n/a
EN3203-010	10	58.9	0.16978	1.20	5.11	6.7678845
EN3203-010	10	70.7	0.14144	0.29	2.57	n/a
EN3203-010	10	51.9	0.19268	0.84	6.47	17.742911
EN3203-010	10	53	0.18868	1.96	4.98	6.1583119
EN3203-010	15	45.4	0.3304	0.98	16.64	23.109953
EN3203-010	15	85.4	0.17564	1.33	9.88	17.007165
EN3203-010	15	77.9	0.19255	2.59	24.77	26.115575
EN3203-010	15	81.8	0.18337	2.05	13.82	20.586492
EN3203-010	15	51.1	0.29354	1.97	7.59	28.604918
EN3203-010	15	88.4	0.16968	1.06	7.90	8.7005507
EN3203-010	15	53.4	0.2809	33.55	467.26	746.33646
EN3203-010	15	61.7	0.24311	3.64	52.21	n/a
EN3203-010	15	66	0.22727	0.49	3.30	3.8883495

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Table 2: Individual 6ß-hydroxyoxymorphone PK Parameters in the Age Group of 12 to 17 Subjects after a Single Dose (note: all subjects-DL)

Subject ID	Dose (mg)	Body Weight (kg)	Dose by Body Weight (mg/kg)	C_{max}	AUC_{0-t}	AUC_{0-inf}
EN3203-010-(b) (6)	5	58.4	0.08562	0.68	3.70	4.3834379
EN3203-010-	5	66.7	0.07496	0.11	0.30	n/a
EN3203-010-	5	65	0.07692	0.22	0.61	0.6945683
EN3203-010-	5	93.1	0.05371	0.05	0.38	0.5835374
EN3203-010-	5	33.9	0.14749	0.23	0.93	1.0364262
EN3203-010-	5	66.4	0.0753	0.16	0.89	n/a
EN3203-010-	5	63.8	0.07837	0.10	0.28	n/a
EN3203-010-	5	61.9	0.08078	0.96	5.27	18.239315
EN3203-010-	10	79.4	0.12594	0.41	2.80	3.4499515
EN3203-010-	10	99.3	0.1007	0.48	2.73	3.6886239
EN3203-010-	10	58.9	0.16978	0.45	2.56	4.7497164
EN3203-010-	10	70.7	0.14144	0.16	1.38	n/a
EN3203-010-	10	51.9	0.19268	0.40	4.42	26.988422
EN3203-010-	10	53	0.18868	1.02	4.35	4.5857692
EN3203-010-	15	45.4	0.3304	0.39	6.90	10.070795
EN3203-010-	15	85.4	0.17564	0.46	3.68	6.0670477
EN3203-010-	15	77.9	0.19255	1.07	10.87	12.676186
EN3203-010-	15	81.8	0.18337	0.77	6.79	15.930026
EN3203-010-	15	51.1	0.29354	0.98	4.99	9.0669585
EN3203-010-	15	88.4	0.16968	1.15	8.46	10.219902
EN3203-010-	15	53.4	0.2809	1.87	12.14	34.409251
EN3203-010-	15	61.7	0.24311	1.47	10.03	12.562123
EN3203-010-	15	66	0.22727	0.30	2.34	4.1538563

3. A follow up to the Applicant's 4/9/19 response regarding Subject EN3203-010-(b) (6) 15 mg oxymorphone dose, was sent on 4/23/19 (3RD IR)

"Reference is made to your response dated April 09, 2019 on the Agency's Information Request dated April 03, 2019. Based on the information submitted, Subject EN3203-010-(b) (6), 15 mg oxymorphone dose, had extremely high Cmax and AUC values, compared to other subjects. Provide discussion/explanation of this subject exhibiting such high Cmax and AUC values.

Applicant's response dated 5/17/19 (Serial #0071):

The Applicant sent in the following response (excerpt related to PK) regarding Subject EN3203-010-(b) (6)

"The pharmacokinetic (PK) data for the subject are summarized in Table 2, Table 3, and Table 4 below. As noted in Table 2 and Table 3, several samples at various time points required a reassay.

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The reasons for reassay and the reasons for the reported concentration used from each reassay are included in the tables. Table 4 summarizes the reported concentration of oxymorphone and 6-β-hydroxyoxymorphone for each time point.

Table 2: Summary of Repeat Analysis Data for Oxymorphone in Human Plasma (Subject (b) (6)

Time Point	Original Conc. (ng/mL)	Reason for Re-assay	Re-assay Conc. (ng/mL)	Reported Conc. (ng/mL)	Reason for Reported Conc.
Baseline	1.443	1	QNS, QNS, QNS	NR	8
4 Hours Post Dose	PC	4	2.544	2.544	6
8 Hours Post Dose	ALQ-17.23>(10.00)	6	33.55	33.55	9
12 Hours Post Dose	PC	4	PC	PC	4
24 Hours Post Dose	QNS	5	14.56	14.56	10

Source: EN3203-010 Bioanalytical Report, Table 7
Reasons for Reassay: 1) PIPD - Peak in pre-dose sample; 4) PC - Poor chromatography; 5) QNS - Quantity not sufficient; 6) ALQ - Above limit of quantitation
Reasons for Reported Concentration: 4) Poor chromatography confirmed; 6). Acceptable chromatography; 8) Not reportable,
QNS to repeat; 9) Value within range; 10) Sample successfully analyzed with dilution

Table 3: Summary of Repeat Analysis Data for 6-β-Hydroxyoxymorphone in Human Plasma (Subject (b) (6)

Time Point	**Original Conc. (ng/mL)**	**Reason for Reassay**	**Reassay Conc. (ng/mL)**	**Reported Conc. (ng/mL)**	**Reason for Reported Conc.**
24 Hours Post Dose	QNS	3	0.2640	0.2640	8

Source: EN3203-010 Bioanalytical Report, Table 8
Reasons for Reassay: 3) QNS - Quantity not sufficient
Reasons for Reported Concentration: 8) Sample successfully analyzed with dilution

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Table 4: Oxymorphone and 6-β-Hydroxyoxymorphone Concentration in Human Plasma (Subject [redacted] (b) (6))

Time Point	Oxymorphone Concentration (ng/mL)	6-β-Hydroxyoxymorphone Concentration (ng/mL)
Baseline	NR	0.000
2 Hours Post Dose	3.913	1.870
4 Hours Post Dose	2.544	1.370
8 Hours Post Dose	33.55	0.4681
12 Hours Post Dose	PC	0.1168
24 Hours Post Dose	14.56	0.2640

Source: EN3203-010 Bioanalytical Report, Table 11 and Table 12
NR=Not reportable; PC=Poor chromatography
Note: Values below the LLOQ (0.02500 ng/mL) are reported as 0.000.

We agree the subject had an extremely high observed oxymorphone concentration at the 8-hour time point and, to a lesser extent, at the 24-hour time point. The peak Cmax oxymorphone concentration for this subject occurred at 8 hours post-dose whereas the mean concentrations for the 5 mg, 10 mg, and 15 mg (excluding this subject) groups all had peak oxymorphone concentrations at the 2-hour time point.

Also of note, the 5 mg, 10 mg, and 15 mg (both including and excluding this subject) groups and the subject all had peak 6-β-hydroxyoxymorphone concentrations at the 2-hour time point. The subject also had the highest concentration of oxymorphone at the two other evaluable time points (2 hours and 4 hours post dose); however, these concentrations were more consistent with the 15 mg group mean values of 1.607 and 1.433 ng/mL, respectively.

There were no corresponding adverse event or safety signals observed in this subject concurrent with high levels of plasma oxymorphone concentrations at 8 hours and 24 hours post baseline. The subject's respiratory rate and pulse oximetry were normal throughout the study and while the systolic and diastolic blood pressures fluctuated between normal and low values, these changes were not considered clinically significant.

It is possible that the reported oxymorphone concentrations are anomalous for this subject; however, there is no supporting evidence for this conclusion in the bioanalytical report. Since the peak concentration was ALQ in the original assay and remained high in the reassay, these results were left as is in the study report so as not to bias the PK results. Of note, the 6-β-hydroxyoxymorphone concentration peaks at 2 hours post dose and decreases over the subsequent time points. These values do not correspond to the respective oxymorphone concentrations at those time points, as the concentration-time profile of this metabolite closely follows the parent drug in the observed data for the population as a whole.

The Agency previously requested Endo to propose dosing regimens for each pediatric age group studied (Question 6, Information Request dated February 28, 2019). Endo's response (dated April 1, 2019) [redacted] (b) (4) nd not based on the PK data from the 15 mg dose group in which Subject [redacted] (b) (6) was enrolled. Further to the Agency's request, the estimated Cmax and AUC values for this recommended dosing regimen are comparable to the steady-state Cmax and AUC values of 10

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mg to 20 mg oral doses of OPANA given every 6 hours as shown in the Prescribing Information for OPANA IR.

Endo has comprehensively analyzed all of the available data for subject (b) (6) The samples in question were reassayed due to various reasons outlined in Table 2 and Table 3, and the abnormally high values persisted. The subject experienced three mild adverse events all of which resolved and were not considered to be related to the study treatment. The subject had one slightly elevated hematology result at screening which was also determined to be not clinically significant. In addition, no safety signals were observed in vital signs data for this subject.

Furthermore, as this subject was part of the 15 mg dosing group, as stated above, these data were not utilized in the recommended dosing regimen which was based on data from the 5 mg and 10 mg dosing groups.

(b) (4)

4.3 Clinical PK and/or PD Assessments

4.3.1 Bioequivalence study EN3319-101

Applicant's SYNOPSIS:

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Finished Product: EN3319 (Oxymorphone Hydrochloride [HCl] Oral Solution)
Name of Active Ingredient: Oxymorphone HCl

Title of Study: An Open-Label, Randomized, Single-Dose, Two-Period, Two-Sequence Crossover Study to Determine the Relative Bioavailability and Pharmacokinetics of EN3319 Compared to OPANA® 5 mg in Healthy Adult Subjects Under Fasted Conditions
Principal Investigator: Kenneth C. Lasseter, MD
Study center(s): Clinical Pharmacology of Miami, Inc., 550 West 84th Street, Miami, FL 33014
Publications (reference): None

Objectives: To determine the relative bioavailability and pharmacokinetics of EN3319 (oxymorphone HCl oral solution 5 mL × 1 mg/mL) compared to OPANA (oxymorphone HCl) 5 mg tablet under fasted conditions

Methodology:

The study utilized an open-label, randomized, single-dose, 2-period, 2-sequence crossover design. Subjects were randomly assigned to receive 1 of 2 treatment sequences: a single 5 mL dose of EN3319 oxymorphone HCl oral solution (1 mg/mL) or OPANA was administered under fasted conditions with each dose of oxymorphone separated by at least a 7-day washout. The treatments were identified as follows:

- Treatment A: EN3319 oxymorphone HCl oral solution 5 mL × 1 mg/mL

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- Treatment B: OPANA 5 mg tablet

Subjects were confined to the study center beginning on the evening prior to dosing (Day -1) until the morning of Day 3 (48 hours post dose). Blood samples for pharmacokinetics were obtained through 48 hours post dose during each period.

End of study evaluations were conducted after the last blood collection on Day 3 of Period 2, or upon early discontinuation from the study.

Number of subjects (planned and analyzed):
Thirty (30) subjects were randomized to ensure that at least 26 subjects completed both study periods.
Planned: 30
Randomized: 30
Safety population: 30
Pharmacokinetic population: 29

Diagnosis and main criteria for inclusion:
Healthy, non-smoking male and female subjects, 18 to 45 years of age, inclusive, with a body mass index (BMI) $\geq$18.5 and $\leq$30.0 kg/m^2.
Test product, dose and mode of administration, lot number:
EN3319 – oxymorphone HCl oral solution 5 mL × 1 mg/mL; lot number 1039660

Duration of treatment:
Each subject received 2 single doses of oxymorphone with a 7-day washout between doses.
Reference therapy, dose and mode of administration, lot number:
OPANA 5 mg tablet, oral administration; lot number 401788NV

Criteria for evaluation:
Pharmacokinetics: Blood samples for pharmacokinetic assessment of oxymorphone and its active metabolite 6-hydroxy-oxymorphone (6-OH-oxymorphone) were obtained. The following parameters were determined for pharmacokinetics: C_{max}, T_{max}, λ_z, C_t, $t_{1/2}$, AUC_{0-t}, and $AUC_{0-\infty}$.
Safety: Safety parameters were monitored throughout the study by collection of adverse events (AEs), vital signs, clinical laboratory evaluations and physical examination.

Statistical methods:
Pharmacokinetic Analyses: All pharmacokinetic results (plasma concentrations and pharmacokinetic variables) were summarized by treatment (EN3319 and OPANA) using appropriate descriptive statistics. Log-transformation (natural log) of exposure measurements (AUC_{0-t}, $AUC_{0-\infty}$, C_{max} of oxymorphone and its metabolite) were performed prior to analysis. The relative bioavailability for the comparison (EN3319 versus OPANA) was derived from a linear mixed effects model with estimated relative bioavailability calculated based on the within subject variability. For each parameter, the analysis was performed based on the log-transformed data in the pharmacokinetic population. An antilog transformation was performed to obtain the final estimated relative bioavailability and the 90% confidence intervals (CI). The parameter, λ_z, was analyzed similarly to the exposure measures without log-transformation. The non-parametric Hodges Lehmann method was used to calculate the point estimates and 95% CIs for the median pair-wise differences of T_{max} values between treatments. Only descriptive statistics were performed for the parameter t½ and C_t.
Safety Analyses: The frequency of AEs was tabulated using the Medical Dictionary for Regulatory Activities (MedDRA, version 12) by system organ class (SOC), preferred terms and treatment. The maximum intensity and frequency of AEs were summarized by treatment.
Vital sign measurements and clinical laboratory evaluations were summarized using descriptive statistics or frequency distributions, as appropriate. Individual laboratory test results that were outside the normal range were flagged as high (H) or low (L).

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The pharmacokinetic profiles of EN3319 and OPANA were similar. The 90% confidence intervals for AUC and C_{max} were all contained within 0.80 and 1.25. A summary of the pharmacokinetic parameters (AUC and C_{max}) for oxymorphone and its metabolite, 6-OH-oxymorphone are presented below.

The plasma concentrations in some subjects at later time points were low or not detectable, therefore the elimination rate constant (λ_z) could not be estimated, and no estimates of half-life or $AUC_{0\text{-}inf}$ could be calculated.

PK Parameter (unit)	n	Mean (SD)	Geometric LS Mean	Ratio of Geometric LS Means	90% CI of the Ratios
Oxymorphone					
$AUC_{0\text{-}t}$ (ng•h/mL)					
EN3319	29	3.742 (1.4073)	3.4776	0.9598	0.9224, 0.9987
OPANA	29	3.945 (1.6712)	3.6234		
$AUC_{0\text{-}\infty}$ (ng•h/mL)					
EN3319	19	4.855 (1.4856)	4.2190	1.0483	0.9753, 1.1268
OPANA	21	4.338 (1.8591)	4.0244		
C_{max} (ng/mL)					
EN3319	29	0.6699 (0.28186)	0.6050	0.9695	0.8723, 1.0776
OPANA	29	0.6932 (0.33706)	0.6241		
6-OH-oxymorphone					
$AUC_{0\text{-}t}$ (ng•h/mL)					
EN3319	29	4.554 (2.2900)	3.9856	0.9205	0.8661, 0.9784
OPANA	29	4.847 (2.3103)	4.3296		
$AUC_{0\text{-}\infty}$ (ng•h/mL)					
EN3319	13	6.246 (1.7754)	5.9284	0.9375	0.8128, 1.0812
OPANA	15	6.585 (2.5028)	6.3237		
C_{max} (ng/mL)					
EN3319	29	0.7096 (0.39076)	0.6306	0.9017	0.8182, 0.9937
OPANA	29	0.7547 (0.29069)	0.6993		

LS Means for AUC0-t, AUC0–∞ and Cmax are on the natural logarithm scale.
Point estimates and 90% CIs for differences on the natural log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale.

NOTE: Listing 16.2.3.1 Subjects Excluded from Pharmacokinetic Population

Subject Number	Randomization Number	Sequence [a]	Reason(s) for Exclusion
[redacted]	(b) (6)	BA	Subject did not meet PK Dosing Criteria

Source:
[a] A = EN3319: Oxymorphone HCL Oral Solution 5 mL x 1 mg/mL; B = OPANA: Oxymorphone HCL Oral 5 mg tablets
Program: l_pkexcl.sas Output: l_pkexcl rtf

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SAFETY RESULTS:
EN3319 was generally well tolerated and there were no clinically significant safety findings after single dose administrations. Of the 30 subjects who received study medication, 6 subjects (20%) reported at least 1 treatment-emergent AE (TEAE) during the study. Of these TEAEs, the most frequently reported events were observed in the SOCs of nervous system disorders (16.7%), gastrointestinal disorders (3.3%), infections and infestations (3.3%), and skin and subcutaneous tissue disorders (3.3%). Overall, dizziness and headache (6.7%) were the most frequently reported TEAEs. Five (5) subjects (16.7%) reported at least 1 treatment-related, TEAE following drug administration. The most frequently reported treatment-related TEAEs were dizziness (6.7%) and headache (6.7%). The majority of the reported TEAEs were considered mild in nature by the investigator. A reported event of herpes zoster was noted as moderate in intensity. No TEAEs were reported as severe in intensity.
No deaths or SAEs were reported in this study. One (1) subject (Subject 0026) was discontinued prior to Period 2 because of the AE, herpes zoster. This subject did receive a single dose of OPANA 5 mg in Period 1.
No clinically meaningful changes were noted for clinical laboratory tests, vital sign measurements, or electrocardiogram results.

CONCLUSION:
(b) (4) The relative bioavailability and pharmacokinetics of EN3319 was similar to OPANA 5 mg tablets in healthy adult subjects under fasted conditions.
Date of the Report: 24-Jan-2011

Reviewer comments: There are no issues identified with the Applicant's synopsis report.

Additional information pertinent from the main study report:

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Name and Address of Investigator	**Clinical Study Unit**
Kenneth C. Lasseter, MD Clinical Pharmacology of Miami, Inc. 550 West 84th Street Miami, FL 33014	Clinical Pharmacology of Miami, Inc. 550 West 84th Street Miami, FL 33014
Sponsor	**Endo Study Authors**
Endo Pharmaceuticals Inc. 100 Endo Boulevard Chadds Ford, PA 19317	Irma Benedek, PhD Steve Xiang, PhD William Fiske, PhD
Statistical Analysis of Data	**Clinical Supply Management**
Endo Pharmaceuticals Inc. 100 Endo Boulevard Chadds Ford, PA 19317	(b) (4)
Facility for Bioanalytical and Pharmacokinetic Analyses	**Facility for Analysis of Clinical Laboratory Samples**

(b) (4)

Rationale for the Study

OPANA is currently available as 5 and 10 mg tablets and as an injection (1 mg/mL). In order to fulfill the OPANA Pediatric Research Equity Act (PREA) post marketing commitment an age appropriate formulation of OPANA is required to conduct the clinical pediatric program in ages 0 to 12 years old.

EN3319 is a new oxymorphone IR liquid formulation that is being developed for oral administration. The bioavailability and pharmacokinetics of this formulation are currently unknown. In order to characterize the bioavailability, pharmacokinetics and safety profile relative to OPANA, EN3319 will be assessed in the healthy adult population prior to use in the pediatric program.

Schedule of Study Assessment

Table 2: Schedule of Study Assessments

	Screening (Day -21 to Day -2)	Study Period (1 and 2)																	
			Day 1 (hours relative to oxymorphone administration)														Day 2		Day 3
		Day -1[a]	0	0.25	0.5	0.75	1	1.5	2	3	4	5	6	8	10	14	18	24	36	48
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Medical/Medication History	X	X[b]																	
Complete Physical Examination	X																		X[c]
Brief Physical Assessment		X																	
Body Weight and Height	X																		
HIV/Hepatitis Screen	X																		
Screen for Substances of Abuse	X	X																	
Clinical Laboratory Tests	X	X[b]																	X[c]
Pregnancy Tests[d] (Females)	X	X																	X[c]
12-Lead Electrocardiogram	X																		
Vital Sign Measurements[e]	X	X	X		X		X		X		X			X			X	X	X
Oxymorphone Administration			X																
PK Sample Collection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Concomitant Medications		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Confinement Research		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→

[a]Results of Day -1 assessments were reviewed by the investigator and the subject deemed eligible to participate or continue in the study prior to receipt of study medication
[b]Conducted at Study Period 1 only
[c]Conducted at Study Period 2, Day 3 of early discontinuation
[d]Serum pregnancy at screen, check-in Day -1, Periods 1 and 2, Period 2 Day 3 and early discontinuation
[e]Blood pressure, pulse, respiration rate and oral body temperature at Screening and Day -1 (both periods); blood pressure, pulse and respiration rate at all other time points
HIV=Human immunodeficiency virus; PK=Pharmacokinetic

9.4.1. Inclusion Criteria

Subjects were included in the study if they:

1. Were informed of the nature and risks of the study and provided written informed consent
2. Were healthy males or females between 18 to 45 years of age, inclusive

a. If female, were practicing abstinence or using a medically acceptable form of contraception (eg, intrauterine device, hormonal birth control, or double barrier method) for at least 1 month prior to

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screening. For the purpose of this study, all females were considered be of childbearing potential unless they had been postmenopausal, biologically sterile, or surgically sterile (ie, hysterectomy, bilateral oophorectomy, or tubal ligation) for more than 1 year
b. Had a negative serum pregnancy test at screening and check-in of each study period
3. Had a body mass index (BMI) ≥18.5 and ≤30.0 kg/m2
4. Were non-smokers (defined as not having smoked or used nicotine-containing products on a regular daily or casual basis for at least 6 months prior to screening and throughout the study)
5. Had no significant diseases in the medical history or evidence of clinically significant findings on physical examination, vital signs, clinical laboratory evaluations (hematology, serum chemistries, urinalysis) or 12-lead electrocardiogram (ECG)
6. Were able to communicate effectively with study personnel and understand and comply with all study requirements.

9.4.2. Exclusion Criteria
Subjects were not enrolled into the study if any of the following exclusion criteria applied:
1. Known hypersensitivity or allergy to oxymorphone or other opioids
2. Women who were pregnant or lactating
3. Any disease or condition (medical or surgical) that might compromise the cardiovascular, hematological, renal, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, or gastrointestinal (including gastric ulcer) systems or other conditions that might interfere with the absorption, distribution, metabolism, or excretion of the study medication or would place the subject at increased risk unless deemed not clinically significant jointly by the investigator and sponsor
4. Elevated AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (γ glutamyl transferase), alkaline phosphatase, bilirubin, BUN (blood urea nitrogen), creatinine levels (>15% above the upper limit of normal reference range of the reporting laboratory); or hemoglobin level or hematocrit level below the lower limit of normal values (>15% below the lower limit of the normal reference range of the reporting laboratory), unless jointly deemed not clinically significant by the investigator and sponsor; increased bilirubin levels resulting from a known history or clinical evidence of Gilbert's syndrome did not exclude subjects
5. Positive screen for Hepatitis B Surface Antigen (HBsAg), Hepatitis C Antibody (anti HCV), or human immunodeficiency virus (HIV) antibody and/or antigen 6. Participated in the treatment phase of a clinical study or received an investigational drug within 30 days prior to the first oxymorphone dose (Period 1, Day 1); for investigational drugs with an elimination half-life greater than 15 days, this time period was extended to 60 days
7. Use of any medication (prescription or over-the-counter [OTC], such as antacids, multivitamins, aspirin, herbal preparations, and nutritional supplements) within 14 days prior to the first oxymorphone dose, unless jointly approved by the investigator and sponsor; prescribed hormonal contraceptives were allowed
8. Use of a drug therapy known to induce or inhibit hepatic drug metabolism within 30 days prior to the first oxymorphone dose
9. A positive screen for substances of abuse
10. Recent history (ie, within 2 years) of alcohol abuse , illicit drug use, or significant mental illness
11. History of difficulty with phlebotomy procedures
12. Donated blood (>400 mL) or blood products within 30 days prior to the first oxymorphone dose
13. Febrile illness within 6 days of Period 1, Day -1
14. Involvement in the planning and/or conduct of the study (applied to both, Endo staff or staff, at the investigational site).

Table 3: Treatment Assignment

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Sequence	Period 1	Period 2	Number of Subjects
1	A	B	15
2	B	A	15

A=EN3319 5 mL × 1 mg/mL (investigational product); B=OPANA 5 mg oral tablets (reference product)

9.7.1 Blood Sample Collection

Pharmacokinetic assessments for oxymorphone and its active metabolite, 6-OH-oxymorphone, were performed for all randomized subjects in the study. Samples of venous blood were obtained in 7 mL K2 EDTA tubes at time 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 14, 18, 24, 36, and 48 hours after each oxymorphone administration. A total 252 mL of blood for plasma pharmacokinetics was obtained from each subject during the study.

Immediately after blood collection, the tube was gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction was separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at approximately 1500 × g. The plasma fraction was withdrawn by pipette and divided into 2 polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All sample collection and freezing tubes were clearly labeled to identify the study, subject, study period and collection time. Labels were fixed to freezing tubes in a manner that prevented the label from detaching after freezing. All plasma samples were placed into a freezer at -70°C or below within 1 hour after collection.

9.7.2. Sample Storage and Shipment

All plasma samples were stored frozen (at -70°C or below) until they were shipped to the analytical facility. Prior to shipping, the samples were packed into thermal insulated containers with sufficient dry ice to assure they remained frozen, and were protected from breakage during shipment. Samples were shipped by overnight, priority courier with documentation to identify the samples. The samples were divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment was processed and shipped.

9.7.3. Analytical Methodology

A simultaneous, validated liquid chromatography-tandem mass spectrophotometry (LC-MS/MS) method was used for the determination of concentrations of oxymorphone and 6-OHoxymorphone from the plasma samples. The analytical report including method validation and description is provided in Appendix 16.1.10.

9.10. Statistical Methodology

Pharmacokinetics and statistical analyses were performed by Endo Pharmaceuticals, Inc. All data collected on the CRFs or electronically transferred to Endo Pharmaceuticals is presented in the data listings.

All statistical analyses including the estimation of pharmacokinetic variables were performed using SAS® (version 9.1 or higher). All pharmacokinetic results were summarized using descriptive statistics.

9.10.1. Determination of Sample Size

A total of 30 subjects were randomized to ensure that 26 subjects completed the study. An assumed intra-subject coefficient of variation of 21% for EN3319 and reference product (OPANA 5 mg) in this study and the expected ratio of means between the 2 treatment groups is 0.95, a sample size of 26 subjects for this study provided at least 90% power to show the 90% confidence intervals (CIs) of geometric mean ratio (EN3319/reference) in pharmacokinetic parameters fall within the limits of 0.8 and 1.25.

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9.10.6. Handling of Missing Values

Plasma concentrations below the limit of quantification (BLQ) were set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations were set to missing. For the computation of pharmacokinetic variables, the BLQ concentrations prior to the first measurable concentration were set to zero and other BLQ concentrations were set to missing. Plasma concentrations that were missing were treated as if they were never drawn. No imputation was performed for the demographic and safety data.

10.1. Disposition of Subjects

Table 5: Subject Disposition

Category	**Overall (N=30) n (%)**
Total Number of Subjects	
Randomized	30
Completed	29 (96.7)
Discontinued	1 (3.3)
Study Population[a]	
Safety	30 (100.0)
PK	29 (96.7)
Reason for Discontinuation	
Adverse Event	1 (3.3)

Table 6: Demographic and Baseline Characteristics by Treatment – Safety Population

Category	**EN3319 (N=29)**	**OPANA (N=30)**	**Overall (N=30)**
Age (years)			
N	29	30	30
Mean (SD)	37.0 (5.90)	37.2 (5.94)	37.2 (5.94)
Median	38.0	38.0	38.0
Min, Max	23, 45	23, 45	23, 45
Gender, n (%)			
Male	19 (65.5)	20 (66.7)	20 (66.7)
Female	10 (34.5)	10 (33.3)	10 (33.3)
Ethnicity, n (%)			
Hispanic	25 (86.2)	26 (86.7)	26 (86.7)
Non – Hispanic	4 (13.8)	4 (13.3)	4 (13.3)
Race, n (%)			
White	26 (89.7)	27 (90.0)	27 (90.0)
Black or African American	3 (10.3)	3 (10.0)	3 (10.0)
Weight (kg)			

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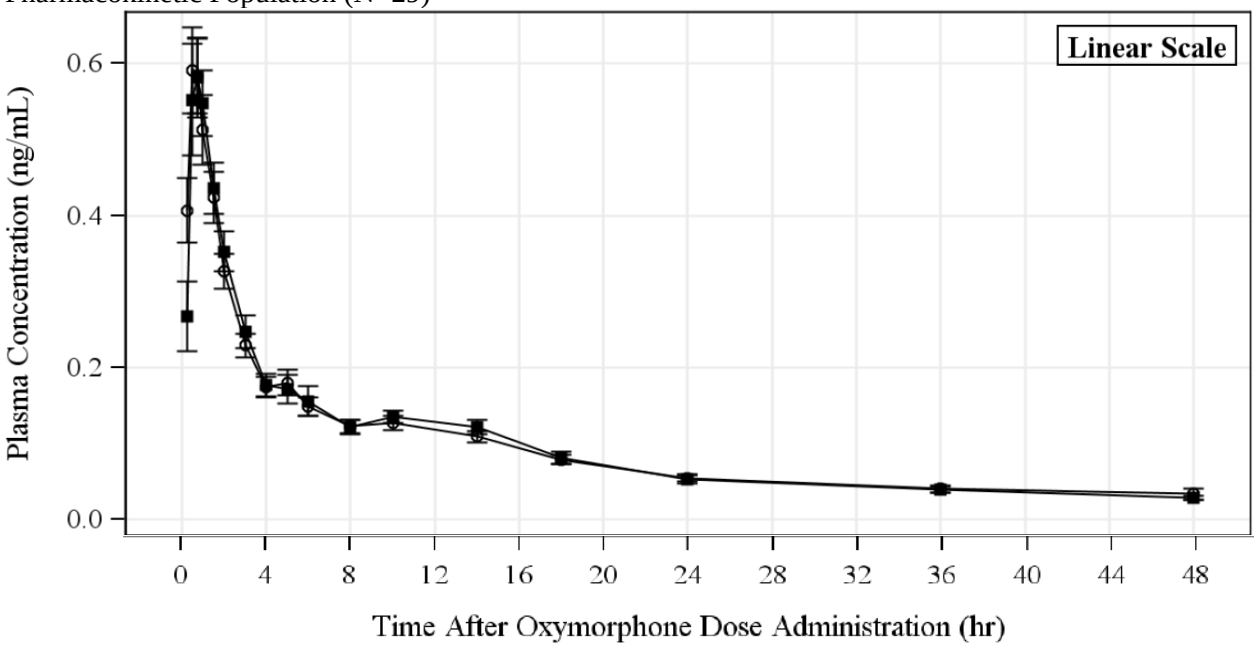
N	29	30	30
Mean (SD)	76.31 (12.807)	76.19 (12.601)	76.19 (12.601)
Median	79.00	78.20	78.20
Min, Max	49.6, 102.8	49.6, 102.8	49.6, 102.8
Height (cm)			
N	29	30	30
Mean (SD)	167.86 (10.409)	167.87 (10.228)	167.87 (10.228)
Median	169.00	168.50	168.50
Min, Max	146.0, 191.0	146.0, 191.0	146.0, 191.0
BMI (kg/m^2)			
N	29	30	30
Mean (SD)	26.93 (2.540)	26.89 (2.505)	26.89 (2.505)
Median	27.36	27.19	27.19
Min, Max	20.1, 30.0	20.1, 30.0	20.1, 30.0

Data Source: Table 14.1.3
EN3319: Oxymorphone HCl Oral Solution 5 mL ×1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: Percentages are based on the number of subjects in each group (N).
BMI=Body mass index; n=Number of Observations; SD=Standard deviation

Figure 2: Mean (±SE) Plasma Concentration of Oxymorphone (ng/mL) Versus Time by Treatment – Pharmacokinetic Population (N=29)



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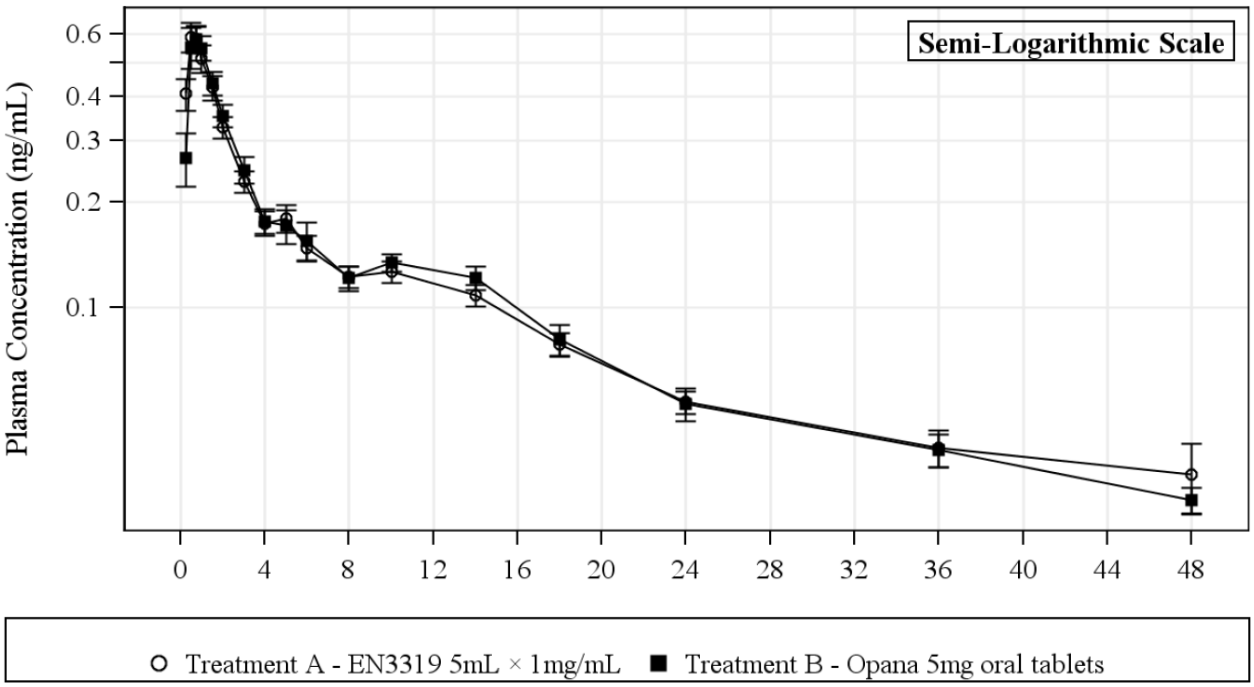

Data Source: Figure 14.2.1

Table 7: Summary of Plasma Pharmacokinetic Parameters of Oxymorphone by Treatment – Pharmacokinetic Population

Category	**EN3319 (N=29)**	**OPANA (N=29)**
AUC_{0-t} (ng·h/mL)		
N	29	29
Mean (SD)	3.742 (1.4073)	3.945 (1.6712)
CV (%)	37.6094	42.3586
AUC_{0-inf} (ng·h/mL)		
N	19	21
Mean (SD)	4.855 (1.4856)	4.338 (1.8591)
CV (%)	30.5973	42.8576
C_{max} (ng/mL)		
N	29	29
Mean (SD)	0.6699 (0.28186)	0.6932 (0.33706)
CV (%)	42.07279	48.62594
T_{max} (hours)		
N	29	29
Median	0.75	0.75
Min, Max	0.3, 5.0	0.3, 6.0
C_t (ng/mL)		
N	29	29

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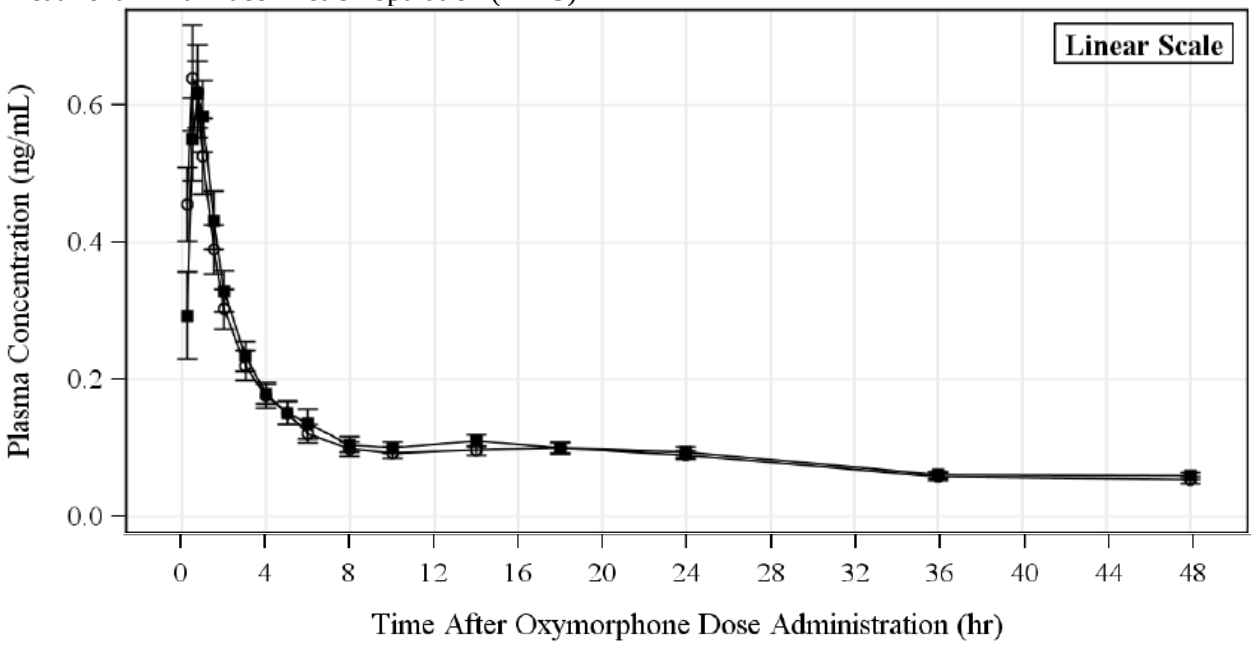
Mean (SD)	0.0407 (0.01584)	0.0335 (0.00679)
CV (%)	38.88291	20.25588
λ_z (1/h)		
N	19	21
Mean (SD)	0.0797 (0.03025)	0.0956 (0.03240)
CV (%)	37.93636	33.89050
$t_{1/2}$ (hours)		
N	19	21
Mean (SD)	10.06 (3.943)	8.12 (2.952)
CV (%)	39.196	36.350

Data Source: Table 14.2.3.1
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: $AUC_{0\text{-inf}}$, λ_z, and t½ for a period are missing if plasma concentration data were not suitable for λ_z estimation.
N=Number of subjects; n=Number of observations; SD=Standard deviation; CV=Coefficient of variation

11.7. Plasma Concentration and Pharmacokinetic Results for 6-Hydroxyoxymorphone

Figure 3 Mean (±SE) Plasma Concentration of 6-Hydroxy-oxymorphone (ng/mL) Versus Time by Treatment – Pharmacokinetic Population (N=29)



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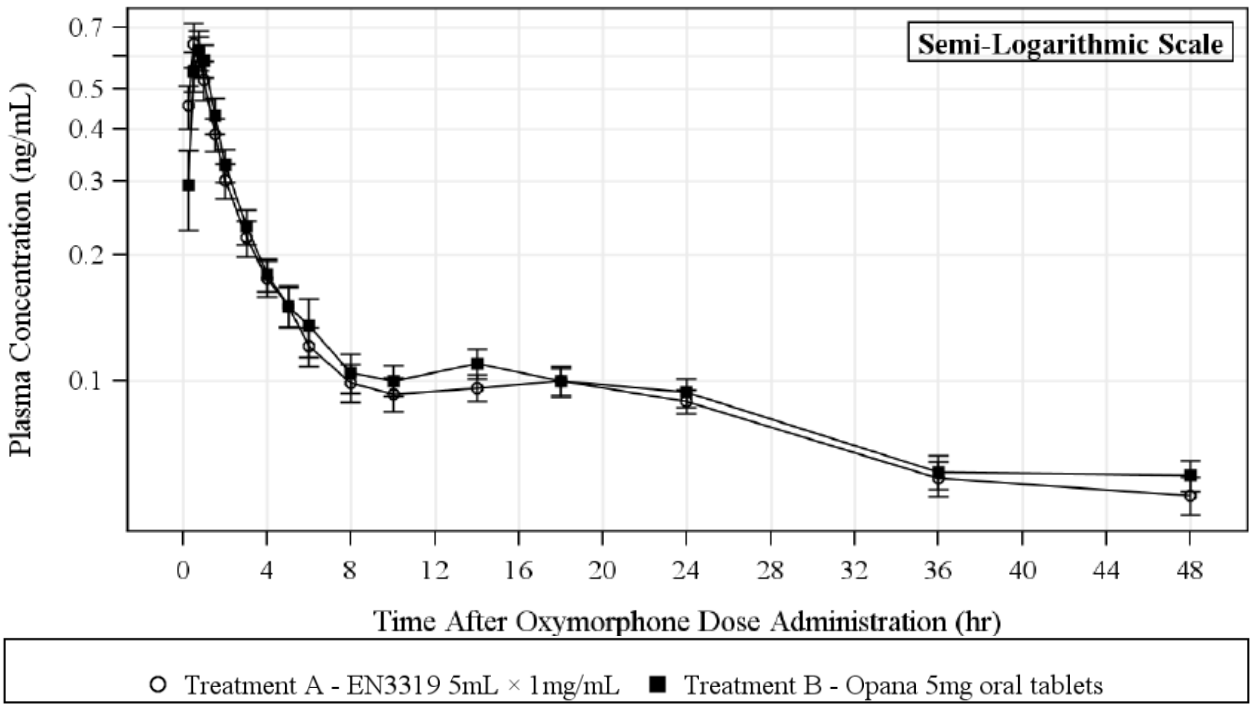

Data Source: Figure 14.2.2

Table 9: Plasma Pharmacokinetic Parameters of 6-Hydroxy-oxymorphone by Treatment

Category	**EN3319 (N=29)**	**OPANA (N=29)**
AUC_{0-t} (ng·h/mL)		
N	29	29
Mean (SD)	4.554 (2.2900)	4.847 (2.3103)
CV (%)	50.2822	47.6601
AUC_{0-inf} (ng·h/mL)		
N	13	15
Mean (SD)	6.246 (1.7754)	6.585 (2.5028)
CV (%)	28.4237	38.0092
C_{max} (ng/mL)		
N	29	29
Mean (SD)	0.7096 (0.39076)	0.7547 (0.29069)
CV (%)	55.06811	38.51526
T_{max} (hours)		
N	29	29
Median	0.50	0.75
Min, Max	0.3, 1.5	0.3, 1.5
C_t (ng/mL)		
N	29	29
Mean (SD)	0.0490 (0.02334)	0.0497 (0.02056)

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CV (%)	47.60986	41.40163
λ_z (1/h)		
N	13	15
Mean (SD)	0.0357 (0.00989)	0.0387 (0.01271)
CV (%)	27.70116	32.83724
$t_{1/2}$ (hours)		
N	13	15
Mean (SD)	21.03 (6.597)	19.61 (5.824)
CV (%)	31.365	29.705

Data Source: Table 14.2.3.2
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: AUC0-inf, λz, and t½ for a period are missing if plasma concentration data were not suitable for λz estimation.
N=Number of subjects; n=Number of observations; SD=Standard deviation; CV=Coefficient of variation

Table 10: Analysis of Plasma Pharmacokinetic Parameters of 6-Hydroxy-oxymorphone

Parameter (unit)	**Treatment[a]**	**n**	**LS Means[b]**	**Difference of LS Means (A-B)**	**Geometric LS Means**	**Ratio of Geometric LS Means (A/B)**	**90% CI of the Ratio (A/B)**	
							Lower	**Upper**
AUC_{0-t} (ng·h/mL)	A	29	1.3827	--	3.9856	0.9205	0.8661	0.9784
	B	29	1.4655		4.3296			
AUC_{0-inf} (ng·h/mL)	A	13	1.7798	--	5.9284	0.9375	0.8128	1.0812
	B	15	1.8443		6.3237			
C_{max} (ng/mL)	A	29	-0.4611	--	0.6306	0.9017	0.8182	0.9937
	B	29	-0.3576		0.6993			

Data Source: Table 14.2.5.2
[a] A = EN3319: Oxymorphone HCL Oral Solution 5 mL × 1 mg/mL; B = OPANA: Oxymorphone HCL Oral 5 mg tablets
[b] LS means for AUC_{0-t}, AUC_{0-inf}, and C_{max} are on the logarithm scale; LS means for λ_z is on the original scale.
Note: A linear mixed effects model was performed on λz and the natural logarithms of AUC_{0-t}, AUC_{0-inf}, and C_{max}. The model included sequence, period and treatment as fixed
effects and subject nested within sequence as a random factor. Point estimates and 90% confidence intervals (CI) for differences on the log scale were exponentiated to obtain
estimates for ratios of geometric means and 90% CIs of the ratios on the original scale. AUC_{0-inf} and λ_z for a period are missing if plasma concentration data were not suitable for λ_z
estimation.
n=Number of observations per treatment. Subjects who completed the study and were PK evaluable throughout will have 2 observations per treatment.

Table 11: Summary of Treatment-Emergent Adverse Events by Treatment – Safety Population

Category	**EN3319 (N=29) n (%)**	**OPANA (N=30) n (%)**	**Overall (N=30) n (%)**
Number of subjects with at least one adverse event	4 (13.8)	4 (13.3)	6 (20.0)
Nervous system disorders	3 (10.3)	3 (10.0)	5 (16.7)
Dizziness	1 (3.4)	2 (6.7)	2 (6.7)
Headache	1 (3.4)	1 (3.3)	2 (6.7)
Somnolence	1 (3.4)	0	1 (3.3)

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Gastrointestinal disorders	1 (3.4)	0	1 (3.3)
Dry mouth	1 (3.4)	0	1 (3.3)
Infections and infestations	0	1 (3.3)	1 (3.3)
Herpes zoster	0	1 (3.3)	1 (3.3)
Skin and subcutaneous tissue disorders	1 (3.4)	0	1 (3.3)
Rash	1 (3.4)	0	1 (3.3)

Data Source: Table 14.3.1.1
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events (n). Percentages are based on the number of subjects in each treatment group (N). Adverse events were coded by System Organ Class and Preferred Term using MedDRA, Version 12.

Table 12: Summary of Treatment-Related, Treatment-Emergent Adverse Events by Treatment – Safety Population

Category	**EN3319 (N=29) n (%)**	**OPANA (N=30) n (%)**	**Overall (N=30) n (%)**
Number of subjects with at least one adverse event	4 (13.8)	3 (10.0)	5 (16.7)
Nervous system disorders	3 (10.3)	3 (10.0)	5 (16.7)
Dizziness	1 (3.4)	2 (6.7)	2 (6.7)
Headache	1 (3.4)	1 (3.3)	2 (6.7)
Somnolence	1 (3.4)	0	1 (3.3)
Gastrointestinal disorders	1 (3.4)	0	1 (3.3)
Dry mouth	1 (3.4)	0	1 (3.3)
Skin and subcutaneous tissue disorders	1 (3.4)	0	1 (3.3)
Rash	1 (3.4)	0	1 (3.3)

Data Source: Table 14.3.1.2
EN3319: Oxymorphone HCl Oral Solution 5 mL × 1 mg/mL; OPANA: Oxymorphone HCl Oral 5 mg tablets
Note: A treatment-related adverse event is defined as an adverse event that is possibly or probably related to study drug. At each level of subject summarization, a subject is counted once if the subject reported one or more events (n). Percentages are based on the number of subjects in each treatment group (N). Adverse events were coded by System Organ Class and Preferred Term using MedDRA, Version 12.

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4.3.2 Phase 3 study EN3203-010

Applicant's SYNOPSIS:

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Finished Product: Oxymorphone HCl tablet
Name of Active Ingredient: Oxymorphone HCl

Reference ID: 4499855

Title of Study: 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

Phase of Development: Phase 3
Principal Investigator: Multicenter
Investigators: 10 investigators, all of whom enrolled subjects
Study Center(s): 10 centers in the United States
Publications (Reference): None
Studied Period (Years): Date first patient enrolled: 17-Feb-2009; Date last patient completed: 18-Apr-2011

Objectives:
Primary:
Single-Dose Period: To determine the safety of oxymorphone immediate release (IR) in children aged >12 to 17 years requiring an opioid to treat their acute postoperative pain of various etiologies.
Multiple-Dose Period: To determine the effectiveness/clinical utility of oxymorphone IR in this subject population.
Secondary:
To determine the pharmacokinetic profile of oxymorphone IR in this subject population;
To determine the appropriate dosing recommendations for oxymorphone IR in this subject population.

Methodology: This open-label, 2-part, ascending-dose, multicenter study was designed to gain experience with a classic, single-dose and multiple-dose postoperative treatment paradigm utilizing oxymorphone IR tablets in >12 to 17-year-old subjects (administrative change) with postoperative pain requiring an opioid. The original planned age group was 6 to 17. However, no subjects had been enrolled into the study prior to the administrative change. An external Data Safety Monitoring Board (DSMB) reviewed all individual and aggregate safety, effectiveness, and pharmacokinetic data prior to dose escalation within each study period. This study was conducted to fulfill a post-marketing commitment.

Single-Dose Period
Three (3) doses of oxymorphone IR were to be studied in ascending fashion (in stepwise order, based on the previous groups' demonstrated safety and tolerability): 5 mg, 10 mg, and 15 mg. The first group of subjects was to be given a single dose of oxymorphone IR 5 mg. With acceptable safety (as reviewed by the DSMB), the next group of subjects was to be dosed with oxymorphone IR 10 mg. If the 10-mg group demonstrated acceptable safety and tolerability, then the final group of subjects was to be administered oxymorphone IR 15 mg. If needed, rescue analgesia was available according to standard of care (SOC) at each institution. (Note: At least 8 evaluable subjects were required at each dose level for the assessment of safety and pharmacokinetics and subsequent determination of dose escalation.)

Study assessments occurred at the screening visit within 14 days of surgery, baseline (within 30 hours after surgery), and 15 and 30 minutes, 1, 2, 3, 4, 6, 8, and 12 hours after the dose. An end of study evaluation was to occur 24 hours after the dose or early termination.

Multiple-Dose Period
Up to 3 doses of oxymorphone were to be studied in ascending fashion (in stepwise order, based on previous groups' demonstrated safety/tolerability and effectiveness). Doses used in the multiple-dose period were determined from the results of the single-dose period (Note: 5 mg, 10 mg, and 15 mg). Following postoperative parenteral analgesia, when oral dosing commenced according to each institution's SOC (within 30 hours post-surgery), dosing was to begin at the lowest dose selected from the single-dose period. Subjects were to be dosed every 4 to 6 hours (*no sooner than every 4 hours and no*

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later than every 6 hours) *for up to 48 hours*. Subjects could receive rescue medication and discontinued in the event that the study medication did not continue to provide adequate pain relief. Dose escalation to the second and third higher doses was to commence once safety and effectiveness (as reviewed by the DSMB) had been determined at the lower dose. (Note: At least 8 evaluable subjects were to be required each dose level for the assessment of safety, effectiveness, and pharmacokinetics and subsequent determination of dose escalation.)

Study assessments occurred at the screening visit within 14 days of surgery, baseline (within 30 hours after surgery), and 15 and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 24, 28, 32, and 36 hours after the first dose. An end of study evaluation was to occur 48 hours after the first dose or early termination.

(Note: 9.4.4. Selection of Doses in the Study
The initial oxymorphone IR dose in the single-dose period was *chosen based on an established equivalent morphine dose (0.3 mg/kg by mouth every 3-4 hours) in children being treated for acute pain*. Due to the limitation of oral tablet dosing in this study, dosing based on a mg/kg basis could not be accomplished; however, dosing began at the lowest equivalent dose of oxymorphone IR (5 mg, which is equivalent to 0.1 mg/kg for a 50-kg child). The doses of 5 mg, 10 mg, and 15 mg used in the multiple-dose period were determined from the results of the single-dose period.)

Number of Patients (Planned and Analyzed):
Planned: 48 subjects total
Safety population: 58 subjects total (13 received 5-mg single dose, 9 received 10-mg single dose, 11 received 15-mg single dose, 9 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)
Pharmacokinetic population: 52 subjects total (11 received 5-mg single dose, 8 received 10-mg single dose, 9 received 15-mg single dose, 8 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)
ITT Population: 58 subjects total (13 received 5-mg single dose, 9 received 10-mg single dose, 11 received 15-mg single dose, 9 received 5-mg multiple doses, 8 received 10-mg multiple doses, 8 received 15-mg multiple doses)

Diagnosis and Main Criteria for Inclusion:
Subjects aged >12 to 17 years with postoperative pain requiring an opioid.

Test Product, Dose and Mode of Administration, Batch Number:

OPANA® (oxymorphone hydrochloride) for oral dosing supplied as 5-mg (NDC #63481-612-70; lot numbers 400865NV and 401427NV) and 10-mg (NDC #63481-613-70; lot numbers 400953NV and 401428NV) IR tablets.

Single-Dose Period: 5 mg, 10 mg, and 15 mg oxymorphone IR.
Multiple-Dose Period: 5 mg, 10 mg, and 15 mg. Dosing began at the lowest dose selected from the single-dose period.
Rescue analgesia was available according to SOC at each institution.

Duration of Treatment:
Single-Dose Period: Within 30 hours after surgery, subjects developing a moderate level of pain as defined by a 100-mm visual analog scale (VAS) received 1 dose.
Multiple-Dose Period: Following postoperative parenteral analgesia, oral dosing commenced according to each institution's SOC (within 30 hours post-surgery) and was repeated every 4 to 6 hours (no sooner than every 4 hours and no later than every 6 hours) for up to 48 hours.

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Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:
Efficacy: Assessments of current pain intensity using a 100-mm VAS obtained over a 6-hour period (single-dose period) or a 48-hour period (multiple-dose period) following dose administration, or until rescue medication is used.
Safety: Adverse events (AEs), respiratory function monitoring, neurological function monitoring, clinical laboratory tests, and vital signs.
Pharmacokinetics: Blood samples for pharmacokinetic assessments of oxymorphone obtained over a 24-hour period (single-dose period) or a 48-hour period (multiple-dose period) following dose administration.
Statistical Methods: No inferential statistical tests were performed. Efficacy data were summarized by descriptive statistics. The pain intensity difference was calculated as the current pain intensity at each post-dose time point minus the current pain intensity score at baseline. Summary statistics of the pain intensity scores using VAS and change from baseline were presented by treatment group and study period for each time point.
The following pharmacokinetic variables were estimated from the plasma concentration data using standard non-compartmental methods: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, □, and $t_{½}$.
Summaries of AEs were presented by system organ class and preferred term. The occurrence of AEs was also tabulated by severity. Serious adverse events (SAEs) and AEs resulting in discontinuation were summarized separately. All laboratory results, vital sign measurements, and other safety variables were summarized by study period and treatment group for each time point using descriptive statistics or frequency distributions.

SUMMARY – CONCLUSIONS: EFFICACY RESULTS:
In both the single-dose and multiple-dose periods, improvement in postoperative pain following pediatric surgery was seen in all treatment groups.
In the single-dose period, the mean pain intensity scores decreased (improved) from baseline at each time point in each of the 3 treatment groups. The largest mean change from baseline was seen at 4 hours post dose in the 5-mg group (mean [standard deviation (SD)] change of -36.2 [25.03]), 3 hours post dose in the 10-mg group (mean change of -29.3 [20.21]), and 2 hours post dose in the 15-mg group (mean change of -33.8 [20.10]).

In the multiple-dose period, the mean pain intensity scores improved from baseline at each time point following the first dose in each of the 3 treatment groups, except in the 10-mg group at 15 minutes and 30 minutes post first dose (mean [SD] changes of 0.5 [9.56] and 3.1 [22.33], respectively). The mean largest changes were seen in each dose group at 1 hour post first dose. In the multiple-dose period, pain intensity also improved from baseline to immediately prior to each subsequent dose (every 4 to 6 hours) in the 5-mg and 15-mg dose groups and immediately prior to each subsequent dose except doses 2, 3, and 4 following the first dose in the 10-mg group.

PHARMACOKINETICS RESULTS:
In the single-dose period, the total plasma exposure, AUC_{0-inf}, of both oxymorphone and 6-OH-oxymorphone increased with increasing dose. Between the 10-mg and 15-mg dose the mean AUC_{0-inf} of oxymorphone increased in a greater than dose proportional manner. However, due to the small number of subjects and the wide variability in the data, it is not possible to make any conclusive interpretation of this observation. The mean C_{max} of oxymorphone was lower in the in the 10-mg group versus the 5-mg group, which may be related to the small number of subjects and a high degree of intersubject variability. AUC_{0-inf} and C_{max} of 6-OH-oxymorphone, on the other hand, appeared to occur in a near proportional manner with oxymorphone dose. The mean half-life of oxymorphone increased

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with increasing dose from 12.1 hours in the 5-mg group to 15.9 hours in the 10-mg group and 20.0 hours in the 15-mg group. The half-life of 6-OH-oxymorphone, however, appeared to be independent of oxymorphone dose.

In the multiple-dose period of this study, pharmacokinetic parameters for oxymorphone and 6-OH-oxymorphone were not evaluated. Rather, their 4-hour plasma concentrations, which mostly represented trough levels from the subsequent dose, were analyzed.

There was a significant amount of variability in the concentration-time scatter plots, but in general there appeared to be a >2-fold increase in median oxymorphone and 6-OH-oxymorphone concentration within each of the 3 dose groups following multiple oxymorphone dosing. In addition, the median oxymorphone plasma concentrations appeared to increase with dose in a nearly dose proportional manner.

SAFETY RESULTS:
Overall, treatment-emergent adverse events (TEAEs) were reported in 42.4% of subjects in the single-dose period, with the lowest incidence in the 5-mg group (23.1%) compared to 44.4% in the 10-mg group and 63.3% in the 15-mg group. During the single dose period, the most frequently reported TEAEs overall were nausea and pyrexia (4 subjects, 12.1% each) and constipation, hypoaesthesia, and vomiting (2 subjects, 6.1% each). Overall, TEAEs were reported in 76.0% of subjects in the multiple- dose period, with the lowest incidence in the 10-mg group (62.5%) compared to 88.9% in the 5-mg group and 75.0% in the 15-mg group. During the multiple dose period, the most frequently reported TEAEs overall were constipation (8 subjects, 32.0%); nausea (7 subjects, 28.0%); oxygen saturation decreased, dizziness, urinary retention, anemia, and headache (4 subjects, 16.0% each); and pyrexia, vomiting, and pruritus (3 subjects, 12.0% each).
No deaths occurred. SAEs were reported for 2 subjects in the single-dose period (moderate intensity atelectasis and fat embolism in 1 subject in the 10-mg group and severe intensity implant failure in 1 subject in the 15-mg group) and 1 subject in the multiple-dose period (5-mg group moderate intensity unequal pupils, anemia, blurred vision, and headache). All of the SAEs resolved, and none were considered related to the study drug. No TEAEs leading to discontinuation occurred during the single-dose period, and 2 subjects discontinued due to TEAEs in the multiple-dose period.
No clinically meaningful trends were noted in laboratory test results, vital signs, or physical examination findings.

CONCLUSION:
(b) (4)

Date of the Report: 24-Apr-2013

Reviewer comments: There are no issues identified with the Applicant's synopsis report.

Additional information pertinent from the main study report:

Figure 1 depicts the overall study design.

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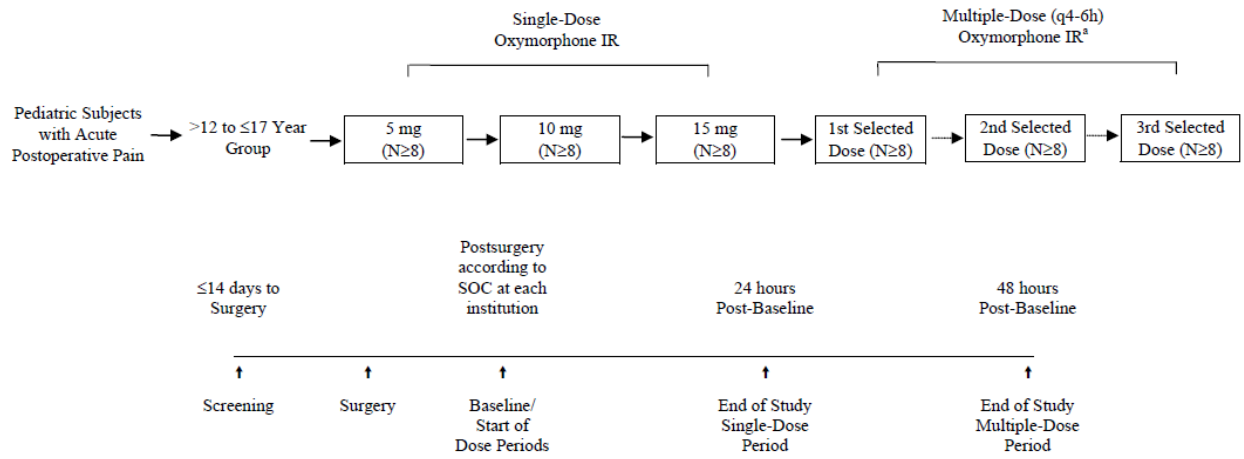
Figure 1: Study Design



[a] Up to 3 ascending doses were to be selected from results of single-dose period. Doses selected for the multiple-dose period were 5 mg, 10 mg, and 15 mg.
IR=Immediate-release; q4-6h=Every 4 to 6 hours; SOC=Standard of care
Note: Dose assignment began at the lowest single dose and proceeded to the next dose after completion of at least 8 evaluable subjects at that dose.

Doses:
5 mg, 0.1 mg/kg for a 50-kg child;
10 mg, 0.2 mg/kg for a 50-kg child;
15 mg, 0.3 mg/kg for a 50-kg child.

9.3.1. Inclusion Criteria

Per administrative change, 2008, for inclusion into the trial, subjects were required to fulfill all of the following criteria:

1. Were males or females >12 to 17 years of age, inclusive Females of child-bearing potential had to be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all menstruating females were considered to be of child-bearing potential unless they were biologically sterile or surgically sterile for more than 1 year.
2. Required postoperative oral opioid analgesia for at least 24 hours (single-dose period) or 48 hours (multiple-dose period) following postoperative parenteral analgesia
3. Were expected to be hospitalized for the duration of the study period
4. Weigh at least 50 kg
5. Had results available, from within 4 weeks preoperatively, of clinical chemistry and hematology laboratory tests (the results must have been reviewed by the Investigator for study eligibility)
6. Were in good health other than the condition under treatment
7. Were able to swallow tablets whole (no chewing, crushing, sucking, etc., was permitted)
8. Were able to complete pain assessment evaluations as determined by preoperative evaluations
9. Were on an intravenous (patient-controlled analgesia [PCA] or non-PCA) analgesic regimen with a short-acting opioid analgesic
10. Have demonstrated the ability to tolerate oral feeding according to the SOC at each institution
11. Were able to have their intravenous opioid discontinued for at least 15 minutes, but not longer than 6 hours before administration of study medication
12. Had achieved a moderate level of pain as defined by a pain intensity score ≥40 on a 100-mm visual analog scale (VAS)
13. Had been informed of the nature of the study and informed consent had been obtained from the legally responsible parent/guardian

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14. Had provided assent in accordance with IRB requirements
15. Had a patent intravenous line in place for venous sampling
16. Had a suitable monitor in place for monitoring apnea, respiratory rate, and pulse oximetry

9.3.2. Exclusion Criteria
Any of the following was regarded as a criterion for exclusion from the trial:
1. Had a known allergy to, or a significant reaction to, oxymorphone or another opioid
2. Had a life expectancy <4 weeks
3. Had a positive pregnancy test (menstruating females only) at screening
4. Were pregnant and/or lactating
5. Have cyanotic heart disease
6. Had any major cardiac, respiratory, hepatic, renal, neurological, or psychological disease that would have precluded participation as assessed by the Investigator
7. Had received preoperative opioids for >72 hours
8. Had abdominal trauma
9. Had increased intracranial pressure
10. Had a history of uncontrolled seizures that were not being managed with anti-convulsants
11. Had a significant prior history of substance abuse or alcohol abuse
12. Had received any investigational medication within 30 days prior to the first dose of study medication, or were scheduled to receive an investigational drug other than oxymorphone during the course of the study
13. Had a previous exposure to oxymorphone
14. Had received a monoamine oxidase inhibitor within 14 days prior to the start of study medication
15. Had received codeine or oxycodone within 72 hours prior to study start
16. Had any other clinically significant condition that would, in the Investigator's opinion, have precluded study participation
17. The Investigator anticipated that the subject would be unable to comply with the protocol
18. Were unable to read, comprehend, and complete the English language assent and questionnaires, as appropriate for age
19. Were unable to communicate effectively with study personnel

9.4 Treatments
9.4.1. Treatments Administered
In the single-dose period, dosing began at *5 mg, which is equivalent to 0.1 mg/kg for a 50-kg child.*
Once safety and the pharmacokinetic profile of oxymorphone IR had been established at this dose level (through review by the DSMB), dosing was to commence at the next higher dose level (*10 mg; 0.2 mg/kg for children who weigh 50 kg*), and after establishment of safety and pharmacokinetics (through review by DSMB), the final dose level of *15 mg (0.3 mg/kg for children who weigh 50 kg*) was to be enrolled.

Doses used in the multiple-dose period were determined from the results of the single-dose period. Up to 3 doses of oxymorphone IR were to be studied in ascending fashion. Based on the results of the single-dose period, doses of 5 mg, 10 mg, and 15 mg were studied in the multiple-dose period in stepwise order, based on the previous group's demonstrated safety/tolerability and effectiveness.

9.4.4. Selection of Doses in the Study
The initial oxymorphone IR dose in the single-dose period was chosen based on an established equivalent morphine dose (0.3 mg/kg by mouth every 3-4 hours) in children being treated for acute pain. Due to the limitation of oral tablet dosing in this study, dosing based on a mg/kg basis could not be accomplished; however, dosing began at the lowest equivalent dose of oxymorphone IR (5 mg, which is equivalent to 0.1 mg/kg for a 50-kg child). The doses of 5 mg, 10 mg, and 15 mg used in the multiple-dose period were determined from the results of the single-dose period.

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9.4.7. Prior and Concomitant Therapy

Medications known to have analgesic effects or to influence the subject's perception of pain were to be avoided during the study. The following restrictions applied:

• No analgesics were permitted after the first dose of study medication

− During the single-dose period, no analgesics were permitted during the 6-hour assessment period; analgesia according to SOC at each institution was permitted after the 6-hour assessment period with the exception of oxycodone, and any products containing oxycodone, which were prohibited throughout the 24-hour pharmacokinetic assessment period

− During the multiple-dose period, no analgesics were permitted during the 48-hour assessment period

• Central nervous system (CNS) depressants, muscle relaxants, and antihistamines that have been given regularly during the pre- and/or postoperative period may be continued during the study period; otherwise they were prohibited from 4 hours prior to stopping the postoperative opioid pain medication until the completion of study observations, except diphenhydramine could have been given only for nausea/vomiting, pruritus, or as a sleep aid

• Antidepressant therapy was to remain stable throughout the study

The use of investigational drugs other than oxymorphone IR was prohibited; FDA-approved drugs used in investigational protocols are permitted. Other medications that were considered necessary for the subject's welfare and that would not have interfered with the response to the study medication were allowed to be given at the discretion of the Investigator.

Any concomitant medication (including vitamin supplements, herbal remedies, and non-prescription medications) used while the subject was on study medication (up to 24 to 48 hours post first dose depending on study period) were to be recorded. The medication name, dosage, date, time, and indication for use were to be recorded. In the event of an AE that was ongoing at the end of the study, any concomitant medications given for that AE were to be recorded until its resolution or as otherwise instructed by the Sponsor.

9.4.7.1. Rescue Medication

Subjects who did not have adequate pain relief from study medication could have been given rescue medication at any time during the study according to each institution's SOC; however, subjects were to be encouraged to wait at least 1 hour after study drug administration to receive rescue medication. If rescue medication was administered, all pain assessments were to discontinue; however, blood samples were to be collected through the last scheduled collection time, if possible.

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study procedures is provided in Table 4 and Table 5.

Table 4: Schedule of Assessments – Single-Dose Period

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Table 4: Schedule of Assessments – Single-Dose Period

Assessment	Visit 1	Visit 2 (Hospital)										
	Pre-Treatment		After First Dose									End-of-Study Evaluation (24 hours post first dose or early termination)
	Screening (within 14 days of surgery)	Baseline (post-surgery when oral dosing commences)	15 min	30 min	1h	2h	3h	4h	6h or rescue	8h	12h	
Informed Consent by parent/guardian	X											
Assent by minor, if IRB-required	X											
Demographics	X											
Medical/Surgical History	X	update										
Physical Examination	X	update										
Assess Entry Criteria	X	re-confirm										
Urine Pregnancy test (females of child-bearing potential only)	X	X										
Study Drug Administration		X										
Blood sample for PK assessment		X				X		X		X	X	X
Vital signs, including pulse oximetry	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests	X											X
Adverse Events			X									
Respiratory and neurology assessment			X									
Concomitant Medications	X	X										
Pain Assessment (VAS)		X	X	X	X	X	X	X	X			

IRB=Institutional Review Board; PK=Pharmacokinetics; VAS=Visual analog scale

Table 5: Schedule of Assessments – Multiple-Dose Period

Assessment	Visit 1	Visit 2 (Hospital)														
	Pre-Treatment		After First Dose													End-of-Study Evaluation (48 hours post first dose or early study termination)
	Screening (within 14 days of surgery)	Baseline (post-surgery when oral dosing commences)	15 min	30 min	1h	2h	3h	4h	6h	8h	12h	24h	28h	32h	36h	
Informed Consent by parent/guardian	X															
Assent by minor, if IRB-required	X															
Demographics	X															
Medical/Surgical History	X	update														
Physical Examination	X	update														
Assess Entry Criteria	X	re-confirm														
Pregnancy test (urine or serum for females of child-bearing potential only)	X	X														
Study Drug Administration (first dose)		X														
Study Drug Administration (dosing every 4 to 6 hours)								X								
Blood sample for PK assessment		X						X		X	X	X	X	X	X	X
Vital signs, including pulse oximetry	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Clinical Laboratory tests	X															X
Respiratory and neurology assessment		X							X							
Adverse Events			X													
Concomitant Medications	X	X							X							
Pain Assessment (VAS)		X	X	X	X	X	X	X	X (every 4 to 6 hours with each dose)							

IRB=Institutional Review Board; PK=Pharmacokinetics; VAS=Visual analog scale

9.5.1.1. Efficacy Measurements

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Efficacy was assessed through the recording of the subject's current pain intensity using a 100-mm VAS. Current pain intensity was to be collected at the following times during the study:
• Single-Dose Period: Immediately prior to dose; 15, 30 minutes, 1, 2, 3, 4, 6 hours postdose; time of rescue
• Multiple-Dose Period: Immediately prior to first dose; 15, 30 minutes, 1, 2, 3, 4, and 6 hours (6 hours only if the subject has not received a second dose of study medication by hour 6) post first dose; immediately prior to each subsequent dose (every 4 to 6 hours) up to 48 hours; time of rescue

In this study each subject was to record their intensity of pain on a 100-mm VAS that was bounded on the left by "no pain" and on the right by "the worst pain imaginable." The subject was instructed to "place a single vertical mark across the line which best indicates the amount of pain you are having right now." The score was the distance in millimeters from the left end of the VAS to the point where the mark crossed the line.

9.5.4. Drug Concentration Measurements
9.5.4.1. Blood Sample Collections
Pharmacokinetic assessments were to be performed for all subjects participating in the study. Samples of venous blood were to be obtained in 2.5 mL K2 EDTA tubes at the following times:
• Single-Dose Period: Serial blood collected at time 0 (Baseline), and at 2, 4, 8, 12, and 24 hours post-dose.
• Multiple-dose period: Serial blood collected at time 0 (Baseline), and at 4, 8, 12, 24, 28, 32, 36, and 48 hours post-dose.

Immediately after collection, the tube was to be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction was to be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at 1500 × g. The plasma fraction was to be withdrawn by pipette and placed into a polypropylene freezing tube. All sample collection and freezing tubes were to be clearly labeled in a manner that identified the subject and the collection time. Labels were to be fixed to the freezing tubes in a manner that prevented the label from becoming detached after freezing. All plasma samples were to be placed into a freezer at -70°C or below within 1 hour after collection.

9.5.4.2. Sample Storage and Shipment
All plasma samples were to be stored frozen (at –70°C or below) until they were shipped to the analytical facility. Prior to shipping, the samples were to be packed into thermal insulated containers in sufficient dry ice to assure they remained frozen and protected from breakage during shipment. Samples were to be shipped by overnight, priority courier. The samples were to be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment (plasma) was to be processed.

9.5.4.3. Analytical Methodology
A simultaneous, validated liquid chromatography-tandem mass spectrophotometry (LC-MS/MS) method was used for the determination of concentrations of oxymorphone and 6-OH-oxymorphone from the plasma samples. Details of the method validation and sample analysis are included in **Appendix 16.1.10. (p.29/317)**

9.7.1. Statistical and Analytical Plans
All statistical analyses were performed using the SAS® (Statistical Analysis System, Cary, NC) software version 8.2 or higher. No inferential statistical tests were performed. The Statistical Analysis Plan (SAP) is provided in Appendix 16.1.9.

9.7.1.5. Pharmacokinetic Analysis

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Pharmacokinetic variables were estimated from the plasma concentration data using standard non-compartmental methods. Actual sample times, rather than scheduled times, were used in the computation of pharmacokinetic parameters. Missing plasma samples were treated as if they were never drawn. Any plasma concentration below the limit of quantification (BLQ) was set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations were set to missing. For the computation of pharmacokinetic variables, the BLQ concentrations prior to the first measurable concentration were set to zero and other BLQ concentrations were set to missing.

10. STUDY PATIENTS

10.1. Disposition of Patients

Table 7: Subject Disposition

Subject Disposition	**Single Dose of Oxymorphone IR**	**Multiple Dose of Oxymorphone IR**	**Overall**
Total Number of Subjects			
Enrolled	33	25	58
Completed	11 (33.3%)	9 (36.0%)	20 (34.5%)
Discontinued	22 (66.7%)	16 (64.0%)	38 (65.5%)
Analysis Population			
Safety	33 (100%)	25 (100%)	58 (100%)
Intent-to-Treat (ITT)	33 (100%)	25 (100%)	58 (100%)
Pharmacokinetic (PK)	28 (84.8%)	24 (96.0%)	52 (89.7%)
Reason for Discontinuation			
Adverse Event	0	2 (8.0%)	2 (3.4%)
Investigator Decision	0	1 (4.0%)	1 (1.7%)
Lack of Efficacy	21 (63.6%)	12 (48.0%)	33 (56.9%)
Withdrew Consent/Assent	1 (3.0%)	1 (4.0%)	2 (3.4%)

Data Source: Table 14.1.1

Note: Percentages are based on the number of enrolled subjects in each treatment group.

Table 8: Subject Disposition by Treatment Group

	Single Dose of Oxymorphone IR			**Multiple Dose of Oxymorphone IR**		
	5 mg	**10 mg**	**15 mg**	**5 mg**	**10 mg**	**15 mg**
Total Number of Subjects						
Enrolled	13	9	11	9	8	8
Completed	7 (53.8%)	0	4 (36.4%)	3 (33.3%)	1 (12.5%)	5 (62.5%)
Discontinued	6 (46.2%)	9 (100%)	7 (63.6%)	6 (66.7%)	7 (87.5%)	3 (37.5%)
Analysis Population						
Safety	13 100%)	9 (100%)	11 (100%)	9 (100%)	8 (100%)	8 (100%)
Intent-to-Treat (ITT)	13 (100%)	9 (100%)	11 (100%)	9 (100%)	8 (100%)	8 (100%)
Pharmacokinetic (PK)	11 (84.6%)	8 (88.9%)	9 (81.8%)	8 (88.9%)	8 (100%)	8 (100%)

Reference ID: 4499855

Reason for Discontinuation						
Adverse Event	0	0	0	1 (11.1%)	0	1 (12.5%)
Investigator Decision	0	0	0	0	1 (12.5%)	0
Lack of Efficacy	6 (46.2%)	9 (100%)	6 (54.5%)	4 (44.4%)	6 (75.0%)	2 (25.0%)
Withdrew Consent/Assent	0	0	1 (9.1%)	1 (11.1%)	0	0

Data Source: Table 14.1.2
Disposition data are listed by subject in Listing 16.2.1.1.

Table 9: Demographics and Baseline Characteristics by Treatment Group – ITT Population

Category	Single Dose of Oxymorphone IR				Multiple Dose of Oxymorphone IR			
	5 mg (N=13)	10 mg (N=9)	15 m	Overall (N=33	5 mg (N=	10 mg (N=	15 mg (N=	Overall (N=2
Age (years)								
n	13	9	11	33	9	8	8	25
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	2 17	13, 17	12, 17	12, 17	14, 16	13, 17	14, 17	13, 17
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%)
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 America	2 (15 4%)	2 (22 2%)	1 (9 1%)	5 (15 2%)	0	1 (12 5%)	0	1 (4 0%)
Other: Father - White, Mother - Mexican	0	0	0	0	0	0	1 (12 5%)	1 (4 0%)
Other: Multiracial (Black/White)	0	0	0	0	0	0	1 (12 5%)	1 (4 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%)
Height (cm)								
n	13	8	9	30	9	8	8	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)

Reference ID: 4499855

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
Weight (kg)								
n	13	9	11	33	9	8	8	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
BMI (kg/m^2)								
n	13	8	9	30	9	8	8	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

11.4.4. Drug Dose and Drug Concentration

11.4.4.1. Single Dose

Plasma concentrations of single dose of oxymorphone IR are summarized by treatment group and time point in Table 14.2.3. Mean plasma concentration versus time is displayed for the single-dose period in Figure 14.2.1.1 for 6-OH-oxymorphone and in Figure 14.2.1.2 for oxymorphone. The plasma pharmacokinetic parameters of a single dose of oxymorphone and 6-OH-oxymorphone are summarized in Table 13.

Figure 14.2.1.2 Mean (+/- SE) Plasma Concentration of Oxymorphone Versus Time by **Single Dose** Treatment for Pharmacokinetic Population

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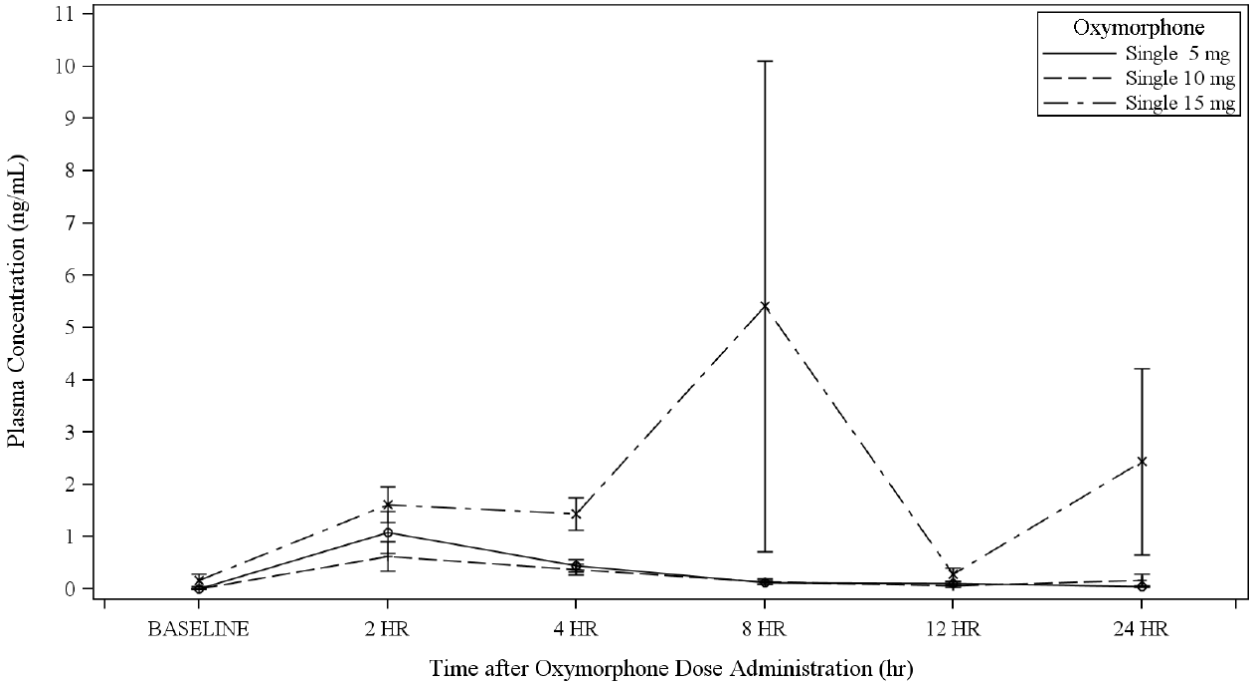
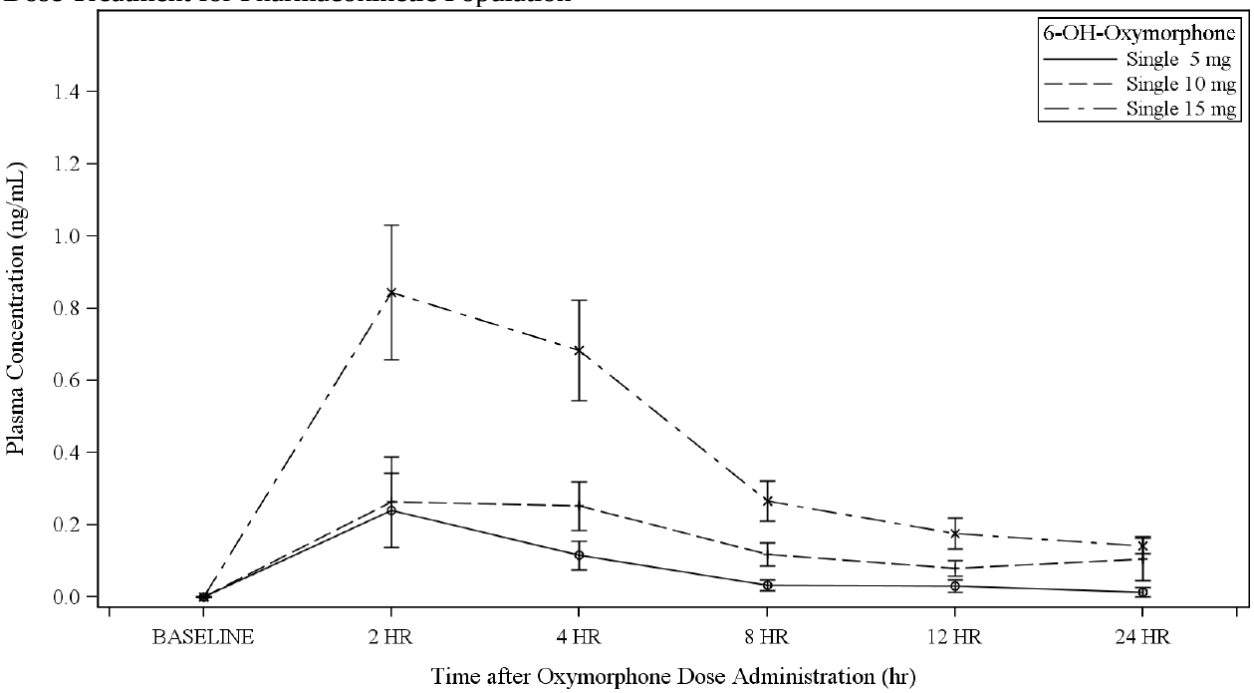


Source: Listing 16.2.5.2
Program: FPK1b.sas Output: FPK1b.rtf

Figure 14.2.1.1 Mean (+/- SE) Plasma Concentration of 6-OH-Oxymorphone Versus Time by Single Dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK1a.sas Output: FPK1a.rtf

Reference ID: 4499855

Table 13: Summary of Plasma Pharmacokinetic Parameters of Single Dose of Oxymorphone by Treatment Group – PK Population (note: all subjects-DL)

Statistics	Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)
AUC_{0-t} (ng*hr/mL)						
n	9	6	9	8	6	9
Mean	6.395	3.766	67.040	1.544	3.040	7.354
SD	6.0752	2.2587	150.7979	1.8794	1.1625	3.3255
SE	2.0251	0.9221	50.2660	0.6645	0.4746	1.1085
CV(%)	94.998	59.984	224.937	121.739	38.233	45.219
Geometric Mean	4.580	2.337	18.638	0.864	2.836	6.559
Minimum	1.18	0.12	3.30	0.28	1.38	2 34
25%	2.965	2.572	7.896	0.338	2.561	4.989
Median	4.040	4.165	13.818	0.748	2.765	6.899
75%	6.918	5.106	24.769	2.313	4.347	10.030
Maximum	20.96	6.47	467.26	5.27	4.42	12.14
AUC_{0-inf} (ng*hr/mL)						
n	9	3	8	5	5	9
Mean	7.632	10.223	109.294	4.987	8.692	12.795
SD	6.6828	6.5195	257.5421	7.5732	10.2430	8.8385
SE	2.2276	3.7641	91.0549	3.3868	4.5808	2.9462
CV(%)	87.565	63.773	235.642	151.844	117.837	69.077
Geometric Mean	5.578	9.043	25.001	2.019	5.954	10.832
Minimum	1.60	6.16	3.89	0.58	3.45	4 15
25%	3.590	6.158	12.854	0.695	3.689	9.067
Median	5.623	6.768	21.848	1.036	4.586	10.220
75%	7.431	17.743	27.360	4.383	4.750	12.676
Maximum	22.26	17.74	746.34	18.24	26.99	34.41
Cmax (ng/mL)						
n	9	6	9	8	6	9
Mean	1.243	0.828	5.295	0.314	0.487	0.940
SD	1.2192	0.6892	10.6386	0.3276	0.2853	0.5212
SE	0.4064	0.2814	3.5462	0.1158	0.1165	0.1737
CV(%)	98.048	83.255	200.934	104.344	58.558	55.452
Geometric Mean	0.767	0.499	2.117	0.204	0.424	0.803
Minimum	0.08	0.04	0.49	0.05	0.16	0 30
25%	0.516	0.288	1.059	0.104	0.402	0.457
Median	0.651	0.735	1.969	0.189	0.430	0.978
75%	1.834	1.203	2.586	0.456	0.478	1.150
Maximum	4.00	1.96	33.55	0.96	1.02	1 87
T_{max} (hour)						

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n	9	6	9	8	6	9
Mean	4.898	3.681	6.193	3.885	4.631	3.785
SD	3.9645	2.4102	6.3784	2.7228	3.7051	3.2552
SE	1.3215	0.9840	2.1261	0.9626	1.5126	1.0851
CV(%)	80.939	65.485	103.000	70.077	80.014	85.998
Minimum	2.00	2.00	2.00	2.00	2.00	2 00
25%	2.083	2.000	2.083	2.042	2.433	2.050
Median	2.350	2.842	4.000	2.250	3.633	2.350
75%	7.917	4.083	8.083	6.083	4.083	4.000
Maximum	13.00	8.32	21.97	8.33	12.00	12.17
λ						
n	9	3	8	5	5	9
Mean	0.209	0.214	0.073	0.281	0.101	0.042
SD	0.2552	0.2962	0.0549	0.2072	0.0965	0.0234
SE	0.0851	0.1710	0.0194	0.0927	0.0431	0.0078
CV(%)	122.107	138.250	75.212	73.688	95.455	55.730
Minimum	0.02	0.02	0.01	0.01	0.01	0 01
25%	0.034	0.019	0.030	0.142	0.048	0.032
Median	0.074	0.069	0.056	0.316	0.053	0.034
75%	0.409	0.555	0.120	0.417	0.150	0.053
Maximum	0.71	0.56	0.16	0.52	0.25	0 09
$t_{1/2}$ (hour)						
n	9	3	8	5	5	9
Mean	12.099	15.900	19.974	19.215	23.635	22.520
SD	9.9336	18.2533	22.4488	37.3737	33.6381	15.3063
SE	3.3112	10.5385	7.9368	16.7140	15.0434	5.1021
CV(%)	82.102	114.803	112.390	194.501	142.321	67.967
Minimum	0.98	1.25	4.29	1.33	2.82	7 58
25%	1.695	1.249	5.916	1.661	4.611	13.042
Median	9.326	10.103	12.371	2.193	13.094	20.650
75%	20.612	36.347	23.398	4.870	14.547	21.513
Maximum	28.06	36.35	72.13	86.02	83.11	58.48

Reference ID: 4499855

The total plasma exposure, AUC0-inf, of both oxymorphone and 6-OH-oxymorphone increased with increasing dose. Between the 10-mg and 15-mg dose the mean AUC0-inf of oxymorphone increased in a greater than dose proportional manner. Due to the small number of subjects as well as the wide variability in the data, it is not possible to make any conclusive statement concerning this apparent non-linearity.

The mean (SD) Cmax of oxymorphone was lowest in the 10-mg group (0.8 [0.7] ng/mL) and higher in the 5-mg group (1.2 [1.2] ng/mL) and 15-mg group (5.3 [10.6] ng/mL). The increase in AUC0-inf and Cmax of 6-OH-oxymorphone, on the other hand, appeared to increase in a near proportional manner with oxymorphone dose.
The median (minimum, maximum) Tmax was similar between the 5-mg and 10-mg groups (2.4 [2.0, 13.0] vs 2.8 [2.0, 8.3] hours), but less than the 15-mg group (4.0 [2.0, 22.0] hours).

The mean (SD) terminal rate constant (λ) was 0.2 (0.3) in the 5-mg group, 0.2 (0.3) in the 10-mg group, and 0.1 (0.1) in the 15-mg group. The mean (SD) half-life of oxymorphone increased with increasing dose from 12.1 (10.0) hours in the 5-mg group to 15.9 (18.3) hours in the 10-mg group and 20.0 (22.4) hours in the 15-mg group. The half-life of 6-OH-oxymorphone, however, appeared to be independent of oxymorphone dose.

Table 14.2.3 Summary of Plasma Concentrations of Single Dose of Oxymorphone by Treatment (Dose) Group for Single Dose Pharmacokinetic Population

		Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
Timepoint	Statistics	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)	5 mg (N=11)	10 mg (N=8)	15 mg (N=9)
Predose (0)	n	11	8	7	9	8	8
	Mean	0	0	0.16413	0	0	0
	SD	0	0	0.329185	0	0	0
	SE	0	0	0.124420	0	0	0
	CV(%)			200.56381			
	Minimum	0	0	0	0	0	0
	25%	0	0	0	0	0	0
	Median	0	0	0.04710	0	0	0
	75%	0	0	0.10500	0	0	0
	Maximum	0	0	0.9038	0	0	0
2 hours	n	10	7	9	10	8	9
	Mean	1.07891	0.62597	1.60719	0.23972	0.26263	0.84372
	SD	1.248582	0.743459	1.020429	0.324273	0.353368	0.559537
	SE	0.394836	0.281001	0.340143	0.102544	0.124935	0.186512
	CV(%)	115.72588	118.76939	63.49152	135.27390	134.55045	66.31762
	Minimum	0	0	0.4853	0	0	0.2804
	25%	0.03733	0.04268	1.05900	0	0.02753	0.45650
	Median	0.58305	0.20210	1.33400	0.10375	0.08644	0.62760
	75%	1.83400	1.20300	1.96200	0.23230	0.42555	1.15000
	Maximum	4.0010	1.9630	3.9130	0.9623	1.0220	1.8700

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4 hours	n	10	7	8	10	8	9
	Mean	0.44460	0.37408	1.43340	0.11523	0.25235	0.68429
	SD	0.354667	0.286141	0.871206	0.126384	0.189329	0.418092
	SE	0.112156	0.108151	0.308018	0.039966	0.066938	0.139364
	CV(%)	79.77164	76.49248	60.77900	109.67686	75.02652	61.09868
	Mininum	0	0	0.4341	0	0	0.1813
	25%	0.10680	0.02964	0.65855	0	0.06445	0.34610
	Median	0.49345	0.44290	1.26950	0.08551	0.29070	0.77450
	75%	0.77090	0.63510	2.29550	0.16130	0.41510	0.98320
	Maximum	0.9185	0.6528	2.5860	0.3720	0.4783	1.3700
8 hours	n	7	6	7	7	7	7
	Mean	0.12760	0.13978	5.40719	0.03241	0.11849	0.26535
	SD	0.104181	0.121717	12.426911	0.039837	0.084624	0.146552
	SE	0.039377	0.049691	4.696931	0.015057	0.031985	0.055391
	CV(%)	81.64389	87.07523	229.82204	122.92810	71.42109	55.22922
	Mininum	0.0361	0	0.0749	0	0	0.0937
	25%	0.07442	0	0.21070	0	0	0.10790
	Median	0.08562	0.14870	0.67700	0.03075	0.15120	0.27410
	75%	0.13690	0.25360	2.01100	0.05176	0.17920	0.38150
	Maximum	0.3501	0.2877	33.5500	0.1098	0.2070	0.4681
12 hours	n	7	8	7	8	8	8
	Mean	0.09940	0.06573	0.27986	0.03003	0.07967	0.17605
	SD	0.096478	0.078527	0.331705	0.047576	0.060229	0.119001
	SE	0.036465	0.027764	0.125373	0.016821	0.021294	0.042073
	CV(%)	97.06045	119.46707	118.52537	158.43588	75.59904	67.59450
	Mininum	0	0	0.0574	0	0	0.0620
	25%	0.03130	0	0.09476	0	0.02932	0.09243
	Median	0.08020	0.03763	0.10310	0.01465	0.08436	0.13510
	75%	0.11340	0.12375	0.52090	0.03527	0.12430	0.25025
	Maximum	0.3001	0.2031	0.9400	0.1404	0.1614	0.3909
24 hours	n	8	5	8	8	5	9
	Mean	0.04178	0.16728	2.43536	0.01306	0.10594	0.14190
	SD	0.036401	0.270393	5.044677	0.036946	0.136648	0.063377
	SE	0.012870	0.120924	1.783563	0.013063	0.061111	0.021126
	CV(%)	87.11934	161.64109	207.14266	282.84271	128.99087	44.66427
	Mininum	0	0	0.0823	0	0	0.0611
	25%	0.01614	0	0.18415	0	0	0.09999
	Median	0.04307	0	0.21885	0	0.03458	0.13470
	75%	0.04983	0.21500	2.01730	0	0.18820	0.16860
	Maximum	0.1162	0.6214	14.5600	0.1045	0.3069	0.2640

Source: Listing 16.2.5.2
Program: TPK1.sas Output: TPK1.rtf Final Date: 22JAN13

Reference ID: 4499855

Table 14.2.4 Summary of Plasma Pharmacokinetic Parameters of Single Dose of Oxymorphone by Treatment (Dose) Group for Pharmacokinetic Population

		Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
Parameter (Unit)	**Statistics**	**5 mg (N=11)**	**10 mg (N=8)**	**15 mg (N=9)**	**5 mg (N=11)**	**10 mg (N=8)**	**15 mg (N=9)**
AUC (0- t) (ng*hr/mL)	n	9	6	9	8	6	9
	Mean	6.395	3.766	67.040	1.544	3.040	7.354
	SD	6.0752	2.2587	150.7979	1.8794	1.1625	3.3255
	SE	2.0251	0.9221	50.2660	0.6645	0.4746	1.1085
	CV(%)	94.998	59.984	224.937	121.739	38.233	45.219
	Geometric Mean	4.580	2.337	18.638	0.864	2.836	6.559
	Mininum	1.18	0.12	3.30	0.28	1.38	2.34
	25%	2.965	2.572	7.896	0.338	2.561	4.989
	Median	4.040	4.165	13.818	0.748	2.765	6.899
	75%	6.918	5.106	24.769	2.313	4.347	10.030
	Maximum	20.96	6.47	467.26	5.27	4.42	12.14
AUC (0-inf) (ng*hr/mL)	n	9	3	8	5	5	9
	Mean	7.632	10.223	109.294	4.987	8.692	12.795
	SD	6.6828	6.5195	257.5421	7.5732	10.2430	8.8385
	SE	2.2276	3.7641	91.0549	3.3868	4.5808	2.9462
	CV(%)	87.565	63.773	235.642	151.844	117.837	69.077
	Geometric Mean	5.578	9.043	25.001	2.019	5.954	10.832
	Mininum	1.60	6.16	3.89	0.58	3.45	4.15
	25%	3.590	6.158	12.854	0.695	3.689	9.067
	Median	5.623	6.768	21.848	1.036	4.586	10.220
	75%	7.431	17.743	27.360	4.383	4.750	12.676
	Maximum	22.26	17.74	746.34	18.24	26.99	34.41
Cmax (ng/mL)	n	9	6	9	8	6	9
	Mean	1.243	0.828	5.295	0.314	0.487	0.940
	SD	1.2192	0.6892	10.6386	0.3276	0.2853	0.5212
	SE	0.4064	0.2814	3.5462	0.1158	0.1165	0.1737
	CV(%)	98.048	83.255	200.934	104.344	58.558	55.452
	Geometric Mean	0.767	0.499	2.117	0.204	0.424	0.803
	Mininum	0.08	0.04	0.49	0.05	0.16	0.30
	25%	0.516	0.288	1.059	0.104	0.402	0.457
	Median	0.651	0.735	1.969	0.189	0.430	0.978
	75%	1.834	1.203	2.586	0.456	0.478	1.150
	Maximum	4.00	1.96	33.55	0.96	1.02	1.87
Tmax (hour)	n	9	6	9	8	6	9
	Mean	4.898	3.681	6.193	3.885	4.631	3.785
	SD	3.9645	2.4102	6.3784	2.7228	3.7051	3.2552
	SE	1.3215	0.9840	2.1261	0.9626	1.5126	1.0851
	CV(%)	80.939	65.485	103.000	70.077	80.014	85.998
	Mininum	2.00	2.00	2.00	2.00	2.00	2.00
	25%	2.083	2.000	2.083	2.042	2.433	2.050
	Median	2.350	2.842	4.000	2.250	3.633	2.350

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	75%	7.917	4.083	8.083	6.083	4.083	4.000
	Maximum	13.00	8.32	21.97	8.33	12.00	12.17
Lambda	n	9	3	8	5	5	9
	Mean	0.209	0.214	0.073	0.281	0.101	0.042
	SD	0.2552	0.2962	0.0549	0.2072	0.0965	0.0234
	SE	0.0851	0.1710	0.0194	0.0927	0.0431	0.0078
	CV(%)	122.107	138.250	75.212	73.688	95.455	55.730
	Mininum	0.02	0.02	0.01	0.01	0.01	0.01
	25%	0.034	0.019	0.030	0.142	0.048	0.032
	Median	0.074	0.069	0.056	0.316	0.053	0.034
	75%	0.409	0.555	0.120	0.417	0.150	0.053
	Maximum	0.71	0.56	0.16	0.52	0.25	0.09
T-half (hour)	n	9	3	8	5	5	9
	Mean	12.099	15.900	19.974	19.215	23.635	22.520
	SD	9.9336	18.2533	22.4488	37.3737	33.6381	15.3063
	SE	3.3112	10.5385	7.9368	16.7140	15.0434	5.1021
	CV(%)	82.102	114.803	112.390	194.501	142.321	67.967
	Mininum	0.98	1.25	4.29	1.33	2.82	7.58
	25%	1.695	1.249	5.916	1.661	4.611	13.042
	Median	9.326	10.103	12.371	2.193	13.094	20.650
	75%	20.612	36.347	23.398	4.870	14.547	21.513
	Maximum	28.06	36.35	72.13	86.02	83.11	58.48

Source: Listing 16.2.5.3
Program: TPK3.sas Output: TPK3.rtf Final Date: 10APR13

11.4.4.2. Multiple Dose

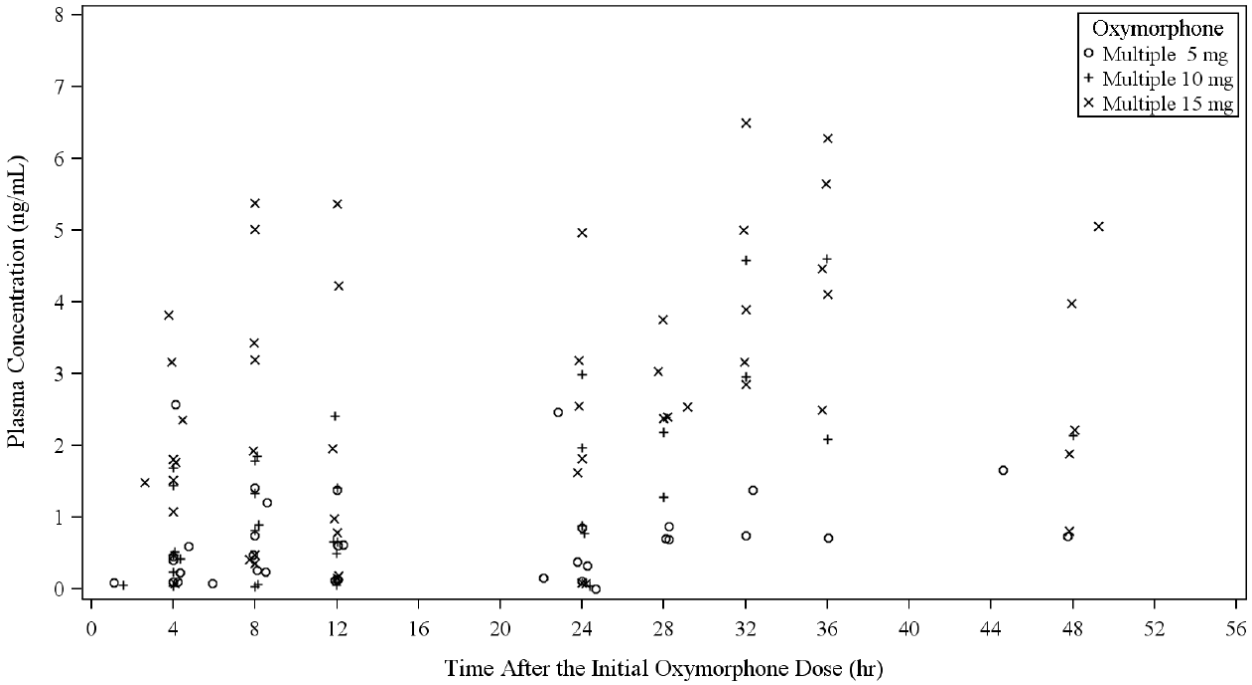
In the multiple-dose period of this study, plasma oxymorphone and 6-OH-oxymorphone concentrations were determined at 4-hour intervals, only; therefore, pharmacokinetic parameters were not evaluated.

Plasma concentrations of multiple-dose oxymorphone are summarized by treatment group and time point in Table 14.2.3.2. A scatter plot plasma concentration of 6-OH-oxymorphone versus previous dose time by multiple-dose treatment is shown in Figure 14.2.2.1, and a scatter plot plasma concentration of oxymorphone versus previous dose time by multiple-dose treatment is shown in Figure 14.2.2.2.

Although there was a significant amount of variability in the concentration-time scatter plots (Figure 14.2.2.1 and Figure 14.2.2.2), in general, there appears to be a >2-fold increase in median oxymorphone and 6-OH-oxymorphone concentration from the end of the initial dose at 4 hours until the final oral doses (24-48 hours after the initial dose) within each of the 3 dose groups. In addition, it appears that the median oxymorphone plasma concentrations increase with dose in nearly a dose proportional manner.

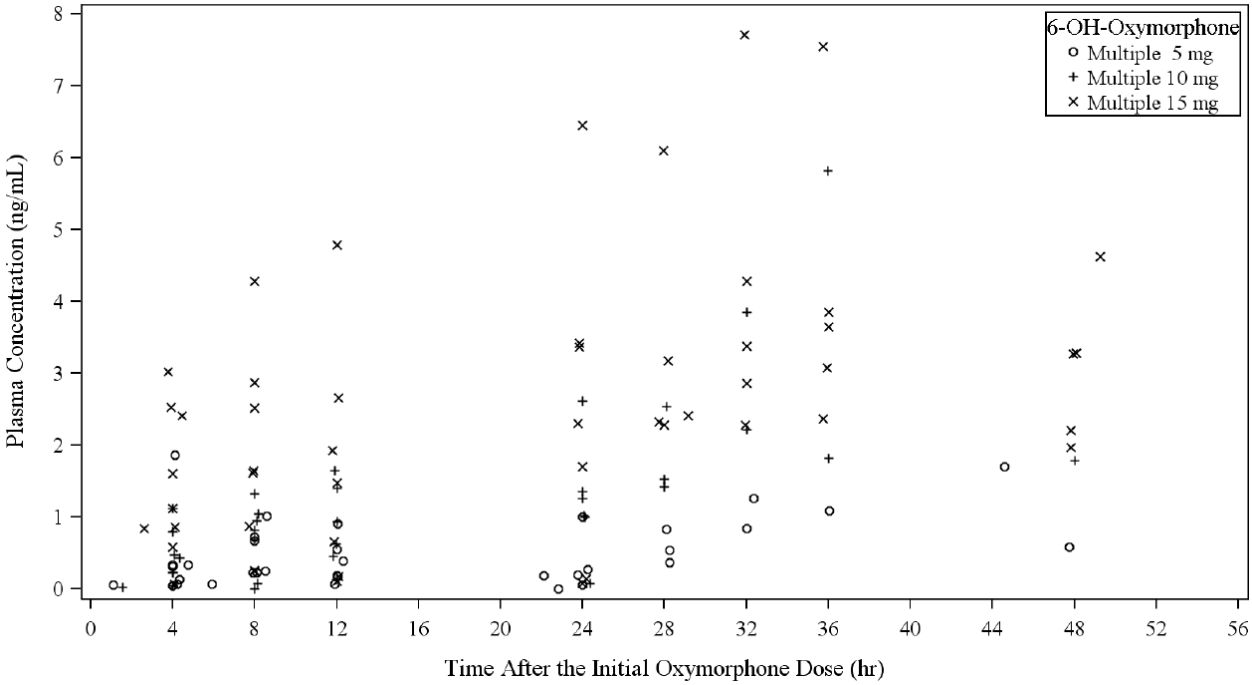
Figure 14.2.2.2 Scatter Plot of Plasma Concentration of Oxymorphone Versus Previous Dose Time by Multiple Dose Treatment for Pharmacokinetic Population

Reference ID: 4499855



Source: Listing 16.2.5.2
Program: FPK2b.sas Output: FPK2b rtf

Figure 14.2.2.1 Scatter Plot of Plasma Concentration of 6-OH-Oxymorphone Versus Previous Dose Time by Multiple Dose Treatment for Pharmacokinetic Population



Source: Listing 16.2.5.2
Program: FPK2a.sas Output: FPK2a rtf

Reference ID: 4499855

Table 14.2.3.2 Summary of Plasma Concentrations of Multiple Dose of Oxymorphone by Treatment (Dose) Group for Multiple Dose Pharmacokinetic Population

		Oxymorphone (ng/mL)			6-OH-Oxymorphone (ng/mL)		
Timepoint	Statistics	5 mg (N=8)	10 mg (N=8)	15 mg (N=8)	5 mg (N=8)	10 mg (N=8)	15 mg (N=8)
Predose (0)	n	7	8	8	7	6	8
	Mean	0.04160	0.32850	0.01511	0	0	0
	SD	0.051246	0.929138	0.042745	0	0	0
	SE	0.019369	0.328500	0.015112	0	0	0
	CV(%)	123.19571	282.84271	282.84271			
	Mininum	0	0	0	0	0	0
	25%	0	0	0	0	0	0
	Median	0.03249	0	0	0	0	0
	75%	0.07157	0	0	0	0	0
	Maximum	0.1393	2.6280	0.1209	0	0	0
4 hours	n	8	7	8	8	7	8
	Mean	0.56655	0.69068	1.94886	0.39606	0.47354	1.52452
	SD	0.832757	0.623060	1.171995	0.606024	0.373681	1.046110
	SE	0.294424	0.235495	0.414363	0.214262	0.141238	0.369856
	CV(%)	146.98875	90.20952	60.13753	153.01321	78.91205	68.61921
	Mininum	0.0776	0.0465	0.0799	0.0399	0.0422	0.0656
	25%	0.10019	0.24330	1.29750	0.06983	0.22330	0.72475
	Median	0.31570	0.47400	1.78950	0.22395	0.43240	1.36000
	75%	0.52500	1.43800	2.75900	0.33950	0.79750	2.46750
	Maximum	2.5730	1.6940	3.8190	1.8620	1.1230	3.0260
8 hours	n	6	7	8	6	7	8
	Mean	0.72122	0.96958	2.52175	0.51748	0.69927	1.78771
	SD	0.493076	0.742611	2.046728	0.332790	0.492023	1.387034
	SE	0.201298	0.280681	0.723627	0.135861	0.185967	0.490391
	CV(%)	68.36730	76.59066	81.16299	64.30930	70.36231	77.58710
	Mininum	0.2330	0.0312	0.3525	0.2278	0	0.2535
	25%	0.25840	0.06412	0.44225	0.22790	0.08039	0.56710
	Median	0.61195	0.89720	2.56150	0.45710	0.81420	1.62550
	75%	1.20600	1.79100	4.21850	0.72000	1.04500	2.69400
	Maximum	1.4060	1.8500	5.3770	1.0150	1.3190	4.2750
12 hours	n	6	6	7	6	6	7
	Mean	0.49530	0.94882	1.95010	0.37808	0.86602	1.68254
	SD	0.493681	0.839298	2.059903	0.309694	0.577783	1.659166
	SE	0.201544	0.342642	0.778570	0.126432	0.235879	0.627106
	CV(%)	99.67305	88.45716	105.63061	81.91335	66.71726	98.61061
	Mininum	0.1187	0.0545	0.1555	0.0676	0.1264	0.1053
	25%	0.12650	0.50040	0.18370	0.17470	0.45700	0.17150
	Median	0.36530	0.65850	0.98100	0.28570	0.78285	1.47100
	75%	0.61600	1.40900	4.22300	0.55270	1.40200	2.65500
	Maximum	1.3800	2.4120	5.3650	0.9021	1.6450	4.7900

Reference ID: 4499855

24 hours	n	7	5	7	6	6	7
	Mean	0.60953	1.33032	2.04354	0.28447	1.22062	2.49299
	SD	0.861570	1.153598	1.735689	0.364193	0.818600	2.210344
	SE	0.325643	0.515905	0.656029	0.148681	0.334192	0.835431
	CV(%)	141.35015	86.71554	84.93529	128.02420	67.06413	88.66235
	Mininum	0	0.0408	0.0722	0	0.0737	0.0796
	25%	0.10740	0.77070	0.08465	0.05293	1.00600	0.13730
	Median	0.31910	0.88710	1.82300	0.19385	1.13700	2.30000
	75%	0.84690	1.96500	3.18300	0.26630	1.36100	3.42400
	Maximum	2.4610	2.9880	4.9710	0.9999	2.6090	6.4480
28 hours	n	3	4	5	3	4	5
	Mean	0.75157	1.54550	2.82080	0.57850	1.50850	3.25560
	SD	0.105814	0.943873	0.583736	0.232924	0.813931	1.629427
	SE	0.061092	0.471937	0.261055	0.134479	0.406965	0.728702
	CV(%)	14.07916	61.07234	20.69400	40.26352	53.95631	50.04996
	Mininum	0.6853	0.3280	2.3790	0.3676	0.5510	2.2790
	25%	0.68530	0.80450	2.40100	0.36760	0.98400	2.32000
	Median	0.69580	1.73100	2.53900	0.53940	1.47200	2.41300
	75%	0.87360	2.28650	3.03300	0.82850	2.03300	3.16900
	Maximum	0.8736	2.3920	3.7520	0.8285	2.5390	6.0970
32 hours	n	2	3	5	2	3	5
	Mean	1.06000	3.34100	4.28140	1.05080	2.63200	4.10240
	SD	0.452548	1.103008	1.488950	0.295853	1.073817	2.144174
	SE	0.320000	0.636822	0.665878	0.209200	0.619969	0.958904
	CV(%)	42.69324	33.01431	34.77717	28.15507	40.79852	52.26633
	Mininum	0.7400	2.4790	2.8520	0.8416	1.8260	2.2840
	25%	0.74000	2.47900	3.16600	0.84160	1.82600	2.86200
	Median	1.06000	2.96000	3.88900	1.05080	2.21900	3.37700
	75%	1.38000	4.58400	5.00400	1.26000	3.85100	4.28300
	Maximum	1.3800	4.5840	6.4960	1.2600	3.8510	7.7060
36 hours	n	1	2	5	1	2	5
	Mean	0.71450	3.34350	4.59860	1.08500	3.81700	4.09700
	SD		1.784030	1.468756		2.825599	2.014804
	SE		1.261500	0.656848		1.998000	0.901048
	CV(%)		53.35817	31.93920		74.02669	49.17755
	Mininum	0.7145	2.0820	2.4910	1.0850	1.8190	2.3670
	25%	0.71450	2.08200	4.10800	1.08500	1.81900	3.07200
	Median	0.71450	3.34350	4.46800	1.08500	3.81700	3.64800
	75%	0.71450	4.60500	5.64200	1.08500	5.81500	3.84700
	Maximum	0.7145	4.6050	6.2840	1.0850	5.8150	7.5510
48 hours	n	3	1	5	3	1	5
	Mean	0.81028	2.13700	2.78800	0.78122	1.78900	3.07200
	SD	0.809334		1.701034	0.840605		1.056546
	SE	0.467269		0.760726	0.485324		0.472502
	CV(%)	99.88285		61.01271	107.60158		34.39278
	Mininum	0.0431	2.1370	0.8130	0.0549	1.7890	1.9720
	25%	0.04305	2.13700	1.88600	0.05486	1.78900	2.20600
	Median	0.73180	2.13700	2.21400	0.58680	1.78900	3.27400
	75%	1.65600	2.13700	3.97700	1.70200	1.78900	3.28000
	Maximum	1.6560	2.1370	5.0500	1.7020	1.7890	4.6280
Early Termination	n	1	1	1	1	1	1
	Mean	0.09051	0.05920	1.48100	0.05799	0.02643	0.83750
	SD						
	SE						
	CV(%)						
	Mininum	0.0905	0.0592	1.4810	0.0580	0.0264	0.8375
	25%	0.09051	0.05920	1.48100	0.05799	0.02643	0.83750
	Median	0.09051	0.05920	1.48100	0.05799	0.02643	0.83750
	75%	0.09051	0.05920	1.48100	0.05799	0.02643	0.83750
	Maximum	0.0905	0.0592	1.4810	0.0580	0.0264	0.8375

Source: Listing 16.2.5.2
Program: TPK2.sas Output: TPK2.rtf

Final Date: 05FEB13

Reference ID: 4499855

11.4.7. Efficacy Conclusions

In both the single-dose and multiple-dose periods, improvement in postoperative pain following pediatric surgery was seen in all treatment groups.

In the single-dose period, the mean pain intensity scores decreased (improved) from baseline at each time point in each of the 3 treatment groups. The largest mean change from baseline was seen at 4 hours post-dose in the 5-mg group (mean change of -36.2 [25.03]), 3 hours post-dose in the 10-mg group (mean change of -29.3 [20.21]), and 2 hours post-dose in the 15-mg group (mean change of -33.8 [20.10]).

In the multiple-dose period, the mean pain intensity scores improved from baseline at each time point following the first dose in each of the 3 treatment groups, except in the 10-mg group at 15 minutes and 30 minutes post first dose (mean [SD] changes of 0.5 [9.56] and 3.1 [22.33], respectively). The mean largest changes were seen in each dose group at 1 hour post first dose.

In the multiple-dose period, pain intensity also improved from baseline to immediately prior to each subsequent dose (every 4 to 6 hours) in the 5-mg and 15-mg dose groups and immediately prior to each subsequent dose except doses 2, 3, and 4 following the first dose in the 10-mg group.

11.4.8. Pharmacokinetic Conclusions

In the single-dose period, the total plasma exposure, AUC0-inf, of both oxymorphone and 6-OH-oxymorphone increased with increasing dose. Between the 10-mg and 15-mg dose the mean AUC0-inf of oxymorphone increased in a greater than dose proportional manner. However, due to the small number of subjects and the wide variability in the data, it is not possible to make any conclusive interpretation of this observation. The mean Cmax of oxymorphone was lower in the in the 10-mg group versus the 5-mg group, which may be related to the small number of subjects and a high degree of intersubject variability. AUC0-inf and Cmax of 6-OH oxymorphone, on the other hand, appeared to increase in a near proportional manner with oxymorphone dose.

The mean half-life of oxymorphone increased with increasing dose from 12.1 hours in the 5-mg group to 15.9 hours in the 10-mg group and 20.0 hours in the 15-mg group. However, given the large interindividual variability, these differences do not appear to be significant. The half-life of 6-OH-oxymorphone, however, appeared to be independent of oxymorphone dose.

In the multiple-dose period of this study, pharmacokinetic parameters for oxymorphone and 6-OH-oxymorphone were not evaluated. Rather, their 4-hour plasma concentrations, which mostly represented trough levels from the subsequent dose, were analyzed.

There was a significant amount of variability in the concentration-time scatter plots, but in general there appeared to be a >2-fold increase in median oxymorphone and 6-OH-oxymorphone concentration within each of the 3 dose groups following multiple oxymorphone dosing. In addition, the median oxymorphone plasma concentrations appeared to increase with dose in a nearly dose proportional manner.

12. SAFETY EVALUATION

12.1. Extent of Exposure

The number of doses of oxymorphone IR taken is summarized by dose and overall for each study period in Table 14.

In the single-dose period, each of the 33 subjects received a single dose of oxymorphone IR, with 13 subjects receiving 5 mg, 9 subjects receiving 10 mg, and 11 subjects receiving 15 mg. In the multiple-dose period, subjects received a mean (SD) of 5.5 (4.66) doses overall. The mean number of doses taken per subject was lowest in the 5-mg group (4.0 [3.97] doses) and highest in the 15-mg group (7.0 [5.13] doses).

Table 14: Exposure to Oxymorphone IR Study Medication – Safety Population

Reference ID: 4499855

Treatment/Statistics	5 mg (N=22)	10 mg (N=17)	15 mg (N=19)	Overall (N=58)
Single Dose				
n	13	9	11	33
Multiple Dose (Number of Doses Taken)				
n	9	8	8	25
Mean (SD)	4.0 (3.97)	5.8 (4.98)	7.0 (5.13)	5.5 (4.66)
Median	2.0	4.5	9.0	4.0
Min, Max	1, 12	1, 13	1, 12	1, 13

12.2.2. Display of Adverse Events

Table 15: Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in Either Treatment Period by Preferred Term—Number (%) of Subjects – Safety Population

	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)
Number of Subjects With at Least One Adverse Event	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%)
Anaemia	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%)
Hypoaesthesia	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%)

Data Source: Table 14.3.1.1
Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages are based on the number of subjects in each treatment group. Adverse events were coded by system organ class and preferred term using MedDRA, Version 11.1.

12.2.3.2. Relationship to Study Drug of Treatment-Emergent Adverse Events
All TEAEs are summarized by system organ class and relationship to study drug in Table 16.

Table 16: Treatment-Related Adverse Events – Safety Population

	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)
Number of Subjects With at Least One Adverse Event	0	2 (22.2%)	1 (9.1%)	3 (9.1%)	5 (55.6%)	0	4 (50.0%)	9 (36.0%)
Gastrointestinal disorders	0	2 (22.2%)	1 (9.1%)	3 (9.1%)	4 (44.4%)	0	2 (25.0%)	6 (24.0%)
Constipation	0	0	1 (9.1%)	1 (3.0%)	2 (22.2%)	0	1 (12.5%)	3 (12.0%)
Nausea	0	2 (22.2%)	1 (9.1%)	3 (9.1%)	2 (22.2%)	0	1 (12.5%)	3 (12.0%)
Vomiting	0	1 (11.1%)	0	1 (3.0%)	1 (11.1%)	0	1 (12.5%)	2 (8.0%)
Investigations	0	0	0	0	0	0	2 (25.0%)	2 (8.0%)
Oxygen saturation decreased	0	0	0	0	0	0	2 (25.0%)	2 (8.0%)
Nervous system disorders	0	0	0	0	2 (22.2%)	0	2 (25.0%)	4 (16.0%)
Dizziness	0	0	0	0	0	0	1 (12.5%)	1 (4.0%)
Headache	0	0	0	0	1 (11.1%)	0	0	1 (4.0%)
Sedation	0	0	0	0	1 (11.1%)	0	1 (12.5%)	2 (8.0%)
Tremor	0	0	0	0	0	0	1 (12.5%)	1 (4.0%)
Renal and urinary disorders	0	0	0	0	0	0	3 (37.5%)	3 (12.0%)
Urinary retention	0	0	0	0	0	0	3 (37.5%)	3 (12.0%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (11.1%)	0	0	1 (4.0%)
Respiratory depression	0	0	0	0	1 (11.1%)	0	0	1 (4.0%)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (11.1%)	0	1 (12.5%)	2 (8.0%)
Pruritus	0	0	0	0	1 (11.1%)	0	1 (12.5%)	2 (8.0%)

Data Source: Table 14.3.1.2
Note: Treatment related AE is defined as an AE that is possibly or probably related to study drug. At each level of subject summarization, a subject is counted once for the AE related to study drug if the subject reported one or more events. Percentages are based on the number of subjects in each treatment group. Adverse events were coded by system organ class and preferred term using MedDRA, Version 11.1.

Additional information:

1. Listing 16.2.5.3 Plasma Pharmacokinetic Parameters of Oxymorphone IR

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=Oxymorphone Treatment = Single Dose 5 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	20.96	22.26	4.0010	7.9166667	0.91850	0.7063	0.98
	3.61	4.67	0.5155	2	0.04275	0.0403	17.20
	2.00	2.08	0.6506	2	0.03613	0.4818	1.44
	1.18	1.60	0.0802	13	0.03228	0.0776	8.94
	2.96	3.59	0.3501	8.3333333	0.04648	0.0743	9.33
	6.92	6.99	1.8370	2.35	0.03130	0.4088	1.70
	4.04	5.62	0.5170	4.25	0.05317	0.0336	20.64
	6.14	7.43	1.4060	2.15	0.04338	0.0336	20.61
	9.74	14.44	1.8340	2.0833333	0.11620	0.0247	28.06

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=Oxymorphone Treatment = Single Dose 10 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	3.35		0.6351	4.0833333	0.07525		
	0.12		0.0427	2	0.02964		
	5.11	6.77	1.2030	2	0.11400	0.0686	10.10
	2.57		0.2877	8.3166667	0.20310		
	6.47	17.74	0.8352	3.25	0.21500	0.0191	36.35
	4.98	6.16	1.9630	2.4333333	0.65280	0.5551	1.25

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=Oxymorphone Treatment = Single Dose 15 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	16.64	23.11	0.9776	8.1666667	0.39160	0.0605	11.46
	9.88	17.01	1.3340	2	0.18370	0.0258	26.89
	24.77	26.12	2.5860	4	0.18460	0.1371	5.06
	13.82	20.59	2.0470	4.0333333	0.23570	0.0348	19.90
	7.59	28.60	1.9690	2.05	0.20200	0.0096	72.13
	7.90	8.70	1.0590	3.35	0.08231	0.1023	6.78
	467.26	746.34	33.5500	8.0833333	14.56000	0.0522	13.29
	52.21		3.6430	21.966667	3.64300		
	3.30	3.89	0.4853	2.0833333	0.09476	0.1614	4.29

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Reference ID: 4499855

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=6-OH-Oxymorphone Treatment = Single Dose 5 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	3.70	4.38	0.6805	7.9166667	0.28530	0.4173	1.66
	0.30		0.1054	2	0.09684		
	0.61	0.69	0.2162	2	0.04512	0.5223	1.33
	0.38	0.58	0.0518	8.3333333	0.02929	0.1423	4.87
	0.93	1.04	0.2323	2.35	0.03454	0.3160	2.19
	0.89		0.1613	4.25	0.03486		
	0.28		0.1021	2.15	0.07417		
	5.27	18.24	0.9623	2.0833333	0.10450	0.0081	86.02

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=6-OH-Oxymorphone Treatment = Single Dose 10 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	2.80	3.45	0.4102	4.0833333	0.03458	0.0529	13.09
	2.73	3.69	0.4783	4.0166667	0.14370	0.1503	4.61
	2.56	4.75	0.4494	2	0.10430	0.0476	14.55
	1.38		0.1614	12	0.16140		
	4.42	26.99	0.4017	3.25	0.18820	0.0083	83.11
	4.35	4.59	1.0220	2.4333333	0.05864	0.2461	2.82

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Listing 16.2.5.3
Plasma Pharmacokinetic Parameters of Oxymorphone IR

Analyte=6-OH-Oxymorphone Treatment = Single Dose 15 mg

Subject ID	AUC[0-t] (ng*hr/mL)	AUC[0-inf] (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	Ct (ng/mL)	lambda	T 1/2 (hr)
(b) (6)	6.90	10.07	0.3909	12.166667	0.16860	0.0531	13.04
	3.68	6.07	0.4565	2	0.07702	0.0322	21.51
	10.87	12.68	1.0710	4	0.16470	0.0914	7.58
	6.79	15.93	0.7745	4.0333333	0.19330	0.0212	32.77
	4.99	9.07	0.9781	2.05	0.13470	0.0330	20.98
	8.46	10.22	1.1500	3.35	0.09999	0.0567	12.22
	12.14	34.41	1.8700	2.35	0.26400	0.0119	58.48
	10.03	12.56	1.4660	2.0333333	0.11370	0.0449	15.44
	2.34	4.15	0.3025	2.0833333	0.06105	0.0336	20.65

Source: the (b) (6) data - the bioanalytical report 1111116.00
Program: lpk2.sas Output: lpk2.rtf Final Date: 22JAN13

Source: en3203-010-compl-drug-concen-data.pdf; p.55-60/60

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4.3.3 Phase 3 study EN3319-302

Applicant's SYNOPSIS:

Title of Study: An Open-label, Non-randomized, Multicenter, Ascending Dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety, and Tolerability of Oral Liquid Oxymorphone HCl Immediate-release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects.
Principal Investigator: Not applicable

Reference ID: 4499855

Investigators: 14 investigators participated in this study. Four other physicians were part of the Independent Data Monitoring Committee (IDMC). See Appendix 16.1.4 for a complete list of investigators and important participants.
Study center(s): 14 study centers participated in this trial. See Appendix 16.1.4 for a complete list of study sites.
Publications (reference): None
Studied period (years): Date first patient enrolled: 13-Dec-2010 Date last patient completed: 06-Oct-2017
Phase of development: 3

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

The secondary objectives were: 1) *to describe the pharmacokinetic (PK) profile* of oxymorphone HCl IR oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies; and 2) *to establish the appropriate dosing recommendations* for oxymorphone HCl IR oral liquid in children aged 2 to ≤12 years requiring an opioid to treat their acute postoperative pain of various etiologies.

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

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

The age groups of subjects were:
A. 6 to ≤12 years
B. 2 to <6 years
C. 0 to < 2 years (Note: this age group was discontinued in Clinical Study Protocol Amendment 2)

Within each age group, there were up to 3 treatment cohorts of at least 6 subjects each:
1. 0.05 mg/kg oxymorphone HCl IR oral liquid
2. 0.10 mg/kg oxymorphone HCl IR oral liquid
3. 0.20 mg/kg oxymorphone HCl IR oral liquid, ***based on recommendation of the IDMC***

Subjects aged 6 to ≤12 years, 2 to <6 years, and 0 to <2 years were ***studied in parallel***; 3 treatment cohorts of the Single-Dose Phase were completed, after which enrollment began for the Multiple-Dose Phase of the study. In the Single-Dose Phase, the *first treatment* cohort of at least 6 subjects from each age group were given a single dose of oxymorphone HCl IR oral liquid *0.05 mg/kg* following postoperative parenteral analgesia according to each institution's standard of care. Administration of the oxymorphone HCl IR oral liquid occurred at the time when (according to each institution's standard of care) oral analgesics were to commence in the subject's postoperative analgesic regimen. Following completion of the first treatment cohort of at least 6 subjects within each age group, data was assessed by

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an external IDMC and, with an acceptable safety, effectiveness and tolerability review and IDMC recommendation, a second treatment cohort of at least 6 subjects in each age group was dosed with oxymorphone HCl IR oral liquid *0.10 mg/kg*. Following completion of the second treatment cohort of at least 6 subjects within each age group, data was assessed by an external IDMC and, with an acceptable effectiveness, safety, and tolerability review and IDMC recommendation, a third treatment cohort of at least 6 subjects in each age group was dosed with oxymorphone HCl IR oral liquid *0.20 mg/kg*.
If needed, non-oxycodone, non-oxymorphone rescue analgesia was available according to standard of care at each institution.
Blood from a patent line was collected to assess PKs, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (e.g., naloxone-based) was readily available for immediate intravenous administration at the discretion of the Investigator.

Multiple-Dose Phase
It was intended that at the end of the Single-Dose Phase for each age group, the IDMC was to recommend up to 3 doses to be used in the Multiple-Dose Phase. *The IDMC recommended that a single- dose of 0.20 mg/kg be administered as postoperative parenteral analgesia.* The Multiple-Dose Phase proceeded using the following age group stratification:
A. 6 to ≤12 years
B. 2 to <6 years

Both age groups were studied in parallel. Following postoperative parenteral analgesia, when oral dosing commenced according to each institution's standard of care, ***dosing began at the dose of 0.20 mg/kg for both age groups***. Subjects were dosed ***every 4 to 6 hours*** (***no sooner than every 4 hours and no later than every 6 hours***) ***for up to 48 hours***. Subjects may have received non-oxycodone, non- oxymorphone rescue medication and discontinued from the study in the event that the oxymorphone HCl IR oral liquid did not provide adequate pain relief.
The IDMC recommended that an additional 3 subjects in the 6 to < 12 years age group was enrolled to assess safety and accumulation of oxymorphone and its principal active metabolite, 6β-hydroxyoxymorphone, beyond 6 doses due to changes observed in vital sign parameters.
Blood from a patent line was collected to assess PK, examine dose proportionality, and estimate effective and safe dosing. An opioid antagonist (e.g., naloxone-based) was readily available for immediate intravenous administration at the discretion of the Investigator.

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

Number of Subjects: Up to 72 subjects were planned for enrollment; up to 18 subjects each, in the 6 to ≤ 12years and 2 to < 6 years age groups in the Single- and Multiple-Doses phases. The exact number was determined by IDMC. Overall 61 subjects were enrolled, 45 subjects in the Single-Dose Phase and 16 subjects in the Multiple-Dose Phase.

Diagnosis and Inclusion/Exclusion Criteria: Acute postoperative pain requiring a strong oral opioid analgesic for moderate-to-severe pain.
Inclusion Criteria:
1. Males or females between 2 to ≤12 years of age. Females of child-bearing potential must have been practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double barrier method). For the purpose of this study, all peri- and post-

Reference ID: 4499855

pubertal females were considered to be of child-bearing potential unless they were biologically sterile or surgically sterile for more than 1 year.

2. Subjects must have been at least 10 kg and body mass index (BMI) ≤30.
3. Scheduled to have a surgery for which oral opioid analgesia was needed to manage postoperative pain for at least 24 hours (Single-Dose Phase) or 48 hours (Multiple-Dose Phase) following intraoperative and/or postoperative parenteral analgesia
4. Be hospital inpatients, expected to be hospitalized for at least 24 hours (Single-Dose Phase) and 48 hours (Multiple-Dose Phase) following the initial administration of oxymorphone IR
5. Lab samples, either drawn intraoperatively (prior to surgical incision) or from within 21 days preoperatively, for clinical chemistry and hematology laboratory analytes (the results must have been reviewed by the Investigator prior to oxymorphone HCl IR oral liquid administration for study eligibility)
6. Able to provide pain assessment evaluations using an age-appropriate instrument provided in the protocol
7. On an intravenous analgesic regimen utilizing a short-acting opioid analgesic following surgery AND anticipated to be switched to an oral opioid as part of the analgesic regimen (according to institution standard of care)
8. Demonstrated the ability to tolerate clear fluids following surgery according to the standard of care at each institution
9. Informed of the nature of the study and written informed consent had been obtained from the legally responsible parent(s)/legal guardian(s)
10. Provided assent in accordance with Institutional Review Board (IRB) requirements
11. Line in place for blood sampling

Exclusion Criteria:

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

Investigational Product, Dosage and Mode of Administration:

EN3319, oxymorphone HCl IR oral liquid 1 mg/mL was administered at doses of 0.05, 0.10, 0.20 mg/kg in the Single-Dose Phase and 0.20 mg/kg in the Multiple-Dose phase (every 4-6 hours) in subjects ages 2

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to <12 years. Subjects <2 years received the 0.05 mg/kg in the Single-Dose Phase before this age group arm was terminated with Amendment 2.

Duration of Study:
Screening Phase – up to 21 days Single-Dose Phase – 1 day Multiple-Dose Phase – 2 days Follow-up telephone call – 14 days

Reference Therapy, Dosage and Mode of Administration: Not applicable

Criteria for evaluation:
Effectiveness: For subjects aged 6 to ≤ 12 years, assessment of current pain intensity was obtained using the FPS-R for up to 12 hours (Single-Dose Phase) or up to 48-hours (Multiple-Dose Phase) following dose administration, or until rescue medication was used in accordance with the Schedule of Study Assessments/Procedures. For subjects aged 2 to <6 years, assessment of current pain intensity was obtained using the FLACC behavioral measurement for up to 12 hours (Single-Dose Phase) or up to 48 hours (Multiple-Dose Phase) following dose administration, or until rescue medication was administered in accordance with the Schedule of Study Assessments/Procedures.

Pharmacokinetics: Blood samples for PK assessments of oxymorphone HCl IR oral liquid were obtained over a 24-hour period (Single-Dose Phase) or over a 48-hour period (Multiple-Dose Phase) following oxymorphone HCl IR oral liquid administration Where possible the following PK parameters were calculated: Cmax, tmax, Clast, AUC0-t, AUC0-∞, AUC0-2, AUC0-4, AUC0-6, AUC0-24, λn, t1/2, CL/F, and V/F.

Safety and Tolerability: Safety was assessed using adverse events (AEs), assessments of respiratory and neurological function, vital signs, urine drug screen, and clinical laboratory tests.

Statistical methods:
Sample Size Consideration: The sample size of 6 subjects in each age group, treatment cohort, and study phase was selected to describe the effectiveness, safety, tolerability, and PK properties of the oxymorphone HCl IR oral liquid in children aged 2 to ≤12 years. With up to 3 treatment cohorts and 6 subjects per treatment cohort, it was planned that up to 36 subjects were enrolled in each study phase. Assuming the % coefficients of variation (CV) for CL/F and V/F are both as high as 72% for pediatric subjects, then with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% confidence interval (CI) for both clearance and volume of distribution is (0.71*X, 1.40*X), where X represents the geometric mean of either clearance or volume of distribution, respectively. In other words, with 18 subjects per age group or 36 subjects per study phase, the 2-sided 95% CIs are within 60% and 140% of the point estimates for the geometric mean estimates of both clearance and volume of distribution for oxymorphone in all age groups.

Analysis Populations:
The safety population included all subjects who received at least 1 dose of oxymorphone HCl IR oral liquid. All safety analyses were performed using this population. The effectiveness population included all subjects who received at least 1 dose of oxymorphone HCl IR oral liquid and who completed at least 1 post-dose pain intensity assessment. All effectiveness analyses were performed using this population.

The PK study population included all subjects who received oxymorphone HCl IR oral liquid as planned and *had sufficient plasma concentration data* to facilitate the calculation of PK variables were evaluable for PK analysis. Final subject evaluability was determined prior to locking the database. All statistical analyses were performed using the SAS® (SAS Institute, Cary, NC) Version 9.3. All CIs were 2-sided.

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Subject Disposition: The numbers of subjects in each analysis data set were presented. The numbers and percentages of subjects who completed or discontinued from the study were summarized by age group, treatment cohort, and study phase for all enrolled subjects. For subjects who discontinued from the study, the reason for discontinuation was tabulated.

Demographics and Baseline Characteristics: Demographic and baseline characteristics including age, sex, race, weight, and BMI were summarized by age group, treatment cohort, and study phase using appropriate descriptive statistics.

Prior and Concomitant Medications: Medications administered prior to and concomitantly with study treatment were listed for the safety population. These medications were coded using the World Health Organization (WHO) drug dictionary.

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

Safety Analysis: Assessment of safety and tolerability was based on the incidence of AEs, AEs resulting in discontinuation, and serious adverse events (SAEs). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 19.0). Summaries of AEs were provided
showing the number and percentage of subjects who experience at least 1 AE. These summaries were presented by system organ class (SOC) and preferred term (PT). The occurrences of AEs were also tabulated by severity. SAEs and AEs resulting in discontinuation will be summarized separately.
Assessment of safety and tolerability were also based on PK analysis (described below), clinical laboratory results, vital sign measurements, respiratory and neurological assessments, and other safety variables, which were summarized by age group, treatment cohort, and study phase for each time point using appropriate descriptive statistics.

Pharmacokinetic Analysis: PK variables (CL/F, V/F, λn, and t½, and dose-normalized Cmax, Clast, AUC0-t, AUC0-∞, AUC0-2, AUC0-4, AUC0-6, and AUC0-24) were summarized by age group using N, mean, standard deviation (SD), geometric mean, %CV, minimum, median, and maximum ***following dosing in the Single-Dose Phase*** and ***the first and seventh doses in the Multiple-Dose Phase*** in order to permit comparison of single-dose and multiple-dose PKs. Parameters were summarized by age group and dose, as appropriate. In addition, a 2-sided 95% CI was constructed for all dose-normalized parameters, CL/F, and V/F, tmax, and Tlast were summarized by age group using median, minimum, and maximum. Descriptive statistics were determined using *SAS* (version 9.2). No statistical comparisons among dose groups or between age groups were conducted and statistical significance is not implied by any statements comparing or contrasting mean or geometric mean values.

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Linearity Assessment: Geometric mean and 95% confidence intervals (CIs) for dose-normalized Cmax, Clast, AUC0-t, AUC0-∞, AUC0-2, AUC0-4, AUC0-6, and AUC0-24, CL/F, and V/F and t1/2 were evaluated to compare linearity among the 3 doses administered in the Single-Dose Phase.
Accumulation Assessment: Limited oxymorphone and 6β-hydroxyoxymorphone concentration data *after administration of Dose 7 to children in both groups did not permit definitive comparisons* oxymorphone or 6β-hydroxyoxymorphone PK characteristics *between Dose 7 and Dose 1*. Where possible comparisons of values for Cmax/Dose and AUC0-2/Dose between Dose 7 and Dose 1 were conducted. Evaluation of the time to reach steady state was accomplished by visual inspection of the pre-dose concentration data.

RESULTS AND CONCLUSIONS

(b) (4)

PHARMACOKINETIC RESULTS:

- Oxymorphone was rapidly absorbed after oral administration, reaching maximum mean plasma oxymorphone concentrations within the range of 0.5 to 4.0 hours across the dose range.
- The t½ following a single-dose of oxymorphone HCl oral liquid could only be determined in 2 to 3 subjects/dose/age group, with the means ranging between 3 to 7.5 hours.
- Mean oxymorphone Cmax and AUC0-t and all partial area values increased with increasing oxymorphone dose in *dose-linear manner following single-dose administration*. AUC0-∞ could only be determined for 2 to 3 subjects/dose/ age group.
- 6β-hydroxyoxymorphone concentrations closely followed that of oxymorphone, reaching maximum mean plasma 6β-hydroxyoxymorphone concentrations within 0.5 to 1.0 hours.
- 6β-hydroxyoxymorphone exposure was approximately 16.4% to 23.8% of the exposure to oxymorphone after single oral doses.
- The PK parameters of oxymorphone and 6β-hydroxyoxymorphone were generally similar in both age groups following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl immediate-release oral liquid.
- *Only children aged 6 years to ≤12 years had sufficient amount of concentration data on Day 7 to evaluate oxymorphone and 6β-hydroxyoxymorphone steady-state PKs*; however, the pre-dose concentrations of oxymorphone for Doses 3 through 7 were similar between the age groups, suggesting a similar steady-state PKs between the age groups.
- *Observed pre-dose oxymorphone concentrations appeared to reach steady state by the third through sixth dose in children aged 6 to ≤12 years*, while pre-dose 6β-hydroxyoxymorphone concentrations appeared reach steady state by the fifth dose in this age group.

SAFETY RESULTS:

- There were no deaths reported in the study.
- Overall, *four (6%) subjects experienced SAEs in the study*. There was a higher proportion of subjects who experienced SAEs in the Multiple-Dose versus the Single-Dose Phase (12.5% versus 4.4%, respectively).
- *Three (18.8%) subjects in the Multiple-Dose Phase discontinued prematurely* due to treatment-related treatment-emergent adverse events (TEAEs). These included: sedation, somnolence, and lethargy.
- Overall, 46 (75.4%) subjects experienced a TEAE in the study. There was a higher proportion of subjects that experienced TEAEs in the Multiple-Dose versus the Single-Dose Phase (87.5% versus 71.1%, respectively).
- The most common system organ class (SOCs) in which TEAEs were reported overall, included: General disorders and administration site conditions (31.1%), gastrointestinal disorders (27.9%), injury, poisoning and procedural complications (19.7%), and skin and subcutaneous tissue disorders (19.7%).
- Overall, pyrexia and vomiting (each 13.1%) were the most frequently occurring TEAEs. By dosing phase, pyrexia (11.1%) was the most frequently occurring TEAE in the Single-Dose Phase and nausea and vomiting (each 25%) were the most frequently occurring TEAEs in the Multiple-Dose Phase.
- No events of apnea were considered TEAE.
- There was a higher proportion of sedation in the Multiple-Dose Phase versus the Single-Dose Phase of the study (15 subjects [93.8%] versus 16 subjects [35.6%], respectively). There were 2 TEAEs of sedation in the Multiple-Dose Phase of the study.
- The incidence of TEAEs was not dose-related. The highest proportion of subjects who reported TEAEs received the lowest dose 0.05 mg/kg in all 3 age groups: 100% in those aged 2 to <6 years, 83.3% in those aged 6 to ≤12 years, and 57.1% in those aged 0 to <2 years.
- There was a higher proportion of treatment-related TEAEs in the Multiple-Dose versus the Single-Dose Phase (62.5% versus 8.9%, respectively).
- The majority of TEAEs were of mild (49.2%) to moderate (19.7%) severity. The proportion of subjects with SAEs was similar between the Single-Dose and Multiple-Dose Phases (6.7% versus 6.3%, respectively).
- A total of 14 (23%) subjects reported at least 1 treatment-related TEAE. The proportion of subjects with TEAEs was higher in the Multiple-Dose versus the Single-Dose Phase (62.50% versus 8.9%, respectively).
- There were no clinically meaningful trends in changes from baseline to end of study in serum chemistry, hematology, or vital sign parameters.

CONCLUSION:

The safety results show that single- and multiple-doses of oxymorphone HCl IR oral liquid were well tolerated in pediatric subjects aged 2 to 12 years for the treatment of postoperative pain requiring an opioid. There were no new safety signals observed. In general, the AEs observed were reflective of the known AE profile for opioids.

Oxymorphone was rapidly absorbed after single-dose oral administration, reached maximum mean plasma oxymorphone concentrations within 1.0 to 1.5 hours, and declined in a multi-exponential manner with the exception of the 0.20 mg/kg dose group in subjects aged 6 to ≤12 years which exhibited an atypical "second peak" at 8 hours. The data contributing to the second peak was derived from 3 subjects with widely varying oxymorphone concentration data. The onset of pain relief occurred at approximately 1 to 1.5 hours after dose administration. The PK characteristics of oxymorphone were determined to be generally similar in both age groups following single-dose administration of 0.05, 0.10, and 0.20 mg/kg oxymorphone HCl IR oral liquid in the Single-Dose Phase. The comparison of geometric mean dose

normalized oxymorphone partial areas for AUC0-2 and AUC0-4, following single- dose administration in the Single-Dose Phase and after Dose 1 in the Multiple-Dose Phase, were in excellent agreement indicating oxymorphone PK characteristics were similar in both study phases.
Similarly, the comparison of geometric mean dose-normalized 6β-hydroxyoxymorphone partial areas for AUC0-2 and AUC0-4 following single-dose administration in the Single-Dose Phase and after Dose 1 in the Multiple-Dose Phase were in excellent agreement indicating that single-dose 6β-hydroxyoxymorphone PK characteristics were similar in both study phases.
Opioids are an established component of pediatric postoperative pain treatment. The effectiveness, PK, and safety results in this study were consistent among age groups, dose groups, and in the Single- and Multiple-Dose phases. The safety findings were consistent with the established safety profile of oxymorphone. (b) (4)

Date of the report: 7-Dec-2018

Reviewer comments: There are no issues identified with the Applicant's synopsis report.

Additional information pertinent from the Applicant's main study report:

Reviewer comments: There are no issues identified with the Applicant's report.

7.3. Dose Rationale

The equianalgesic ratio of oral oxycodone to oral oxymorphone has been determined to be approximately 2 to 1 (Gabrail et al, 2004) conferring an equianalgesic ratio of oral morphine to oral oxymorphone of approximately 3 to 1. The recommended starting dose of oral morphine for a child/adult <50 kg is 0.3 mg/kg (AHCPR, 1992). *Thus, from previous findings that have established equianalgesic ratios, the predicted equianalgesic dose of liquid oxymorphone that should provide equivalent analgesia to 0.3 mg/kg of oral morphine is 0.1 mg/kg. Because the safety and effectiveness of oxymorphone have not been fully assessed in a pediatric population, a starting dose of 0.05 mg/kg oxymorphone HCl IR oral liquid was chosen for the current study, which represents approximately half of the predicted equianalgesic starting dose of oral morphine.*

9.4.3.1. Single-Dose Phase
The intended treatment assignment for the Single-Dose Phase, according to Protocol Amendment 2 is summarized in Table 1.

Table 1: Treatment Assignment – Single-Dose Phase

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

a As determined by the IDMC

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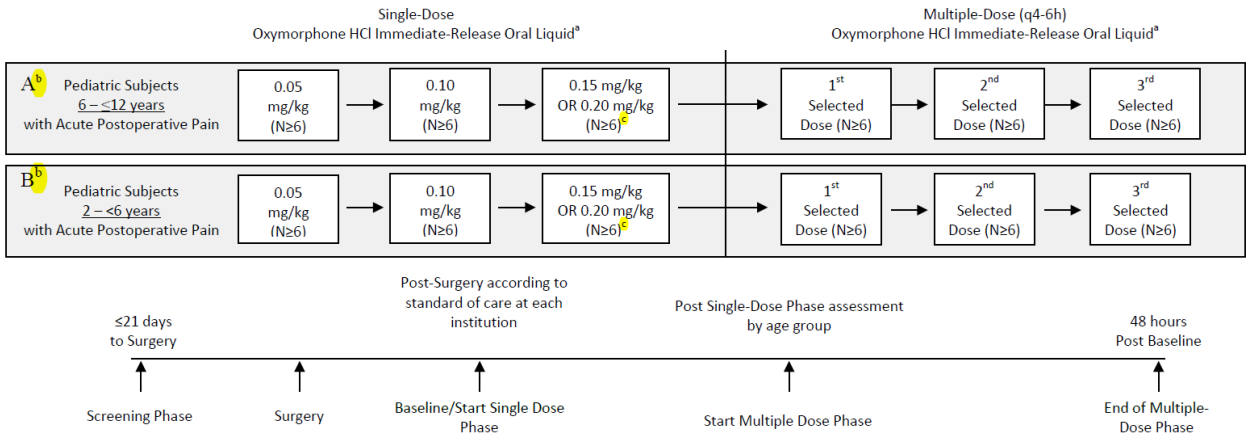
9.5. Effectiveness and Safety Variables

9.5.1. Effectiveness and Safety Measurements Assessed and Flow Chart

The study design for Study EN3319-302 is illustrated in Figure 1. For a schedule of study assessments and procedures, refer to Appendix 16.1.1, Protocol [Section 7.1].

Figure 1: Study Design



FOOTNOTES:

[a] Up to 3 ascending dose levels for the Multiple-Dose Phase could have been selected from the results of the Single-Dose Phase by the IDMC.

[b] The original study design included age groups inclusive of 0 - 2 years. A subject was enrolled into one of the treatment cohorts in either the Single-Dose Phase or the Multiple-Dose Phase; a subject could not progress from one treatment cohort to the next treatment cohort.

[c] Dose was to be selected based on IDMC recommendation and review of the results of the 0.10 mg/kg cohort. The IDMC recommended to proceed with a dose of 0.20 mg/kg. The IDMC could have also recommended to proceed directly into the Multiple-Dose Phase

IR=Immediate Release; q4-6=Every 4 to 6 hours

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

9.5.4. Drug Concentration Measurements

Blood samples (0.5 mL each) for PK analyses were obtained at the following times:

• Single-Dose Phase: Serial blood samples were collected at time 0 (Baseline), at 15 and 30 minutes, and at 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post-dose.

• Multiple-Dose Phase: Serial blood samples were collected at: time 0 (Baseline), at 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***.

A validated microvolume liquid chromatography dual mass spectrometry (LC-MS/MS) analytical method was used for the determination of the concentrations of oxymorphone and 6β-hydroxyoxymorphone in the plasma samples. The microvolume assay required 50 µL of plasma per sample. Details of the method validation and sample analysis are included in the Bioanalytical Report for Study EN3319-302 (Appendix 16.1.10).

9.7.1.6. Pharmacokinetic Analysis

Plasma concentrations below limit of quantification (BLQ) were set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations were set to missing. For the computation of PK variables, the BLQ concentrations prior to the first measurable concentration were set to 0 and other BLQ concentrations were set to missing.

No values of λn, t½, or AUC0-∞ were reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile. Nominal sample collection times were used for the determination of mean concentrations and for presentation of mean concentration-time data in tables and figures.

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10.1. Demographic and Other Baseline Characteristics

Overall, the mean (SD) age of subjects in the Safety Population was 5.2 (3.50) years in the Single-Dose Phase and 7.4 (3.31) years in the Multiple-Dose Phase (Table 4). Subjects in the Single-Dose Phase weighed less (mean weight 23.36 kg) and were shorter (mean height 109.77 cm) compared with subjects enrolled in the Multiple-Dose Phase (32.82 kg and 128.09 cm, respectively). This is expected given the counts and distribution of subjects in the younger and older age groups in the Single- and Multiple-Dose Phases.

Table 4: Demographics and Baseline Characteristics by Dose Phase (Safety Population)

Age (years)	Single-Dose Phase (N=45)	Multiple-Dose Phase (N=16)	Overall (N=61)
N	45	16	61
Mean	5.2	7.4	5.8
Standard Deviation	3.50	3.31	3.56
Median	5.0	7.5	5.0
Min, Max	<1, 12	2, 12	<1, 12
Age Group, n (%)			
A: 6 - ≤ 12 years	19 (42.2)	10 (62.5)	29 (47.5)
B: 2 - < 6 years	19 (42.2)	6 (37.5)	25 (41.0)
C: 0 - < 2 years	7 (15.6)	0	7 (11.5)
Gender, n (%)			
Female	21 (46.7)	5 (31.3)	26 (42.6)
Male	24 (53.3)	11 (68.8)	35 (57.4)
Race, n (%)			
American Indian or Alaska Native	1 (2.2)	0	1 (1.6)
Asian	3 (6.7)	0	3 (4.9)
Black or African American	8 (17.8)	4 (25.0)	12 (19.7)
White	33 (73.3)	12 (75.0)	45 (73.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (6.7)	0	3 (4.9)
Not Hispanic or Latino	42 (93.3)	16 (100.0)	58 (95.1)
Weight (kg)			
N	45	16	61
Mean	23.36	32.82	25.84
Standard Deviation	14.897	18.517	16.311
Median	19.50	27.70	20.50
Min, Max	4.0, 80.8	16.0, 75.0	4.0, 80.8

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Height (cm)			
N	43	15	58
Mean	109.77	128.09	114.51
Standard Deviation	24.590	23.293	25.382
Median	113.00	131.00	115.00
Min, Max	55.0, 158.1	91.0, 163.7	55.0, 163.7
Body Mass Index (kg/m^2)			
N	43	15	58
Mean	17.81	19.28	18.19
Standard Deviation	4.176	4.706	4.326
Median	16.50	17.80	16.70
Min, Max	12.7, 32.3	14.2, 30.7	12.7, 32.3

Source: Table 14.1.4.1
Note: Percentages are based on the number of subjects ('N') in each dose phase or overall.

10.1.1. Demographics in the Single-Dose Phase

Table 5: Demographics and Baseline Characteristics by Age and Dose Group in Single-Dose Phase (Safety Population)

	6 to ≤12 Years Age Group			2 to <6 Years Age Group			0 to < 2 Years Age Group
	0.05 mg/kg (N=6)	0.10 mg/kg (N=6)	0.20 mg/kg (N=7)	0.05 mg/kg (N=6)	0.10 mg/kg (N=6)	0.20 mg/kg (N=7)	0.05 mg/kg (N=6)
Age (years)							
N	6	6	7	7	6	6	7
Mean	8.3	8.7	9.0	3.4	3.5	3.5	0.4
Standard Deviation	1.75	1.86	2.16	1.27	1.38	1.38	0.53
Median	7.5	9.0	9.0	3.0	3.5	3.5	<1
Min, Max	7, 11	6, 11	6, 12	2, 5	2, 5	2, 5	<1, 1
Gender, n (%)							
Female	1 (16.7)	2 (33.3)	6 (85.7)	2 (28.6)	3 (50.0)	6 (100.0)	1 (14.3)
Male	5 (83.3)	4 (66.7)	1 (14.3)	5 (71.4)	3 (50.0)	0	6 (85.7)
Race, n (%)							
American Indian or Alaska Native	0	0	1 (14.3)	0	0	0	0
Asian	0	2 (33.3)	0	0	1 (16.7)	0	0
Black or African American	2 (33.3)	1 (16.7)	0	3 (42.9)	1 (16.7)	0	1 (14.3)

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White	4 (66.7)	3 (50.0)	6 (85.7)	4 (57.1)	4 (66.7)	6 (100.0)	6 (85.7)
Ethnicity, n (%)							
Hispanic or Latino	0	0	1 (14.3)	0	0	2 (33.3)	0
Not Hispanic or Latino	6 (100.0)	6 (100.0)	6 (85.7)	7 (100.0)	6 (100.0)	4 (66.7)	7 (100.0)
Weight (kg)							
N	6	6	7	7	6	6	7
Mean	35.25	30.33	37.26	18.76	15.77	17.88	9.10
Standard Deviation	11.725	17.731	20.613	4.026	4.303	4.869	3.106
Median	39.80	23.45	33.10	18.20	14.70	17.65	8.70
Min, Max	20.1, 46.4	14.7, 64.2	19.7, 80.8	12.7, 24.2	11.4, 22.8	12.7, 26.2	4.0, 12.4
Height (cm)							
N	6	5	7	7	6	5	7
Mean	129.83	130.54	130.80	106.36	96.82	107.42	72.93
Standard Deviation	14.442	19.704	16.645	10.111	11.618	15.752	9.760
Median	131.00	131.00	125.00	105.00	95.25	108.50	73.00
Min, Max	113.0, 153.0	98.5, 149.8	110.0, 158.1	93.0, 120.5	82.5, 117.5	84.0, 124.0	55.0, 86.0
Body Mass Index (kg/m^2)							
N	6	5	7	7	6	5	7
Mean	20.35	17.52	20.59	16.43	16.70	16.24	16.51
Standard Deviation	4.371	6.354	6.044	1.568	2.948	2.293	2.554
Median	20.25	15.20	19.20	16.00	16.30	16.30	16.80
Min, Max	15.7, 26.6	12.8, 28.6	13.9, 32.3	14.7, 18.6	14.0, 22.3	12.7, 18.5	13.2, 20.7

Source: Table 14.1.4.3.
Note: Percentages are based on the number of subjects ('N') in each dose group in each age group in Single-Dose Phase.

10.1.2. Demographics in the Multiple-Dose Phase

Table 6: Demographics and Baseline Characteristics by Age Group in Multiple-Dose Phase (Safety Population)

	6 to ≤ 12 years Age Group (N=10)	2 to < 6 years Age Group (N=6)
Age (years)		
N	10	6
Mean	9.6	3.8
Standard Deviation	1.90	1.17
Median	9.5	4.0
Min, Max	7, 12	2, 5

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Gender, n (%)		
Female	5 (50.0)	0
Male	5 (50.0)	6 (100.0)
Race, n (%)		
Black or African American	3 (30.0)	1 (16.7)
White	7 (70.0)	5 (83.3)
Ethnicity, n (%)		
Not Hispanic or Latino	10 (100.0)	6 (100.0)
Weight (kg)		
N	10	6
Mean	41.81	17.83
Standard Deviation	18.103	2.701
Median	38.80	16.70
Min, Max	20.5, 75.0	16.0, 23.1
Height (cm)		
N	10	5
Mean	141.61	101.06
Standard Deviation	14.794	6.026
Median	139.00	104.00
Body Mass Index (kg/m^2)		
N	10	5
Mean	20.03	17.78
Standard Deviation	5.443	2.575
Median	17.90	16.30
Min, Max	14.2, 30.7	15.6, 21.4

Source: Table 14.1.4.4
Max=maximum; Min=Minimum
Note: Percentages are based on the number of subjects ('N') in each age group in Multiple-Dose Phase.

11.4. Pharmacokinetics

11.4.1. Demographic and Pre-treatment Characteristics

Table 18: Summary Demographic and Pre-treatment Characteristics

Study Phase	Single-Dose Phase		Multiple-Dose Phase	
Age Group	6 to ≤12 years	2 to <6 years	6 to ≤12 years	2 to ≤6 years
Age (years)				
N	19	19	10	5
Mean (SD)	9 (2)	3 (1)	10 (2)	4 (1)
Median	9	3	10	4
Minimum, Maximum	6, 12	2, 5	7, 12	2, 5

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Gender n (%)				
Male	10 (52.6)	8 (42.1)	5 (50.0)	5 (100.0)
Female	9 (47.4)	11 (57.9)	5 (50.0)	0 (0.0)
Race n (%)				
American Indian or Alaska Native	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (10.5)	1 (5.3)	0 (0.0)	0 (0.0)
Black or African American	3 (15.8)	4 (21.0)	3 (30.0)	1 (20.0)
White	13 (68.4)	14 (73.7)	7 (70.0)	4 (80.0)
Ethnicity n (%)				
Hispanic or Latino	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	18 (94.7)	17 (89.5)	10 (100.0)	5 (100.0)
Height (cm)				
N	18	18	10	4
Mean (SD)	130 (16)	103 (13)	142 (15)	100 (7)
Weight (kg)				
N	19	19	10	5
Mean (SD)	34.4 (16.6)	17.5 (4.3)	41.8 (18.1)	16.8 (0.9)
BMI (kg/m^2)				
N	18	18	10	4
Mean (SD)	19.7 (5.5)	16.5 (2.2)	20.0 (5.4)	16.9 (1.8)

Source: Study EN3319-302 Pharmacokinetic Report [Supportive Tables ST-1.4, ST-1.8, ST-1.9, and ST-1.10].

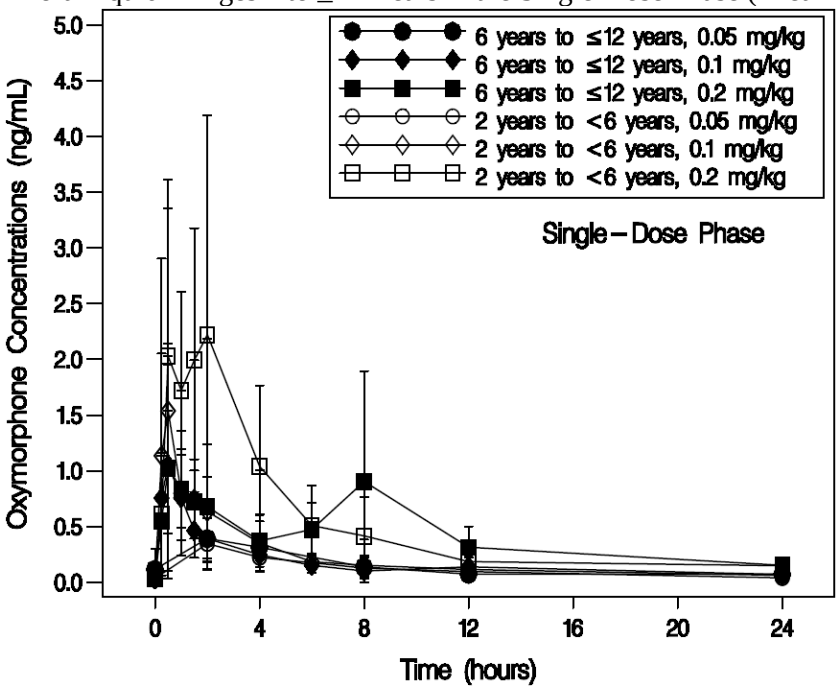
11.4.2. Bioanalytical Method Performance

All plasma samples collected were provided to the bioanalytical laboratory; 952 samples were analyzed for each analyte. Plasma oxymorphone and 6β-hydroxyoxymorphone concentrations were determined using a validated microvolume liquid chromatography-mass spectrometry (LC-MS/MS) analytical method. The microvolume assay required 50 µL of plasma per sample. The lower limit of quantitation for oxymorphone was 0.0250 ng/mL. The lower limit of quantitation for 6β-hydroxyoxymorphone was 0.0200 ng/mL.

11.4.3.3. Pharmacokinetics of Oxymorphone (Single-Dose Phase)

After administration of a single-dose of oxymorphone HCl IR oral liquid, oxymorphone reached maximum mean plasma oxymorphone concentrations within 1.0 to 1.5 hours. The 0.20 mg/kg dose group in the 6 to ≤12-year age group which exhibited an atypical "second peak" at 8 hours. The mean concentration data at this 8-hour time point was derived from only 3 subjects and the oxymorphone concentrations varied widely (1.99, 0.517, and 0.105 ng/mL), thus partially, explaining this anomalous second peak. Mean plasma oxymorphone concentrations were generally similar in the 6 to ≤12-year age group and the 2 to <6-year age group following single-dose in the 0.05 and 0.1 mg/kg dose groups and were variable and somewhat higher in the 0.20 mg/kg dose group in the Single-Dose Phase (Figure 10).

Figure 10: Mean (SD) Plasma Oxymorphone Concentrations Following Administration of Oxymorphone IR oral liquid in Ages 2 to ≤12 Years in the Single-Dose Phase (linear-linear coordinates)

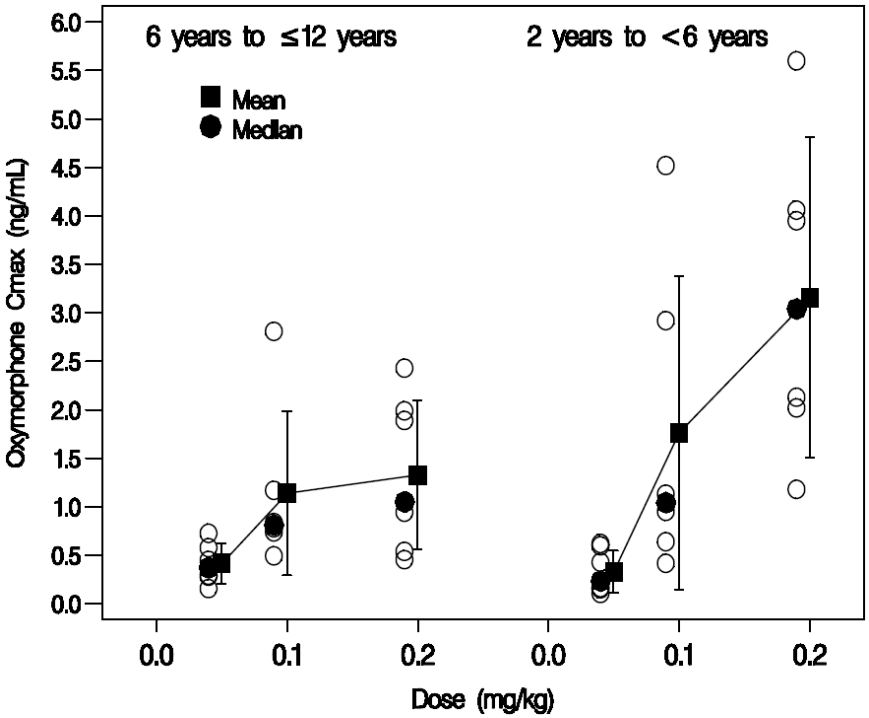


Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 1]

Following single-dose administration, mean oxymorphone Cmax increased in a linear manner with increasing oxymorphone dose. Mean oxymorphone Cmax, Clast, and AUC values were generally higher in the 2 to < 6 years age group, especially in the 0.20 mg/kg dose group. Mean oxymorphone Cmax following single-dose administration of 0.05, 0.1, and 0.20 mg/kg oxymorphone HCl IR oral liquid in the Single-Dose Phase were 0.415, 1.14, and 1.33 ng/mL, respectively, in the 6 to ≤12 years age group and 0.33, 1.76, and 3.16 ng/mL, respectively, in the 2 to < 6 years age group. However as shown in Figure 11 and Figure 12 there was a substantial amount of intersubject variability.

Figure 11: Individual, Median, and Mean (SD) Oxymorphone Cmax Following Administration of 0.05, 0.1, and 0.20 mg/kg of Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Single-Dose Phase

Reference ID: 4499855

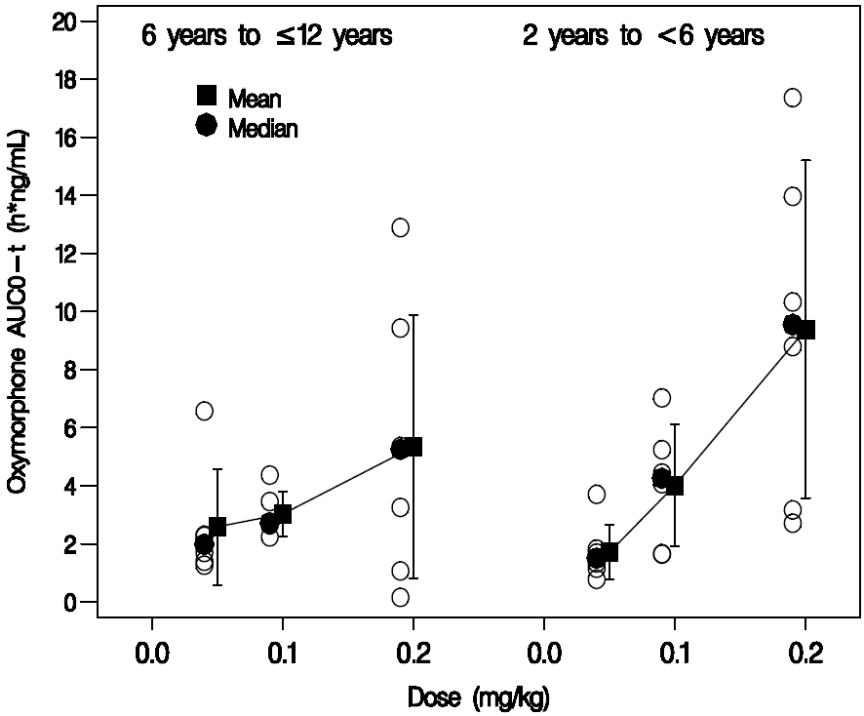


Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 9]
Open circles reflect individual subject data.

Following single-dose administration, mean oxymorphone AUC0-t increased with increasing oxymorphone dose. Mean oxymorphone AUC0-t values were 2.56, 3.01, and 5.32 h*ng/mL, respectively, in the 6 to ≤12 years age group and 1.69, 3.99, and 9.37 h*ng/mL, respectively, in the 2 to < 6 years age group (Figure 12).

Figure 12: Individual, Median, and Mean (SD) Oxymorphone AUC0-t Following Administration of 0.05, 0.1, and 0.20 mg/kg of Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Single-Dose Phase

Reference ID: 4499855

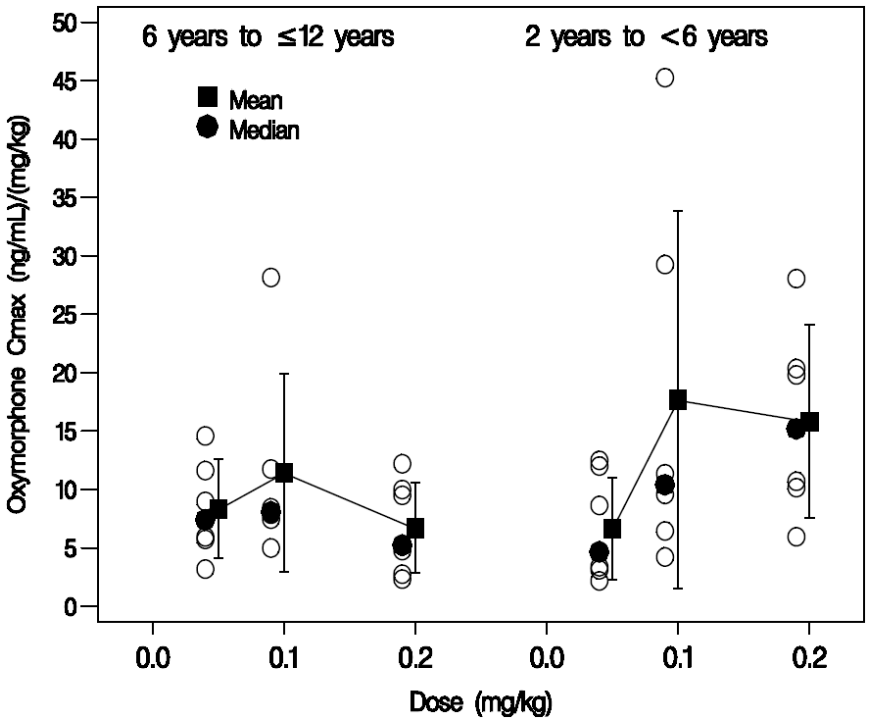


Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 10]
Open circles reflect individual subject data.

Dose-normalized oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.20 mg/kg oxymorphone HCl IR oral liquid were evaluated to assess potential age-related differences (Figure 13, Figure 14, and Table 19).

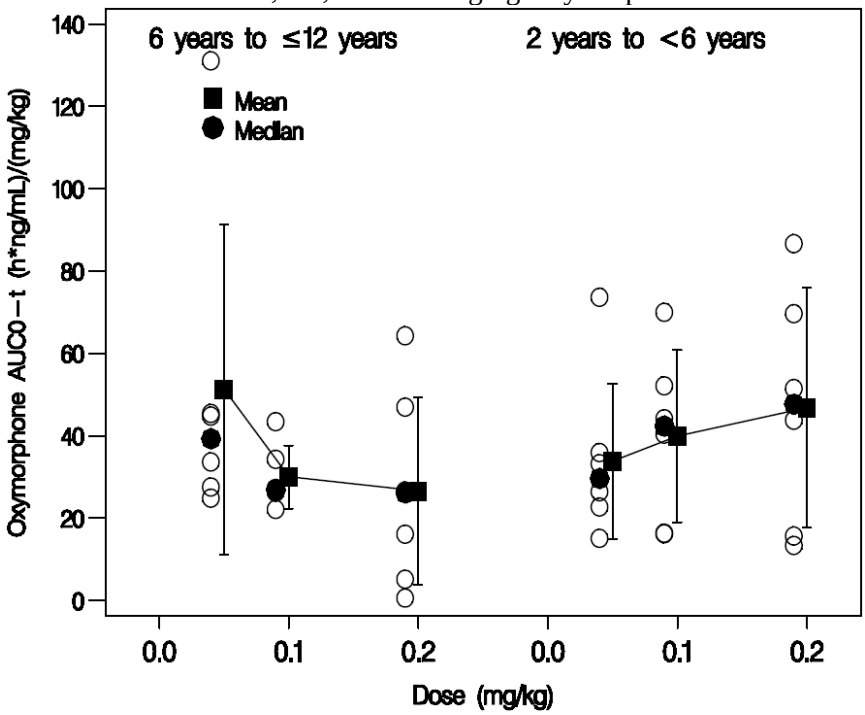
Figure 13: Individual, Median, and Mean (SD) Oxymorphone Cmax/Dose Following Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Single-Dose Phase

Reference ID: 4499855



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 9]
Open circles reflect individual subject data.

Figure 14: Individual, Median, and Mean (SD) Oxymorphone AUC0-t/Dose Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone HCl IR oral liquid in Ages 2 to ≤12 Years



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 10]
Open circles reflect individual subject data.

Reference ID: 4499855

The dose-normalized PK parameters were combined across the single dose levels of oxymorphone in order to assess any potential age-related differences (Table 19). The rationale for combining the dose levels for this comparison is that the overall exposure (AUC0-t) of oxymorphone increased with dose in a near dose proportional manner.

Geometric mean dose-normalized oxymorphone Cmax and AUC values were slightly higher in the 2 to < 6 years age group, although the ratios were close to 1 and the 95% CIs overlapped for each respective parameter. As a result, the PK parameter values of oxymorphone were determined to be generally similar in both age groups following single-dose administration of 0.05, 0.1, and 0.20 mg/kg oxymorphone HCl IR oral liquid.

Table 19: Dose Normalized Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg of Oxymorphone HCl IR Oral Liquid in the Ages 2 to ≤12 Years

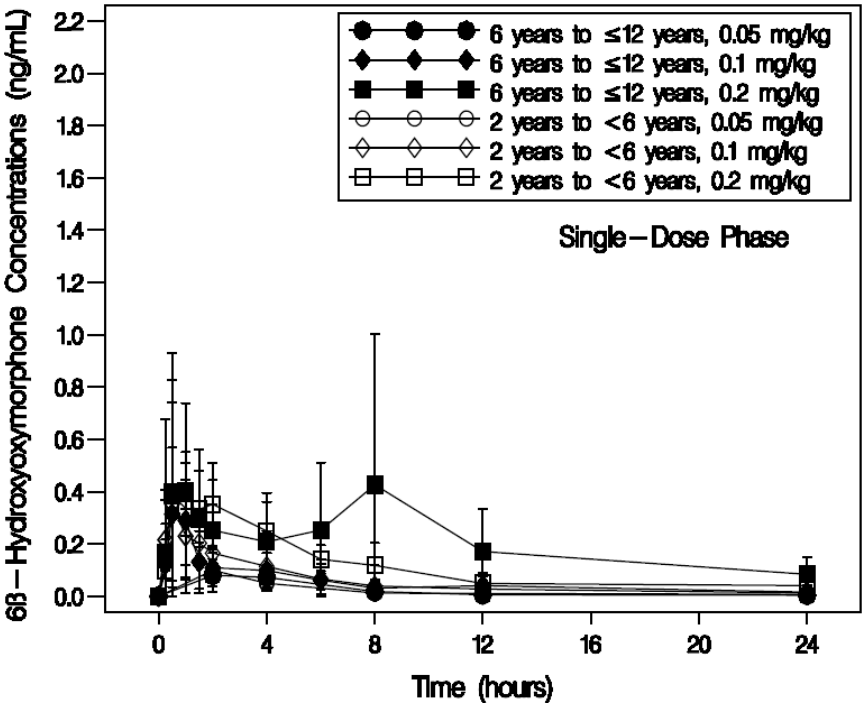
Parameter	**6 to ≤12 Years Age Group**	**2 to <6 Years Age Group**	**Geometric Mean Ratio (6 to ≤12 years / 2 to < 6 years)**
C_{max}/Dose [(ng/mL)/(mg/kg)]	7.24 (5.38 / 9.74)	9.46 (6.35 / 14.1)	1.31
AUC_{0-t}/Dose [(h*ng/mL)/(mg/kg)]	25.4 (15.1 / 42.6)	33.9 (25.4 / 45.3)	1.33
$AUC_{0-\infty}$/Dose [(h*ng/mL)/(mg/kg)]	34.7 (23.5 / 51.3)	46.3 (25.0 / 85.9)	1.33
CL/F (L/h/kg)	28. 8 (19.5 / 42.6)	21.6 (11.6 / 40.1)	0.750
V/F (L/kg)	171 (95 /308)	126 (70.2 / 226)	0.737

Data Source: Study EN3319-302 Pharmacokinetic Report [Table 6 and Supportive Tables ST-4.7 to ST-4.8.]
Natural log-transformed dose-normalized parameters were analyzed and 2-sided 95% CI were constructed. Values presented are geometric mean (95% CI).

11.4.3.4. Pharmacokinetics of 6β-Hydroxyoxymorphone (Single-Dose Phase)
Concentrations declined in a multi-exponential manner with the exception of the 0.20 mg/kg dose group in the 6 to ≤12 years age group which exhibited an atypical “second peak” at 8 hours. As noted in Section 11.4.3.3 the data contributing to this second peak was derived from 3 subjects widely varying data (Figure 15).

Figure 15: Mean (SD) Plasma 6β-Hydroxyoxymorphone Concentrations Following Administration of Oxymorphone HCl IR oral liquid in Ages 2 to ≤12 Years in the Single-Dose Phase (linear-linear coordinates)

Reference ID: 4499855

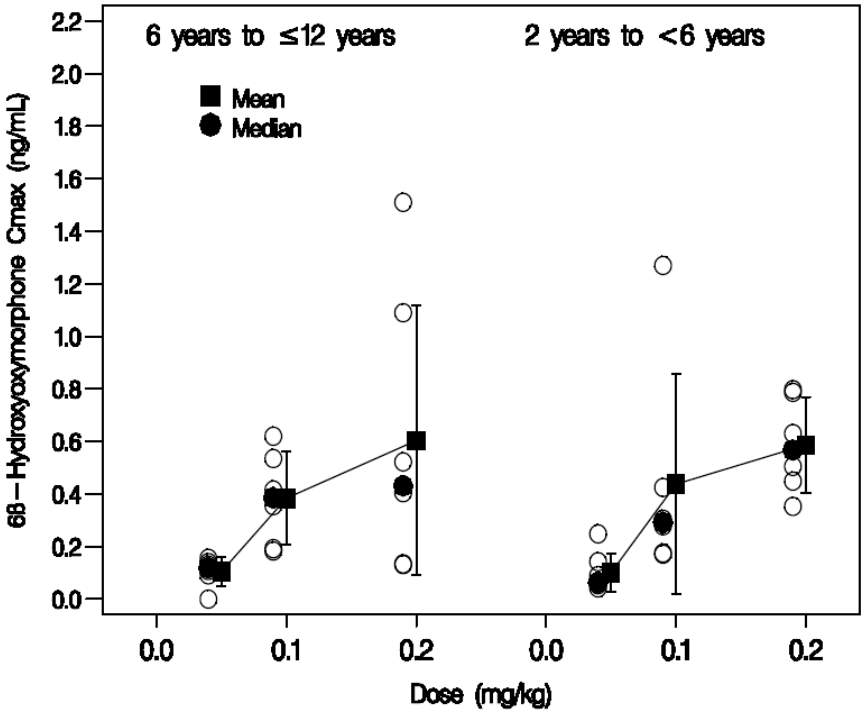


Data Source: Study EN3319-302 PK Report [Figure 1]

Mean 6β-hydroxyoxymorphone Cmax and AUC0-t and all partial area values increased with increasing oxymorphone dose in a linear manner following increasing single doses, although AUC0-∞ exhibited variable PK characteristics in the 6 to ≤12 years age group (Figure 16 and Figure 17).

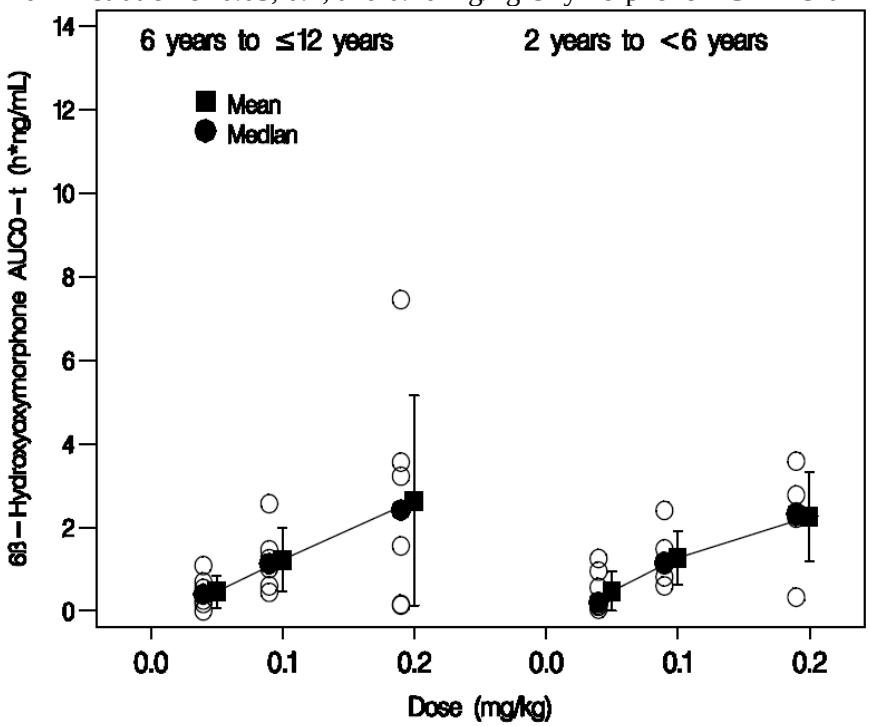
Figure 16: Individual, Median, and Mean (SD) 6β-Hydroxyoxymorphone Cmax Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years

Reference ID: 4499855



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 12]
Open circles reflect individual subject data.

Figure 17: Individual, Median, and Mean (SD) 6β-Hydroxyoxymorphone AUC0-t Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 13]
Open circles reflect individual subject data.

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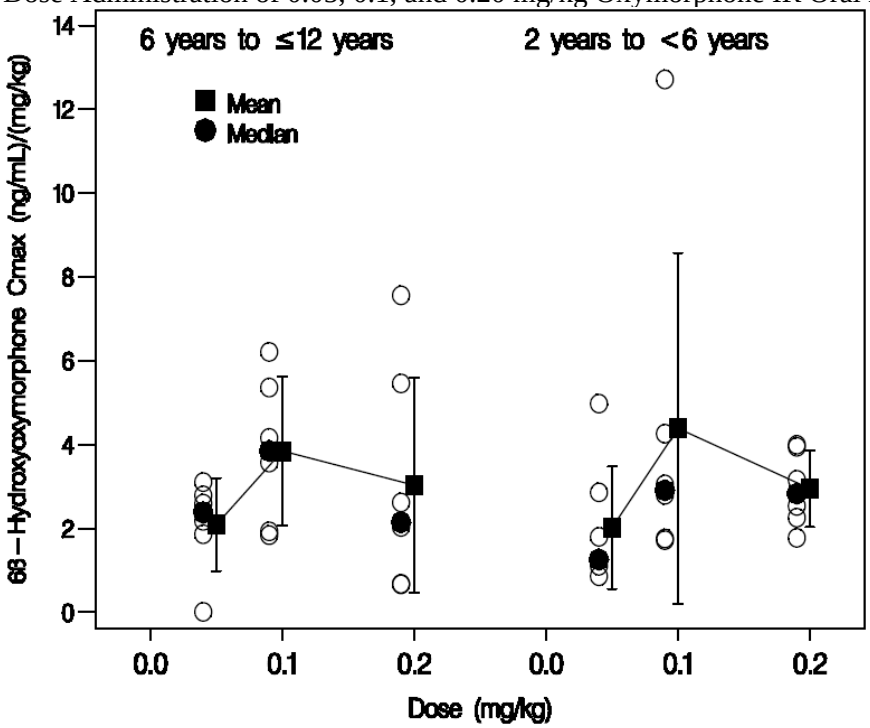
Dose-normalized 6β-hydroxyoxymorphone PK parameter values (Cmax/Dose and AUC0-t/Dose) following single-dose administration of 0.05, 0.1, and 0.20 mg/kg oxymorphone IR oral liquid were evaluated to assess potential age-related differences (Figure 18 and Figure 19).

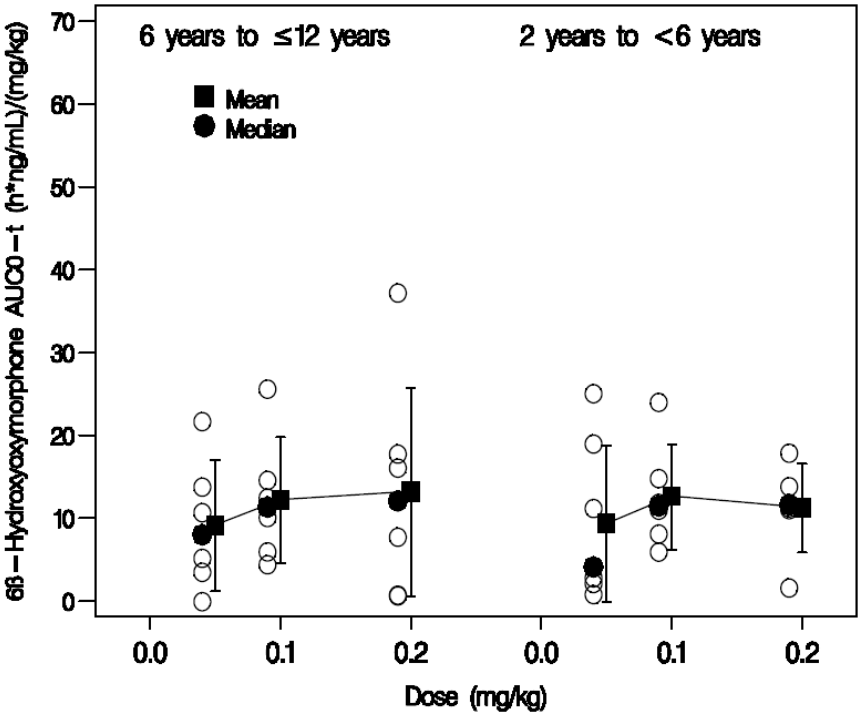
Figure 18: Individual, Median, and Mean (SD) 6β-Hydroxyoxymorphone Cmax/Dose Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone IR Oral Liquid in Ages 2 to ≤12 Years



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 12]
Open circles reflect individual subject data.

Figure 19: Individual, Median, and Mean (SD) 6β-Hydroxyoxymorphone AUC0-t/Dose Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone IR Oral Liquid in Ages 2 to ≤12 Years

Reference ID: 4499855



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 13]
Open circles reflect individual subject data.

Geometric mean dose-normalized 6β-hydroxyoxymorphone Cmax and AUC values were slightly lower in the 2 to < 6 years age group, although due to the variability in the parameters values, the ratios were close to 1 and the 95% CIs overlapped for each respective parameter. As a result, the PK characteristics of 6β-hydroxyoxymorphone were determined to be generally similar in both age groups following single-dose administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone IR Oral Liquid (Table 20).

Table 20: Statistical Assessment of Dose-normalized 6β-hydroxyoxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years

Parameter	**6 to ≤12 Years Age Group**	**2 to <6 Years Age Group**	**Geometric Mean Ratio (6 to ≤12 Years / 2 to < 6 Years)**
C_{max}/Dose [(ng/mL)/(mg/kg)]	2.61 (1.88 / 3.63)	2.45 (1.81 / 3.33)	0.938
AUC_{0-t}/Dose [(h*ng/mL)/(mg/kg)]	8.37 (4.90 / 14.3)	8.06 (5.11 / 12.7)	0.963
$AUC_{0-\infty}$/Dose [(h*ng/mL)/(mg/kg)]	21.6 (4.23 / 110)	16.2 (11.7 / 22.6)	0.750

Data Source: Study EN3319-302 Pharmacokinetic Report [Table 10 and Supportive Tables ST-5.7 to ST-5.8].
Natural log-transformed dose-normalized parameters were analyzed and 2-sided 95% CI were constructed. Values presented are geometric mean (95% CI).

11.4.3.5. Pharmacokinetics of Oxymorphone (Multiple-Dose Phase)

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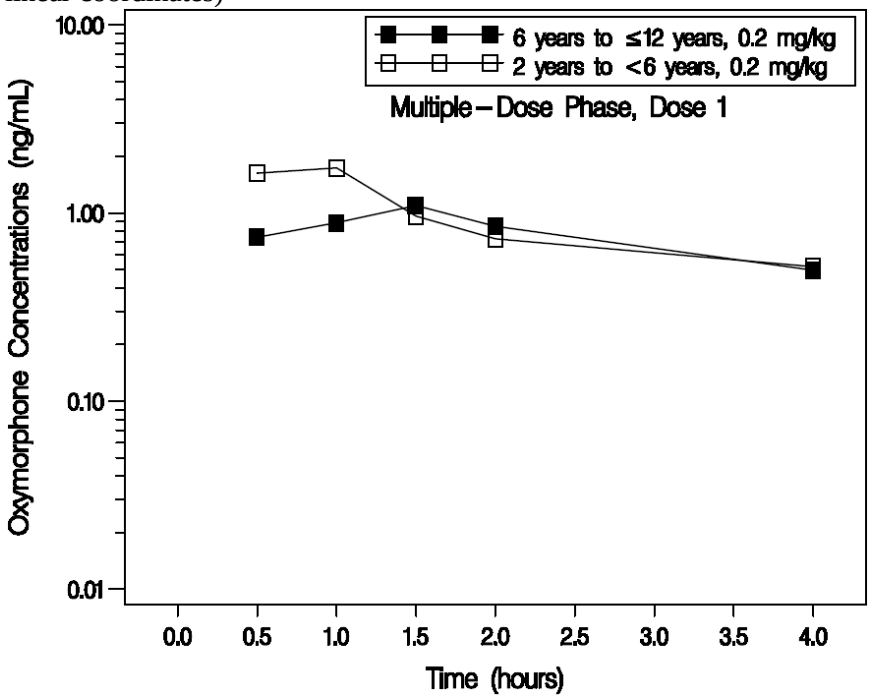
Following multiple-dose administration of 0.20 mg/kg oxymorphone HCl IR oral liquid for up to 7 doses in children aged 2 to ≤12 years, oxymorphone was rapidly absorbed. Plasma oxymorphone concentrations were BLQ at the pre-dose time point before Dose 1 in all subjects in both age groups and measureable plasma oxymorphone concentrations were observed before Dose 7 in all subjects in both age groups (Study EN3319-302 Pharmacokinetic Report). Coefficients of variation were similar between age groups after Dose 1 and ranged from 53.2% to 117.5% in children aged 6 to ≤12 years and from 44.6% to 89.2% in children aged 2 to < 6 years. Coefficients of variation in children aged 6 to ≤12 years were low after Dose 7 and ranged from 5.7% to 36.5%. Limited measureable plasma oxymorphone concentration data collected from Dose 7 prevented determination of coefficients of variation in children aged 2 to < 6 years. The highest mean plasma oxymorphone concentrations after Dose 1 (1.1 ng/mL in children aged 6 to ≤12 years and 1.74 ng/mL in children aged 2 to < 6 years) were observed at 1.5 hours and 1.0 hour, respectively.

Following the highest mean concentration after Dose 1, mean plasma oxymorphone concentrations declined in an exponential manner through the end of the dosing interval which was approximately 4 hours in all but 3 subjects who received the second dose at approximately 6 hours. The highest mean plasma oxymorphone concentrations after Dose 1 (1.1 ng/mL in children aged 6 to ≤12 years and 1.74 ng/mL in children aged 2 to < 6 years) were observed at 1.5 hours and 1.0 hour, respectively. Mean plasma oxymorphone concentrations after Dose 1 were higher in children aged 2 to < 6 years at the 0.5- and 1-hour time points and were nearly identical in both age groups at 1.5, 2, and 4 hours (Figure 20).

Figure 20: Mean Plasma Oxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 (log-linear coordinates)



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 6]
Open circles reflect individual subject data.

After Dose 1 in the Multiple-Dose Phase, mean plasma oxymorphone concentrations were higher in children aged 6 to ≤12 years than in children aged 2 to < 6 years at the 0.5-hour and 1.0-hour collections and nearly identical in both age groups at the remaining collection times (evaluable data were available

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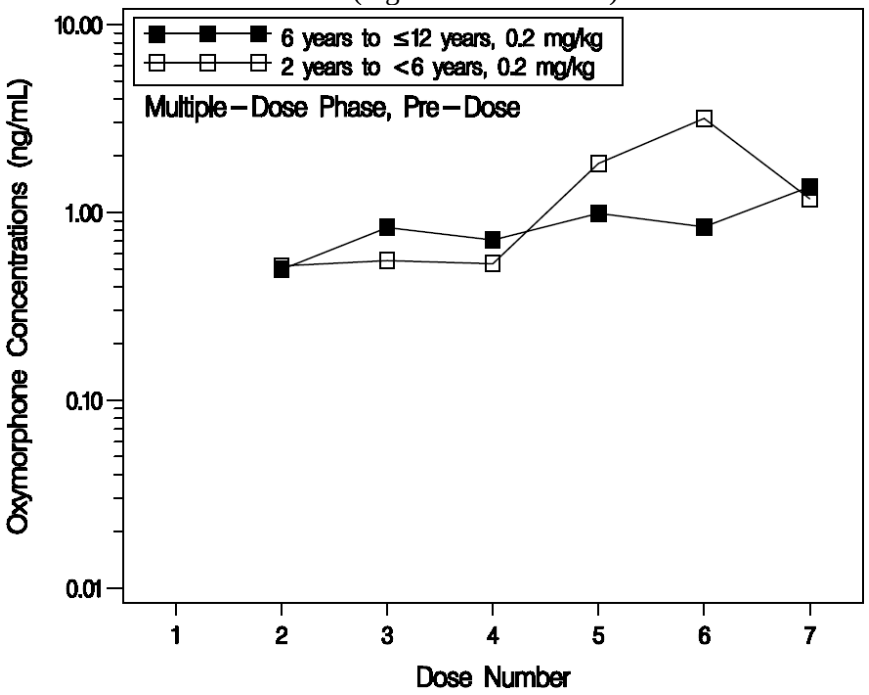
only from children aged 6 to ≤12 years after Dose 7) (Figure 21). Measurable pre-dose plasma oxymorphone concentrations were observed prior to Doses 2 to 7 in all subjects in both age groups who had sample collections at these times in the Multiple-Dose Phase and mean pre-dose oxymorphone concentration were generally similar in both age groups. The highest mean plasma oxymorphone concentrations after Dose 7 in children aged 6 to ≤12 years (2.35 ng/mL) were observed at 1.5 hours. Insufficient data in children aged 2 years to <6 years after Dose 7 precluded determination of PK parameter estimates for this age group after Dose 7. Observed pre-dose oxymorphone concentrations appeared to reach steady state by the third through sixth dose in children aged 6 to ≤12 years.

Figure 21: Mean Plasma Pre-Dose Oxymorphone Concentrations Following Single-Dose and Multiple-Dose Administration of Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 to Dose 7 (loglinear coordinates)



Source: Study EN3319-302 Pharmacokinetic Report [Figure 8]

PK parameters values for oxymorphone HCl IR oral liquid in the Multiple-Dose Phase are provided in Table 21.

Mean oxymorphone Cmax following single-dose administration of 0.20 mg/kg oxymorphone HCl IR oral liquid after Dose 1 in the Multiple-Dose Phase was 1.16 (NOTE: 1.46) ng/mL and in children aged 6 to ≤12 years and 2.58 ng/mL in children aged 2 to <6 years. Mean oxymorphone Cmax following multiple-dose administration after Dose 7 could only be evaluated in children aged 6 to ≤12 years and was 2.66 ng/mL. Median tmax for oxymorphone ranged from 0.867 to 1.79 hours in the third dose /age group with evaluable data. Mean oxymorphone Dose 1 Clast values were 0.452 ng/mL and in children aged 6 to ≤12 years and 0.508 ng/mL in children aged 2 to < 6 years. Mean oymorphone Dose 7 Clast in children aged 6 to ≤12 years and was 2.3 ng/mL.

Median Tlast ranged from was approximately 4 hours in both age groups after Dose 1 and approximately 2 hours in children aged 6 to ≤12 years after Dose 7, corresponding to the end of the respective sample collection intervals. Mean oxymorphone Dose 1 AUC0-t values were 3.49 h*ng/mL in children aged 6 to ≤12 years and 3.88 h*ng/mL in the 2 to < 6 years age group and mean oxymorphone AUC0-∞ values were 4.01 h*ng/mL in the 6 to ≤12 years age group and 4.53 h*ng/mL in the 2 to < 6 years age group.

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Mean Dose 7 oxymorphone AUC0-t was 4.24 h*ng/mL in children aged 6 to ≤12 years. Mean oxymorphone t½ could be determined only following single-dose administration of 0.20 mg/kg oxymorphone after Dose 1 and was 2.18 hours in children aged 6 to ≤12 years (n=3 of 10) and 1.17 hours in the 2 to < 6 years age group (n=3 of 5). As in the Single-Dose Phase, these estimates should be interpreted with caution since they were based upon 3 subjects in each age group. Mean oxymorphone Cmax, Clast, and AUC values were generally higher in the 2 to <6 years age group.

Table 21: Summary of the Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 and Dose 7

	C_{max}	T_{max}	C_{last}	T_{last}	AUC_{0-t}	AUC_{0-inf}	AUC_{0-2}	AUC_{0-4}	AUC_{0-6}	AUC_{0-24}	$t_{1/2}$
	(ng/mL)	(hr)	(ng/mL)	(hr)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h)
0.20 mg/kg – Children Aged 6 to ≤12 years – Dose 1											
n	10	10	10	10	10	3	9	8	3	3	3
Median	1.39	1.55	0.469	4.02	2.84	3.71	1.63	2.84	3.19	3.72	2.06
Geo. Mean	0.887	1.21	0.323	3.88	1.82	3.84	1.25	2.47	3.23	3.84	2.15
Lower95%CI	0.34	0.81	0.154	3.16	0.577	1.6	0.544	0.962	1.71	1.6	1.29
Upper95%CI	2.31	1.82	0.675	4.76	5.72	9.25	2.85	6.33	6.11	9.23	3.59
Mean	1.46	1.37	0.452	4	3.49	4.01	1.79	3.64	3.3	4.01	2.18
SD	1.16	0.599	0.286	0.971	3.22	1.43	1.45	3.07	0.848	1.42	0.459
CV(%)	79.9	43.8	63.3	24.3	92.2	35.7	81	84.4	25.7	35.5	21
Minimum	0.068	0.433	0.0515	1.88	0.0548	2.75	0.103	0.21	2.51	2.75	1.8
Maximum	4.23	2.05	0.827	5.87	11	5.56	5.23	10.4	4.2	5.55	2.69
0.20 mg/kg – Children Aged 2 to < 6 years – Dose 1											
n	5	5	5	5	5	3	5	5	4	3	3
Median	2	0.867	0.47	4.37	3.07	3.53	2.05	2.96	3.85	3.53	0.937
Geo. Mean	2.33	0.834	0.416	4.16	3.7	4.21	2.08	3.39	4.06	4.21	1.07
Lower95%CI	1.22	0.4	0.161	2.36	2.43	1.36	1.01	2.41	2.42	1.36	0.295
Upper95%CI	4.45	1.74	1.07	7.33	5.62	13	4.26	4.79	6.83	13	3.85
Mean	2.58	0.967	0.508	4.47	3.88	4.53	2.34	3.51	4.24	4.53	1.17
SD	1.24	0.622	0.32	1.68	1.45	2.21	1.16	1.11	1.47	2.21	0.632
CV (%)	48.2	64.3	62.9	37.5	37.4	48.8	49.5	31.6	34.7	48.7	54
Minimum	1.14	0.467	0.135	1.97	2.81	2.99	0.855	2.75	2.94	2.99	0.687
Maximum	3.9	2	0.941	6.2	6.25	7.06	3.85	5.43	6.31	7.06	1.88
0.20 mg/kg – Children Aged 6 to ≤12 years – Dose 7											
n	3	3	3	3	3	0	3	0	0	0	0
Median	3.03	1.5	2.33	2.13	4.4	.	4.01	.	.	.	.

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Geo. Mean	2.57	1.79	2.22	2.09	4.17	.	3.96	.	.	.	.
Lower95%CI	1.11	0.191	0.949	1.9	2.4	.	2.5	.	.	.	.
Upper 95%CI	5.97	16.8	5.17	2.29	7.24	.	6.25	.	.	.	.
Mean	2.66	1.21	2.3	2.09	4.24	.	4	.	.	.	.
SD	0.805	1.1	0.745	0.077	0.9	.	0.728	.	.	.	.
CV (%)	30.2	90.5	32.4	3.7	21.2	.	18.2	.	.	.	.
Minimum	1.74	0	1.54	2	3.27	.	3.27	.	.	.	.
Maximum	3.22	2.13	3.03	2.13	5.05	.	4.72	.	.	.	.

Source: Study EN3319-302 Pharmacokinetic Report [Table 7]

11.4.3.6. Pharmacokinetics of 6β-Hydroxyoxymorphone (Multiple-Dose)

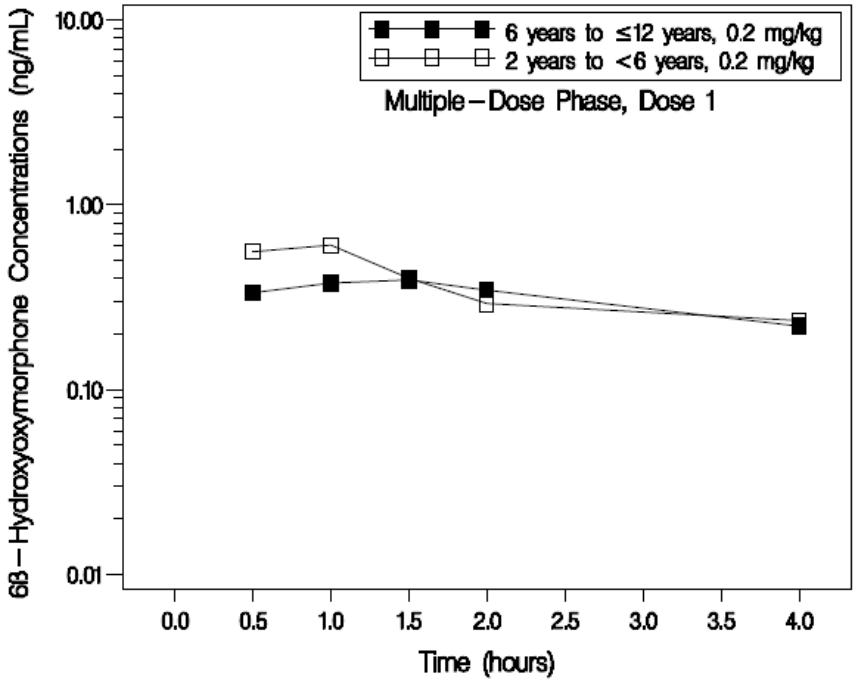
All pre-dose 6β-hydroxyoxymorphone concentrations and before Dose 1 in the Multiple-Dose Phase were BLQ. 6β-hydroxyoxymorphone appeared to be formed rapidly after oral administration of oxymorphone HCl IR oral liquid in the Multiple-Dose Phase. Plasma 6β-hydroxyoxymorphone concentrations were consistently lower than oxymorphone concentrations in both study phases and in each respective age group.

Following the highest mean concentration after Dose 1, mean plasma 6β-hydroxyoxymorphone concentrations declined in an exponential manner through the end of the dosing interval which was approximately 4 hours in all but 3 subjects who received the second dose at approximately 6 hours. Measureable plasma 6β-hydroxyoxymorphone concentrations were observed at the end of the dosing interval (ie, approximately 4 to 6 hours) after Dose 1 in all subjects in both age groups (with the exception of 2 subjects with missing values at 4 hours), although the log-linear terminal elimination phase was generally not well characterized in the individual data sets. Measureable plasma 6β-hydroxyoxymorphone concentrations were observed at the last sample collection (ie, 2 hours) after Dose 7 in all subjects aged 6 to ≤12 years with reported concentrations (n=3 of 3).

The highest mean plasma 6β-hydroxyoxymorphone concentrations were after Dose 1 was observed in the 6 to ≤12 years age group at 1 hour and in the 2 to < 6 years age group at 1.5 hours. Mean plasma 6β-hydroxyoxymorphone concentrations after Dose 1 were higher in children aged 2 to < 6 years at the 0.5- and 1-hour time points and were nearly identical in both age groups at 1.5, 2, and 4-hours (Figure 22).

Figure 22: Mean Plasma 6β-Hydroxyoxymorphone Concentrations Following Single- Dose Administration of Oxymorphone HCl IR Oral Liquid in 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 (log-linear coordinates)

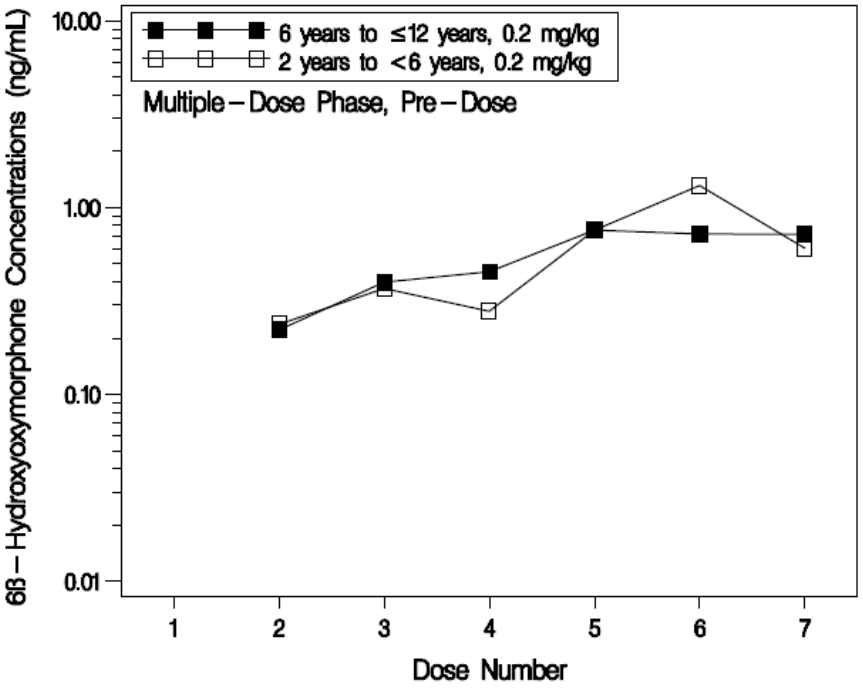
Reference ID: 4499855



Source: Study EN3319-302 Pharmacokinetic Report [Figure 6]

Measureable pre-dose plasma 6β-hydroxyoxymorphone concentrations were observed prior to Doses 2 to 7 in all subjects in both age groups who had sample collections at these times in the Multiple-Dose Phase. Mean pre-dose 6β-hydroxyoxymorphone concentration were generally similar in both age groups with the exception of the higher pre-dose concentrations in children age 2 to < 6 years before Dose 6 which was based on n=1 value; all other pre-dose 6β-hydroxyoxymorphone concentrations for this dose number and age group were BLQ. Observed pre-dose 6β-hydroxyoxymorphone concentrations appeared to reach steady state by the fifth dose in children aged 6 to ≤12 years. Assuming no time-dependent changes in 6β-hydroxyoxymorphone PK characteristics with multiple-dosing, the observed 6β-hydroxyoxymorphone t½ values observed during the 4 hour collection interval in the Multiple-Dose Phase (ie, geometric means were approximately 3.3 hours) would be expected to result in the attainment of 95% of steady state within approximately 15 to 16 hours (ie, 5 t½) (Figure 23).

Figure 23: Mean Plasma Pre-Dose 6β-Hydroxyoxymorphone Concentrations Following Single-Dose and Multiple-Dose Administration of Oxymorphone IR Oral Liquid in Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 to Dose 7 (log-linear coordinates)



Data Source: Study EN3319-302 Pharmacokinetic Report [Figure 8]

PK parameter values for 6β-hydroxyoxymorphone in the Multiple-Dose Phase are presented in Table 22.

Table 22: Summary 6β-Hydroxyoxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.20 mg/kg Oxymorphone IR Oral Liquid in Children Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 and Dose 7

	C_{max}	T_{max}	C_{last}	T_{last}	AUC_{0-t}	AUC_{0-inf}	AUC_{0-2}	AUC_{0-4}	AUC_{0-6}	AUC_{0-24}	$t_{1/2}$
	(ng/mL)	(hr)	(ng/mL)	(hr)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h)
0.20 mg/kg – Children Aged 6 to ≤12 years – Dose 1											
n	10	10	10	10	10	3	9	8	3	3	3
Median	0.441	1.58	0.218	4.02	1.07	2.29	0.708	1.07	1.22	2.2	3.88
Geo. Mean	0.325	1.39	0.153	3.81	0.636	2.05	0.466	0.973	1.4	2.01	3.31
Lower 95%CI	0.125	0.862	0.0787	3	0.168	0.769	0.207	0.418	0.771	0.774	0.874
Upper 95%CI	0.841	2.26	0.297	4.84	2.41	5.46	1.05	2.27	2.53	5.24	12.5
Mean	0.547	1.67	0.201	3.97	1.35	2.15	0.677	1.39	1.42	2.11	3.61
SD	0.472	1.01	0.118	1.05	1.27	0.769	0.556	1.19	0.361	0.748	1.67
CV(%)	86.2	60.5	58.9	26.3	93.8	35.7	82.1	85.3	25.3	35.4	46.2
Minimum	0.0204	0.433	0.0204	1.58	0.0068	1.32	0.0538	0.128	1.22	1.32	1.82
Maximum	1.59	4.02	0.394	5.87	4.23	2.84	1.95	3.96	1.84	2.81	5.12
0.20 mg/kg – Children Aged 2 to < 6 years – Dose 1											
n	5	5	5	5	5	3	5	5	4	3	3

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Median	0.962	0.867	0.202	4.37	0.962	1.16	0.968	1.13	1.87	1.16	1.24
Geo. Mean	0.658	0.96	0.172	4.16	1.24	1.26	0.663	1.13	1.42	1.26	1.29
Lower 95%CI	0.238	0.327	0.0513	2.36	0.431	0.0915	0.224	0.456	0.337	0.0915	0.357
Upper 95%CI	1.82	2.82	0.576	7.33	3.54	17.2	1.96	2.81	5.97	17.2	4.69
Mean	0.829	1.37	0.225	4.47	1.61	1.79	0.863	1.37	1.83	1.78	1.42
SD	0.541	1.5	0.139	1.68	1.19	1.73	0.598	0.854	1.25	1.72	0.73
CV(%)	65.2	109.6	61.8	37.5	74.2	96.7	69.4	62.4	68.3	96.6	51.6
Minimum	0.24	0.467	0.0333	1.97	0.396	0.455	0.238	0.382	0.431	0.455	0.788
Maximum	1.5	4.03	0.398	6.2	3.09	3.74	1.63	2.57	3.13	3.73	2.22
0.2 mg/kg – Children Aged 6 to ≤12 years – Dose 7											
n	3	3	3	3	3	1	3	1	1	1	1
Median	1.31	1.5	1.02	2.13	2.04	7.66	1.9	3.27	4.34	7.38	4.9
Geo. Mean	1.35	1.13	1.17	2.09	2.21	7.66	2.1	3.27	4.34	7.38	4.9
Lower 95%CI	0.592	0.149	0.393	1.9	1.24	.	1.29	.	.	.	.
Upper 95%CI	3.1	8.57	3.5	2.29	3.94	.	3.4	.	.	.	.
Mean	1.41	1.36	1.25	2.09	2.25	7.66	2.12	3.27	4.34	7.38	4.9
SD	0.473	0.85	0.585	0.077	0.547	.	0.434	.	.	.	.
CV(%)	33.7	62.5	46.6	3.7	24.3	.	20.4	.	.	.	.
Minimum	0.988	0.45	0.823	2	1.84	7.66	1.84	3.27	4.34	7.38	4.9
Maximum	1.92	2.13	1.92	2.13	2.87	7.66	2.62	3.27	4.34	7.38	4.9
0.20 mg/kg – Children Aged 2 to < 6 years – Dose 7											
N	0										

11.4.4. Comparison of Oxymorphone Pharmacokinetic Parameters by Phase and Age Group

Oxymorphone PK parameters following multiple-dose administration of 0.20 mg/kg oxymorphone HCl IR oral liquid in the 2 to ≤12 years age group in the Multiple-Dose Phase from Dose 1 and Dose 7 were dose-normalized. The rationale for combining the dose levels for this comparison is that the overall exposure (AUC0-t) of oxymorphone increased with dose in a near dose proportional manner.

Geometric mean dose-normalized oxymorphone Cmax and AUC values were generally higher in children aged 2 to < 6 years after Dose 1 in the Multiple-Dose Phase and the geometric mean ratios (GMRs) exceeded 2 for both Cmax and AUC0-t primarily due to higher oxymorphone concentrations early in the dosing interval at 0.5 and 1.0 hours, although caution should be used in comparing apparent differences in oxymorphone PKs between the age groups since sample collections for this study day were limited to the length of the dosing interval (i.e., approximately 4 to 6 hours) (Table 23).

Geometric mean dose-normalized oxymorphone Cmax and AUC values were generally higher in children aged 2 to < 6 years after Dose 1, although the ratio for AUC0-∞Dose was close to 1 and the 95% CIs overlapped for each respective parameter. The GMRs (B/A) were 2.62, 2.04, and 1.10 for dose-normalized Cmax, AUC0-t and AUC0-∞, respectively, after Dose 1. Similar trends were observed for all

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partial areas evaluated. Geometric mean t½ estimates were 2.15 hours in children aged 6 to ≤12 years (n=3 of 10) and 1.07 hours in the 2 to <6 years age group (n=3 of 5). CL/F appeared to be somewhat higher in the 6 to ≤12 years age group compared to the 2 to <6 years age group and geometric mean V/F was approximately 2-fold larger in the 6 to ≤12 years age group compared to the 2 to <6 years age group, although caution should be used in the interpretation of these estimates since they were based on relatively few subjects.

Table 23: Statistical Assessment of Dose-Normalized Oxymorphone PK Parameter Values Following Administration of 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Children Aged 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 and Dose 7

Parameter	6 to ≤12 Years Age Group (Age Group A)	2 to <6 Years Age Group (Age Group B)	Geometric Mean Ratio (B/A)
C_{max}/Dose – Dose 1 [(ng/mL)/(mg/kg)]	4.43 (1.70 / 11.6)	11.6 (6.10 / 22.2)	2.62
C_{max}/Dose – Dose 7 [(ng/mL)/(mg/kg)]	12.9 (5.53 / 29.8)	ND	ND
AUC_{0-t}/Dose – Dose 1 [(h*ng/mL)/(mg/kg)]	9.08 (2.89 / 28.6)	18.5 (12.1 / 28.1)	2.04
AUC_{0-t}/Dose – Dose 7 [(h*ng/mL)/(mg/kg)]	20.9 (12.0 / 36.2)	ND	ND

Data Source: Study EN3319-302 Pharmacokinetic Report [Table 14]
ND = could not be determined.
Natural log-transformed dose-normalized parameters were analyzed and 2-sided 95% CI were constructed. Values presented are geometric mean (95% CI).

Limited oxymorphone concentration data after administration of Dose 7 in children from both groups did not permit definitive comparisons of oxymorphone PK characteristics between Dose 7 and Dose 1. Individual Cmax/Dose and AUC0-2/Dose estimates were higher after Dose 7 than after Dose 1 in 2 of the 3 subjects aged 6 years to ≤12 years with matched Dose 7 and Dose 1 estimates (Study EN3319-302 Pharmacokinetic Report [Supportive Tables ST-4.13 and ST-4.15]). Observed pre-dose oxymorphone concentrations tended to increase with increasing dose in both age groups.

Further comparison of geometric mean dose-normalized oxymorphone partial areas for AUC0-2 and AUC0-4 following single-dose administration in the Single-Dose Phase and after Dose 1 in the Multiple-Dose Phase were in excellent agreement indicating oxymorphone PK characteristics were similar in both study phases (Study EN3319-302 Pharmacokinetic Report [Table 6 and Table 8]).

11.4.5. Comparison of 6β-hydroxyoxymorphone Pharmacokinetic Parameters by Phase and Age Group
As was done with oxymorphone PK analyses, the PK parameters were dose-normalized and since the exposure of 6β-hydroxyoxymorphone appeared to increase in a dose proportional manner with dose, the dose-normalized PK parameters were combined for the single-doses of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl solutions in order to assess potential age-related differences. Comparison of geometric mean dose normalized 6β-hydroxyoxymorphone partial areas for AUC0-2 and AUC0-4 following single-dose administration in the Single-Dose Phase and after Dose 1 in the Multiple-Dose Phase were in excellent agreement indicating 6β−hydroxyoxymorphone PK characteristics were similar in both study phases (Study EN3319-302 Pharmacokinetic Report [Table 10 and Table 12]).
Insufficient data after administration of Dose 7 from both groups did not allow for any meaningful comparison of 6β-hydroxyoxymorphone PK characteristics between Dose 7 and Dose 1. Observed pre-dose 6β-hydroxyoxymorphone concentrations tended to increase with increasing dose in both age groups.

Geometric mean dose normalized values for 6β-hydroxyoxymorphone Cmax and AUC0-t were higher in the 2 to < 6 years age group than the 6 to ≤12 years age group after Dose 1 in the Multiple-Dose Phase.

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The GMRs exceeded 2 for both Cmax and AUC0-t primarily due to higher 6β-hydroxyoxymorphone concentrations early in the dosing interval at 0.5- and 1.0-hours.
Caution should be used in comparing the apparent differences in the PK characteristics of 6β-hydroxyoxymorphone between age groups, since sample collections on this study day were limited by the dosing interval (ie, range approximately 4 to 6 hours) (Table 24).
The geometric mean 6β-hydroxyoxymorphone values for AUC0-t/Dose for both age groups in the Single-Dose Phase were 8.37 and 8.06 [(h*ng/mL)/(mg/kg)], respectively, and oxymorphone geometric mean AUC0-t/Dose for both age groups in the Single-Dose Phase were 25.4 and 33.9 [(h*ng/mL)/(mg/kg)], respectively, indicating that exposure to 6β-hydroxyoxymorphone was approximately16.4 to 23.8% of the exposure to oxymorphone.

Table 24: Statistical Assessment of Dose Normalized 6β-hydroxyoxymorphone PK Parameters Following Single-Dose Administration of 0.20 mg/kg Oxymorphone HCl IR Oral Liquid in Ages 2 to ≤12 Years in the Multiple-Dose Phase from Dose 1 and Dose 7

Parameter	**6 to ≤12 Years Age Group**	**2 to <6 Years Age Group**	**Geometric Mean Ratio (6 to ≤12 Years/ 2 to <6 Years)**
C_{max}/Dose – Dose 1 [(ng/mL)/(mg/kg)]	1.62 (0.626 / 4.21)	3.29 (1.19 / 9.08)	2.03
C_{max}/Dose – Dose 7 [(ng/mL)/(mg/kg)]	6.77 (2.96 / 15.5)	ND	ND
Ratio Dose 7 / Dose 1	4.18	ND	ND
AUC_{0-t}/Dose – Dose 1 [(h*ng/mL)/(mg/kg)]	3.50 (1.11 / 11.2)	6.18 (2.15 / 17.7)	1.76
AUC_{0-t}/Dose – Dose 7 [(h*ng/mL)/(mg/kg)]	11.1 (6.20 / 19.7)	ND	ND
Ratio Dose 7 / Dose 1	3.17	ND	ND

Data Source: Study EN3319-302 Pharmacokinetic Report [Table 16]
ND=not detected
Note: Natural log-transformed dose normalized parameters were analyzed and 2-sided 95% CI were constructed.
Values presented are geometric mean (95% CI).

11.4.6. Pharmacokinetic Conclusions

• Oxymorphone was rapidly absorbed after oral administration, reaching maximum mean plasma oxymorphone concentrations within the range of 0.5 to 4.0 hours across the dose range.
• The t½ following a single-dose of oxymorphone HCl oral liquid could only be determined in 2 to 3 subjects/dose/age group, with the means ranging between 3 and 7.5 hours.
• Mean oxymorphone Cmax and AUC0-t and all partial area values increased with increasing oxymorphone dose in dose-linear manner following single-dose administration. AUC0-∞ could only be determined for only 2 to 3 subjects/dose/age group.
• 6β-hydroxyoxymorphone concentrations closely followed that of oxymorphone, reaching maximum mean plasma 6β-hydroxyoxymorphone concentrations within 0.5 to 1.0 hours.
• 6β-hydroxyoxymorphone exposure was approximately16.4% to 23.8% of the exposure to oxymorphone after single oral doses.
• The PK parameters of oxymorphone and 6β-hydroxyoxymorphone were generally similar in both age groups following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl immediate-release oral liquid.
• Only children aged 6 years to ≤12 years had sufficient amount of concentration data on Day 7 to evaluate oxymorphone and 6β-hydroxyoxymorphone steady-state PK; however, the predose concentrations of oxymorphone for Doses 3 through 7 were similar between the age groups, suggesting a similar steady-state PK between the age groups.

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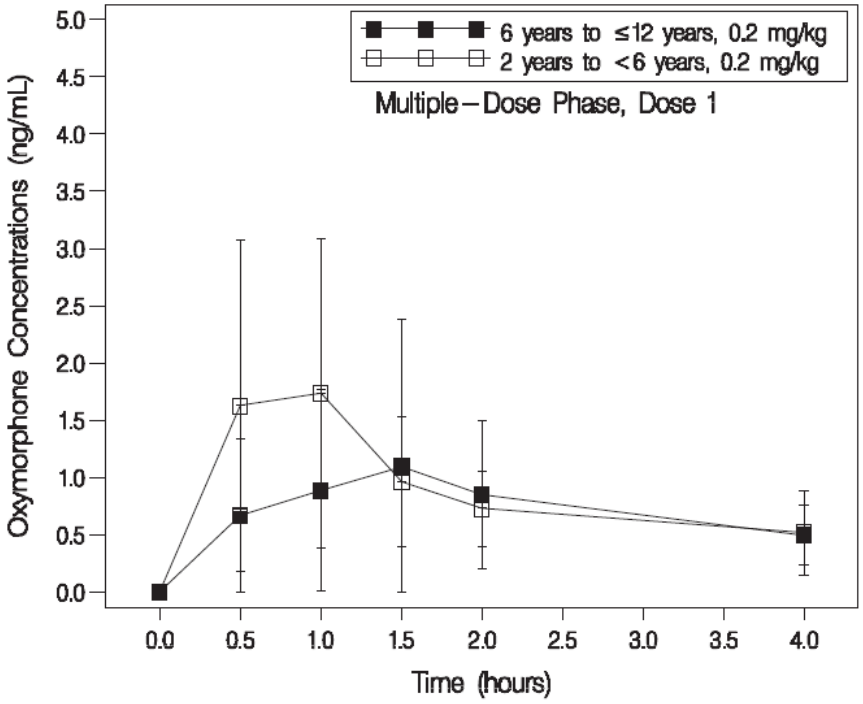
• Observed pre-dose oxymorphone concentrations appeared to reach steady state by the third through sixth dose in children aged 6 to ≤12 years, while pre-dose 6β-hydroxyoxymorphone concentrations appeared to reach steady state by the fifth dose in this age group.

PK report (en3319-302-pk.pdf)

1. Mean (SD) Plasma Oxymorphone and 6β-Hydroxyoxymorphone Concentrations Following Single-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 (linear-linear coordinates)



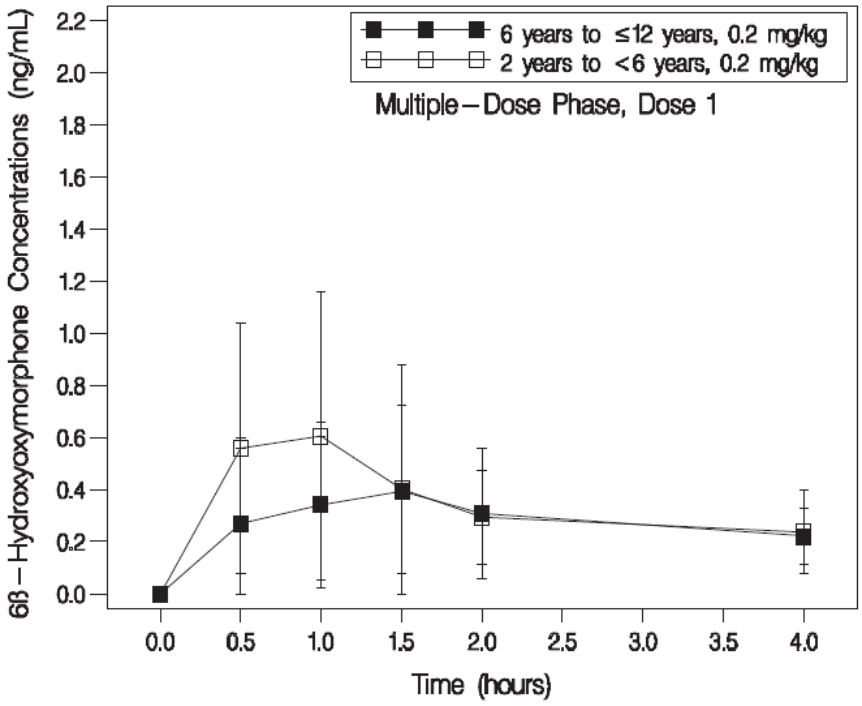
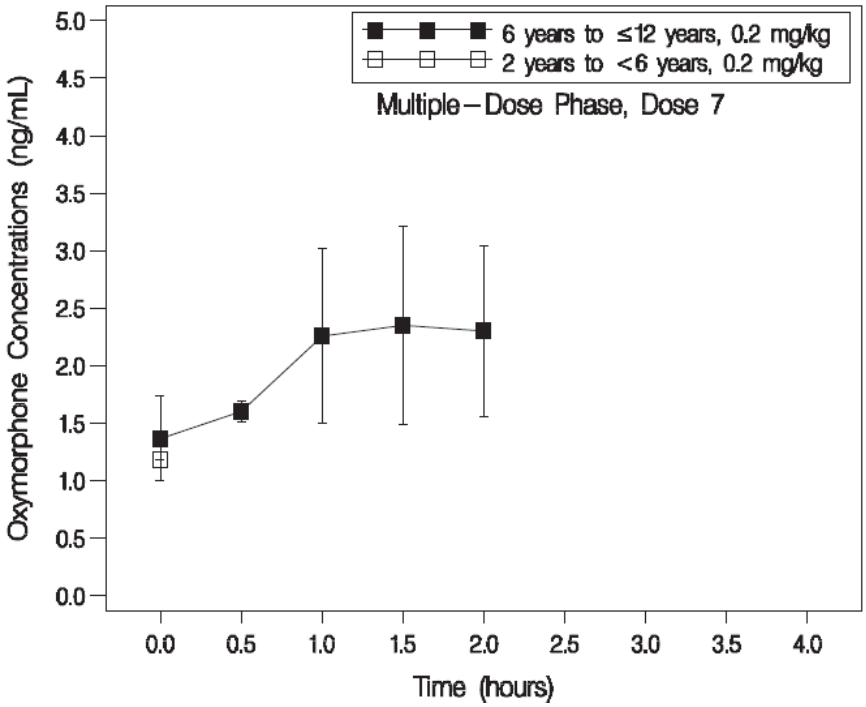


Figure 3. Mean (SD) Plasma Oxymorphone and 6β-Hydroxyoxymorphone Concentrations Following Multiple-Dose Administration of Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 7 (linear-linear coordinates)



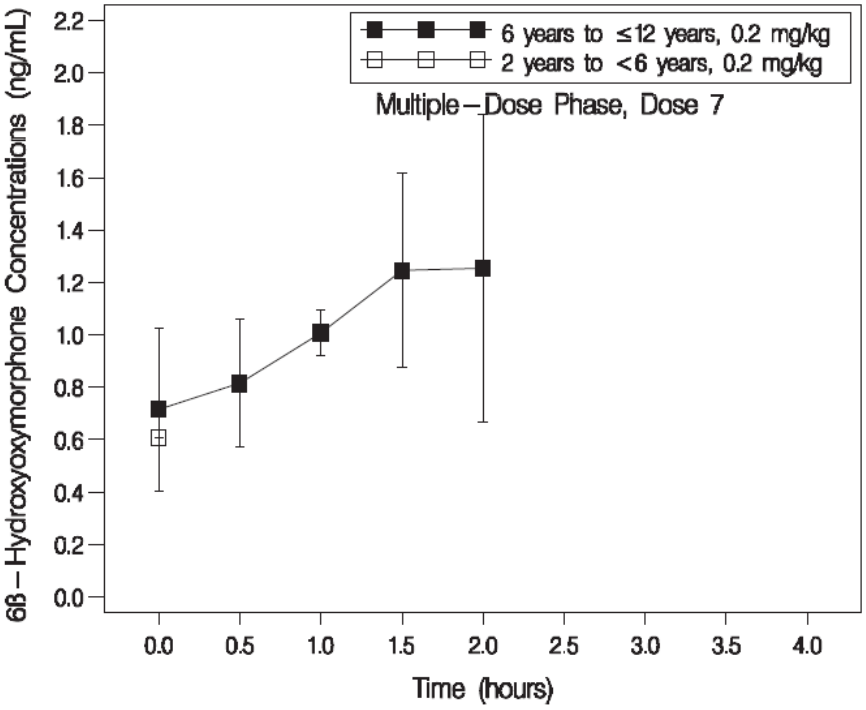


Table 5. Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Single-Dose Phase

	Cmax	Tmax	Clast	Tlast	AUC0-t	AUC0-inf	AUC0-2	AUC0-4	AUC0-6	AUC0-24	T1/2
	(ng/mL)	(h)	(ng/mL)	(h)	(h*ng/m	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL	(h)
0.05 mg/kg – Children Aged 6 years to ≤12 years											
n	6	6	6	6	6	2	6	6	6	3	2
Median	0.371	2.95	0.0542	12	1.96	2.43	0.436	1.06	1.42	2.43	2.87
Geo. Mean	0.367	3.06	0.059	14.2	2.14	2.43	0.347	0.937	1.38	3.34	2.86
Lower 95%CI	0.205	1.9	0.0283	8.89	1.14	2.01	0.151	0.493	0.763	0.817	1.38
Upper 95%CI	0.659	4.94	0.123	22.6	4.02	.	0.801	1.78	2.49	13.7	.
Mean	0.415	2.7	0.0759	15.4	2.56	.	0.44	1.08	1.57	3.75	.
SD	0.211	1.66	0.072	7.01	2	0.0516	0.298	0.601	0.912	2.32	0.232
CV(%)	51	61.7	94.9	45.5	78	2.1	67.7	55.4	57.9	61.9	8.1
Minimum	0.157	0	0.0299	8.02	1.25	2.39	0.137	0.433	0.712	2.39	2.7
Maximum	0.727	4.25	0.221	24.6	6.56	2.46	0.876	1.88	3.15	6.43	3.03
0.05 mg/kg – Children Aged 2 years to <6 years											
n	7	7	7	7	7	2	7	7	7	3	2
Median	0.234	2.05	0.0367	12	1.48	3.22	0.185	0.603	0.971	2.04	5.01
Geo. Mean	0.269	2.49	0.0516	12.5	1.52	3.02	0.232	0.652	0.95	2.43	4.91

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Lower 95%CI	0.14	1.81	0.0281	9.25	0.972	0.0328	0.108	0.345	0.556	0.713	0.387
Upper 95%CI	0.516	3.44	0.0945	16.9	2.38	279	0.498	1.23	1.62	8.28	62.4
Mean	0.33	2.64	0.0618	13.2	1.69	3.22	0.306	0.795	1.1	2.65	5.01
SD	0.217	1.03	0.0389	5.06	0.943	1.56	0.228	0.528	0.676	1.4	1.4
CV(%)	65.9	39.1	62.9	38.4	55.7	48.3	74.6	66.4	61.4	52.7	27.9
Minimum	0.106	2	0.0255	8	0.759	2.12	0.0829	0.302	0.465	1.66	4.02
Maximum	0.622	4.28	0.11	24.1	3.69	4.32	0.607	1.62	2.39	4.25	6
0.1 mg/kg – Children Aged 6 years to ≤12 years											
n	6	6	6	6	6	2	6	6	6	4	2
Median	0.81	1.04	0.0683	18	2.7	3.01	1.15	1.73	1.95	2.7	7.5
Geo. Mean	0.961	1.06	0.0852	17	2.93	2.93	0.729	1.61	2.03	2.93	5.42
Lower 95%CI	0.516	0.491	0.0379	11.4	2.28	.	0.156	0.89	1.42	1.89	.
Upper 95%CI	1.79	2.28	0.192	25.3	3.77	.	3.4	2.9	2.9	4.52	.
Mean	1.14	1.38	0.11	18	3.01	3.01	1.17	1.8	2.13	3.01	7.5
SD	0.847	1.3	0.0847	6.55	0.766	0.946	0.787	0.833	0.744	0.905	7.33
CV(%)	74.3	94.6	77.3	36.3	25.5	31.4	67.3	46.3	34.9	30	97.8
Minimum	0.494	0.5	0.0359	12	2.22	2.34	0.0397	0.58	1.23	2.32	2.32
Maximum	2.81	3.98	0.224	24.1	4.35	3.68	2.47	3.12	3.41	4.35	12.7
0.1 mg/kg – Children Aged 2 years to <6 years											
n	6	6	6	6	6	3	6	6	6	4	3
Median	1.04	0.8	0.0542	16	4.24	1.94	1.05	2.23	3.05	2.96	5.49
Geo. Mean	1.25	1.03	0.0591	13.7	3.47	2.96	1.3	2.37	2.8	3.13	3.4
Lower 95%CI	0.482	0.412	0.0333	6.67	1.83	0.424	0.562	1.36	1.63	1.11	0.29
Upper 95%CI	3.23	2.57	0.105	28.1	6.6	20.6	3	4.14	4.81	8.83	39.8
Mean	1.76	1.45	0.0671	16	3.99	3.69	1.71	2.66	3.11	3.69	4.38
SD	1.62	1.39	0.0376	8.04	2.09	3.12	1.44	1.42	1.47	2.44	2.9
CV(%)	91.7	95.9	56.1	50.2	52.4	84.7	84.2	53.2	47.3	66.3	66.2
Minimum	0.417	0.5	0.0303	3.97	1.63	1.83	0.598	1.17	1.35	1.82	1.09
Maximum	4.52	3.98	0.126	24.2	7.01	7.29	4.16	4.88	5.26	7.01	6.57
0.2 mg/kg – Children Aged 6 years to ≤12 years											
n	7	7	7	7	7	3	6	5	5	4	3
Median	1.05	1	0.17	12.6	5.23	5.65	1.51	2.83	3.37	5.28	5.3
Geo. Mean	1.12	1.21	0.211	7.75	2.86	6.2	1.34	2.3	3.17	5.69	4.35
Lower 95%CI	0.611	0.372	0.0995	2.43	0.672	1.5	0.701	0.948	1.6	2.89	0.673
Upper 95%CI	2.06	3.95	0.446	24.7	12.2	25.6	2.57	5.6	6.28	11.2	28.2
Mean	1.33	2.49	0.269	12.6	5.32	6.92	1.53	2.71	3.52	6.11	5.13
SD	0.772	3.17	0.182	9.85	4.53	4.02	0.75	1.41	1.56	2.83	3.16
CV(%)	58.1	127.1	67.7	78.3	85.1	58	48.9	52.3	44.4	46.3	61.5
Minimum	0.455	0.283	0.0549	1.05	0.137	3.69	0.451	0.692	1.28	3.68	1.9

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Maximum	2.43	8	0.524	24.1	12.9	11.4	2.54	4.65	5.6	10.2	8.21
0.2 mg/kg – Children Aged 2 years to <6 years											
n	6	6	6	6	6	2	5	5	5	2	2
Median	3.04	1.26	0.112	22.3	9.54	14.3	3.02	5.59	7.86	14	4.39
Geo. Mean	2.77	1.14	0.182	13.1	7.55	13.9	2.69	5.38	6.63	13.6	4.32
Lower 95%CI	1.51	0.44	0.0379	3.57	3.34	.	1.52	2.54	2.99	.	.
Upper 95%CI	5.08	2.94	0.872	47.9	17.1	.	4.74	11.4	14.7	.	.
Mean	3.16	1.59	0.645	18.4	9.37	14.3	2.91	6.14	7.6	14	4.39
SD	1.65	1.38	1.3	8.97	5.81	5.01	1.21	3.26	3.82	4.72	1.16
CV(%)	52.4	87.3	201.9	48.9	62.1	35	41.6	53.1	50.3	33.7	26.4
Minimum	1.18	0.483	0.0569	1.07	2.69	10.8	1.51	2.08	2.31	10.7	3.57
Maximum	5.6	4	3.3	24.1	17.3	17.9	4.52	11.1	13	17.3	5.21

Source: Supportive Tables ST-4.1 and ST-4.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 62-64/642)

Table 7. Summary Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7

	Cmax	Tmax	Clast	Tlast	AUC0-t	AUC0-inf	AUC0-2	AUC0-4	AUC0-6	AUC0-24	T1/2
	(ng/mL)	(h)	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1											
n	10	10	10	10	10	3	9	8	3	3	3
Median	1.39	1.55	0.469	4.02	2.84	3.71	1.63	2.84	3.19	3.72	2.06
Geo. Mean	0.887	1.21	0.323	3.88	1.82	3.84	1.25	2.47	3.23	3.84	2.15
Lower 95%CI	0.34	0.81	0.154	3.16	0.577	1.6	0.544	0.962	1.71	1.6	1.29
Upper 95%CI	2.31	1.82	0.675	4.76	5.72	9.25	2.85	6.33	6.11	9.23	3.59
Mean	1.46	1.37	0.452	4	3.49	4.01	1.79	3.64	3.3	4.01	2.18
SD	1.16	0.599	0.286	0.971	3.22	1.43	1.45	3.07	0.848	1.42	0.459
CV(%)	79.9	43.8	63.3	24.3	92.2	35.7	81	84.4	25.7	35.5	21
Minimum	0.068	0.433	0.0515	1.88	0.0548	2.75	0.103	0.21	2.51	2.75	1.8
Maximum	4.23	2.05	0.827	5.87	11	5.56	5.23	10.4	4.2	5.55	2.69
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1											
n	5	5	5	5	5	3	5	5	4	3	3
Median	2	0.867	0.47	4.37	3.07	3.53	2.05	2.96	3.85	3.53	0.937
Geo. Mean	2.33	0.834	0.416	4.16	3.7	4.21	2.08	3.39	4.06	4.21	1.07

Reference ID: 4499855

Lower 95%CI	1.22	0.4	0.161	2.36	2.43	1.36	1.01	2.41	2.42	1.36	0.295
Upper 95%CI	4.45	1.74	1.07	7.33	5.62	13	4.26	4.79	6.83	13	3.85
Mean	2.58	0.967	0.508	4.47	3.88	4.53	2.34	3.51	4.24	4.53	1.17
SD	1.24	0.622	0.32	1.68	1.45	2.21	1.16	1.11	1.47	2.21	0.632
CV(%)	48.2	64.3	62.9	37.5	37.4	48.8	49.5	31.6	34.7	48.7	54
Minimum	1.14	0.467	0.135	1.97	2.81	2.99	0.855	2.75	2.94	2.99	0.687
Maximum	3.9	2	0.941	6.2	6.25	7.06	3.85	5.43	6.31	7.06	1.88
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7											
n	3	3	3	3	3	0	3	0	0	0	0
Median	3.03	1.5	2.33	2.13	4.4	.	4.01	.	.	.	.
Geo. Mean	2.57	1.79	2.22	2.09	4.17	.	3.96	.	.	.	.
Lower 95%CI	1.11	0.191	0.949	1.9	2.4	.	2.5	.	.	.	.
Upper 95%CI	5.97	16.8	5.17	2.29	7.24	.	6.25	.	.	.	.
Mean	2.66	1.21	2.3	2.09	4.24	.	4	.	.	.	.
SD	0.805	1.1	0.745	0.077	0.9	.	0.728	.	.	.	.
CV(%)	30.2	90.5	32.4	3.7	21.2	.	18.2	.	.	.	.
Minimum	1.74	0	1.54	2	3.27	.	3.27	.	.	.	.
Maximum	3.22	2.13	3.03	2.13	5.05	.	4.72	.	.	.	.
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7											
n	0	0	0	0	0	0	0	0	0	0	0
Median	.	.	.	.	.	.	.	.	.	.	.
Geo. Mean	.	.	.	.	.	.	.	.	.	.	.
Lower 95%CI	.	.	.	.	.	.	.	.	.	.	.
Upper 95%CI	.	.	.	.	.	.	.	.	.	.	.
Mean	.	.	.	.	.	.	.	.	.	.	.
SD	.	.	.	.	.	.	.	.	.	.	.
CV(%)	.	.	.	.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.	.	.	.	.

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.66-67/642)

NOTE: REPEAT of ABOVE with columns deleted: AUC0-2 – AUC0-6

Summary oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase are shown in Table 7.

Table 7 Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05, 0.1, and 0.2 mg/kg Oxymorphone HCl Oral Liquid in Children Aged 2 years to ≤12 years in the Single-Dose Phase

Reference ID: 4499855

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Median	0.371	2.95	1.96	2.43	2.87
Geo. Mean	0.367	3.06	2.14	2.43	2.86
Lower 95%CI	0.205	1.9	1.14	2.01	1.38
Upper 95%CI	0.659	4.94	4.02	.	.
Mean	0.415	2.7	2.56	.	.
SD	0.211	1.66	2	0.0516	0.232
CV(%)	51	61.7	78	2.1	8.1
Minimum	0.157	0	1.25	2.39	2.7
Maximum	0.727	4.25	6.56	2.46	3.03
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	2	2
Median	0.234	2.05	1.48	3.22	5.01
Geo. Mean	0.269	2.49	1.52	3.02	4.91
Lower 95%CI	0.14	1.81	0.972	0.0328	0.387
Upper 95%CI	0.516	3.44	2.38	279	62.4
Mean	0.33	2.64	1.69	3.22	5.01
SD	0.217	1.03	0.943	1.56	1.4
CV(%)	65.9	39.1	55.7	48.3	27.9
Minimum	0.106	2	0.759	2.12	4.02
Maximum	0.622	4.28	3.69	4.32	6
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	2	2
Median	0.81	1.04	2.7	3.01	7.5
Geo. Mean	0.961	1.06	2.93	2.93	5.42
Lower 95%CI	0.516	0.491	2.28	.	.
Upper 95%CI	1.79	2.28	3.77	.	.
Mean	1.14	1.38	3.01	3.01	7.5
SD	0.847	1.3	0.766	0.946	7.33
CV(%)	74.3	94.6	25.5	31.4	97.8
Minimum	0.494	0.5	2.22	2.34	2.32
Maximum	2.81	3.98	4.35	3.68	12.7
0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	3	3
Median	1.04	0.8	4.24	1.94	5.49
Geo. Mean	1.25	1.03	3.47	2.96	3.4
Lower 95%CI	0.482	0.412	1.83	0.424	0.29
Upper 95%CI	3.23	2.57	6.6	20.6	39.8
Mean	1.76	1.45	3.99	3.69	4.38
SD	1.62	1.39	2.09	3.12	2.9
CV(%)	91.7	95.9	52.4	84.7	66.2
Minimum	0.417	0.5	1.63	1.83	1.09

Maximum	4.52	3.98	7.01	7.29	6.57
0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	3	3
Median	1.05	1	5.23	5.65	5.3
Geo. Mean	1.12	1.21	2.86	6.2	4.35
Lower 95%CI	0.611	0.372	0.672	1.5	0.673
Upper 95%CI	2.06	3.95	12.2	25.6	28.2
Mean	1.33	2.49	5.32	6.92	5.13
SD	0.772	3.17	4.53	4.02	3.16
CV(%)	58.1	127.1	85.1	58	61.5
Minimum	0.455	0.283	0.137	3.69	1.9
Maximum	2.43	8	12.9	11.4	8.21
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Median	3.04	1.26	9.54	14.3	4.39
Geo. Mean	2.77	1.14	7.55	13.9	4.32
Lower 95%CI	1.51	0.44	3.34	.	.
Upper 95%CI	5.08	2.94	17.1	.	.
Mean	3.16	1.59	9.37	14.3	4.39
SD	1.65	1.38	5.81	5.01	1.16
CV(%)	52.4	87.3	62.1	35	26.4
Minimum	1.18	0.483	2.69	10.8	3.57
Maximum	5.6	4	17.3	17.9	5.21

Source: Supportive Tables ST-4.1 and ST-4.4 and Appendix I.
. Not determined, or not reported due to insufficient data for reliable estimate.
(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p. 62-64/642)

Summary oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7 are presented in Table 7.

Table 7. Summary Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid in Children Aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Median	1.39	1.55	2.84	3.71	2.06
Geo. Mean	0.887	1.21	1.82	3.84	2.15
Lower 95%CI	0.34	0.81	0.577	1.6	1.29
Upper 95%CI	2.31	1.82	5.72	9.25	3.59
Mean	1.46	1.37	3.49	4.01	2.18
SD	1.16	0.599	3.22	1.43	0.459

CV(%)	79.9	43.8	92.2	35.7	21
Minimum	0.068	0.433	0.0548	2.75	1.8
Maximum	4.23	2.05	11	5.56	2.69
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Median	2	0.867	3.07	3.53	0.937
Geo. Mean	2.33	0.834	3.7	4.21	1.07
Lower 95%CI	1.22	0.4	2.43	1.36	0.295
Upper 95%CI	4.45	1.74	5.62	13	3.85
Mean	2.58	0.967	3.88	4.53	1.17
SD	1.24	0.622	1.45	2.21	0.632
CV(%)	48.2	64.3	37.4	48.8	54
Minimum	1.14	0.467	2.81	2.99	0.687
Maximum	3.9	2	6.25	7.06	1.88
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	0	0
Median	3.03	1.5	4.4	.	.
Geo. Mean	2.57	1.79	4.17	.	.
Lower 95%CI	1.11	0.191	2.4	.	.
Upper 95%CI	5.97	16.8	7.24	.	.
Mean	2.66	1.21	4.24	.	.
SD	0.805	1.1	0.9	.	.
CV(%)	30.2	90.5	21.2	.	.
Minimum	1.74	0	3.27	.	.
Maximum	3.22	2.13	5.05	.	.
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Median	.	.	.	.	.
Geo. Mean	.	.	.	.	.
Lower 95%CI	.	.	.	.	.
Upper 95%CI	.	.	.	.	.
Mean	.	.	.	.	.
SD	.	.	.	.	.
CV(%)	.	.	.	.	.
Minimum	.	.	.	.	.
Maximum	.	.	.	.	.

Source: Supportive Tables ST-4.9 to ST-4.12 and Appendix I.

. Not determined, or not reported due to insufficient data for reliable estimate. (Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.66-67/642)

Summary 6-OH-Oxymorphone PK parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the single-dose phase are shown in Table 8.

Reference ID: 4499855

Summary 6-OH-Oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl oral solution in children aged 2 years to ≤12 years in the Multiple-Dose Phase from Dose 1 and Dose 7 are presented in Table 9.

Table 8 Summary 6-OH-oxymorphone pharmacokinetic parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCL oral solution in children aged 2 years to ≤12 years in the single-dose phase

	Cmax	Tmax	Clast	Tlast	AUC0-t	AUC0-inf	AUC0-2	AUC0-4	AUC0-6	AUC0-24	T1/2
	(ng/mL)	(h)	(ng/mL	(h)	(h*ng/m	(h*ng/mL)	(h*ng/m	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h)
n	6	5	5	5	6	1	5	5	3	1	1
Median	0.119	2.02	0.0328	8	0.399	1.83	0.108	0.261	0.463	1.09	20.5
Geo. Mean	0.123	2.68	0.0404	7.65	0.451	1.83	0.0805	0.261	0.486	1.09	20.5
Lower	0.0953	1.64	0.0217	3.13	0.181	.	0.034	0.16	0.317	.	.
Upper	0.158	4.39	0.0754	18.7	1.12	.	0.191	0.424	0.747	.	.
Mean	0.104	2.86	0.0453	9.66	0.459	1.83	0.0956	0.277	0.491	1.09	20.5
SD	0.0555	1.17	0.0272	8.25	0.396	.	0.055	0.104	0.0873	.	.
CV(%)	53.4	41	60.1	85.4	86.3	.	57.5	37.5	17.8	.	.
Minimum	0	2	0.0251	4.02	0	1.83	0.0352	0.155	0.422	1.09	20.5
Maximum	0.155	4.25	0.0926	24	1.09	1.83	0.155	0.415	0.589	1.09	20.5
n	7	7	7	7	7	1	7	6	3	1	1
Median	0.0632	2.05	0.0425	4.02	0.205	1.11	0.0425	0.174	0.466	1.09	4.48
Geo. Mean	0.0838	2.74	0.0394	6.41	0.265	1.11	0.0649	0.209	0.438	1.09	4.48
Lower	0.0475	1.93	0.0277	2.87	0.0845	.	0.0305	0.106	0.113	.	.
Upper	0.148	3.88	0.0559	14.4	0.833	.	0.138	0.413	1.7	.	.
Mean	0.1	2.91	0.0418	8.86	0.467	1.11	0.088	0.253	0.481	1.09	4.48
SD	0.073	1.11	0.0152	7.82	0.473	.	0.0792	0.184	0.242	.	.
CV(%)	72.7	38.1	36.4	88.2	101.4	.	90	72.7	50.4	.	.
Minimum	0.0425	2	0.0252	2	0.0425	1.11	0.0275	0.11	0.247	1.09	4.48
Maximum	0.248	4.28	0.0632	24	1.25	1.11	0.242	0.583	0.73	1.09	4.48
n	6	6	6	6	6	1	6	6	6	3	1
Median	0.386	1.04	0.0507	12.1	1.13	0.535	0.447	0.634	0.726	1.25	2.31
Geo. Mean	0.346	1.06	0.0508	12.6	1.04	0.535	0.222	0.575	0.752	0.991	2.31
Lower	0.202	0.491	0.0294	6.98	0.537	.	0.0327	0.281	0.429	0.259	.
Upper	0.593	2.28	0.0877	22.8	2.02	.	1.5	1.18	1.32	3.79	.
Mean	0.384	1.38	0.0568	14.4	1.22	0.535	0.425	0.7	0.862	1.08	2.31
SD	0.177	1.3	0.0292	7.86	0.761	.	0.319	0.505	0.566	0.484	.
CV(%)	46.3	94.6	51.5	54.7	62.2	.	75.1	72.2	65.6	44.8	.
Minimum	0.183	0.5	0.0271	6.05	0.444	0.535	0.0061	0.22	0.443	0.535	2.31
Maximum	0.62	3.98	0.103	24.1	2.57	0.535	0.956	1.66	1.97	1.46	2.31
n	6	6	6	6	6	4	6	6	6	5	4
Median	0.292	1.07	0.027	18	1.14	1.65	0.282	0.559	0.799	1.18	7.41
Geo. Mean	0.333	1.29	0.0302	13.3	1.15	1.63	0.327	0.655	0.831	1.37	5.39
Lower	0.153	0.479	0.019	6.12	0.693	0.809	0.136	0.397	0.52	0.863	0.758

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Upper	0.726	3.48	0.0481	28.9	1.9	3.3	0.784	1.08	1.33	2.17	38.3
Mean	0.437	1.86	0.0332	16.1	1.27	1.76	0.445	0.73	0.907	1.45	8.67
SD	0.419	1.69	0.0183	9.05	0.637	0.762	0.415	0.417	0.438	0.588	8.06
CV(%)	95.7	90.8	55.1	56.3	50.3	43.4	93.1	57.2	48.3	40.6	92.9
Minimum	0.171	0.5	0.0211	3.97	0.598	0.944	0.134	0.453	0.527	0.943	1.28
Maximum	1.27	4.07	0.0693	24.2	2.4	2.78	1.22	1.53	1.68	2.4	18.6
n	7	7	7	7	7	2	6	5	5	4	2
Median	0.431	1.45	0.153	12.6	2.42	7.58	0.551	1.12	1.51	3.18	18.7
Geo. Mean	0.428	1.76	0.13	7.75	1.32	6.65	0.416	0.937	1.37	2.84	9.75
Lower	0.18	0.608	0.0461	2.43	0.308	.	0.139	0.28	0.47	1.33	.
Upper	1.02	5.1	0.367	24.7	5.64	.	1.24	3.14	3.98	6.08	.
Mean	0.603	3.08	0.204	12.6	2.64	7.58	0.634	1.25	1.72	3.08	18.7
SD	0.513	3.42	0.188	9.85	2.52	5.12	0.64	0.906	1.07	1.32	22.5
CV(%)	85	110.8	92.1	78.3	95.2	67.6	101	72.3	62.4	42.9	120.6
Minimum	0.131	0.5	0.0201	1.05	0.138	3.95	0.114	0.188	0.336	1.55	2.75
Maximum	1.51	8.05	0.522	24.1	7.45	11.2	1.86	2.7	3.21	4.39	34.6
n	6	6	6	6	6	2	5	5	5	2	2
Median	0.568	1.29	0.043	22.3	2.32	2.76	0.436	1.24	1.55	2.61	5.18
Geo. Mean	0.562	1.28	0.0553	13.1	1.84	2.74	0.494	1.16	1.57	2.61	4.85
Lower	0.4	0.435	0.0184	3.57	0.746	.	0.23	0.916	1.48	1.2	.
Upper	0.791	3.78	0.167	47.9	4.55	.	1.06	1.48	1.66	5.68	.
Mean	0.587	1.93	0.0994	18.4	2.26	2.76	0.574	1.18	1.57	2.61	5.18
SD	0.182	1.71	0.144	8.97	1.07	0.399	0.344	0.224	0.071	0.226	2.55
CV(%)	31.1	88.6	144.5	48.9	47.5	14.5	59.9	19	4.5	8.7	49.3
Minimum	0.353	0.483	0.022	1.07	0.33	2.47	0.241	0.916	1.48	2.45	3.37
Maximum	0.797	4.02	0.39	24.1	3.58	3.04	1.04	1.46	1.66	2.77	6.98

Source: Supportive Tables ST-5.1 and ST-5.4 and Appendix I.

. Not determined, or not reported due to insufficient data for reliable estimate.

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.71-73/642)

Table 9 Summary 6OH-oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone hcl immediate-release oral liquid in children aged 2 years to ≤12 years in the multiple-dose phase from dose 1 and dose 7

	Cmax	Tmax	Clast	Tlast	AUC0-t	AUC0-inf	AUC0-2	AUC0-4	AUC0-6	AUC0-24	T1/2
	(ng/mL)	(h)	(ng/mL	(h)	(h*ng/	(h*ng/mL)	(h*ng/mL)	(h*ng/mL)	(h*ng/mL	(h*ng/mL	(h)
n	10	10	10	10	10	3	9	8	3	3	3
Median	0.441	1.58	0.218	4.02	1.07	2.29	0.708	1.07	1.22	2.2	3.88
Geo. Mean	0.325	1.39	0.153	3.81	0.636	2.05	0.466	0.973	1.4	2.01	3.31
Lower	0.125	0.862	0.0787	3	0.168	0.769	0.207	0.418	0.771	0.774	0.874
Upper	0.841	2.26	0.297	4.84	2.41	5.46	1.05	2.27	2.53	5.24	12.5
Mean	0.547	1.67	0.201	3.97	1.35	2.15	0.677	1.39	1.42	2.11	3.61

Reference ID: 4499855

SD	0.472	1.01	0.118	1.05	1.27	0.769	0.556	1.19	0.361	0.748	1.67
CV(%)	86.2	60.5	58.9	26.3	93.8	35.7	82.1	85.3	25.3	35.4	46.2
Minimum	0.0204	0.433	0.0204	1.58	0.0068	1.32	0.0538	0.128	1.22	1.32	1.82
Maximum	1.59	4.02	0.394	5.87	4.23	2.84	1.95	3.96	1.84	2.81	5.12
n	5	5	5	5	5	3	5	5	4	3	3
Median	0.962	0.867	0.202	4.37	0.962	1.16	0.968	1.13	1.87	1.16	1.24
Geo. Mean	0.658	0.96	0.172	4.16	1.24	1.26	0.663	1.13	1.42	1.26	1.29
Lower	0.238	0.327	0.0513	2.36	0.431	0.0915	0.224	0.456	0.337	0.0915	0.357
Upper	1.82	2.82	0.576	7.33	3.54	17.2	1.96	2.81	5.97	17.2	4.69
Mean	0.829	1.37	0.225	4.47	1.61	1.79	0.863	1.37	1.83	1.78	1.42
SD	0.541	1.5	0.139	1.68	1.19	1.73	0.598	0.854	1.25	1.72	0.73
CV(%)	65.2	109.6	61.8	37.5	74.2	96.7	69.4	62.4	68.3	96.6	51.6
Minimum	0.24	0.467	0.0333	1.97	0.396	0.455	0.238	0.382	0.431	0.455	0.788
Maximum	1.5	4.03	0.398	6.2	3.09	3.74	1.63	2.57	3.13	3.73	2.22
n	3	3	3	3	3	1	3	1	1	1	1
Median	1.31	1.5	1.02	2.13	2.04	7.66	1.9	3.27	4.34	7.38	4.9
Geo. Mean	1.35	1.13	1.17	2.09	2.21	7.66	2.1	3.27	4.34	7.38	4.9
Lower	0.592	0.149	0.393	1.9	1.24	.	1.29	.	.	.	.
Upper	3.1	8.57	3.5	2.29	3.94	.	3.4	.	.	.	.
Mean	1.41	1.36	1.25	2.09	2.25	7.66	2.12	3.27	4.34	7.38	4.9
SD	0.473	0.85	0.585	0.077	0.547	.	0.434	.	.	.	.
CV(%)	33.7	62.5	46.6	3.7	24.3	.	20.4	.	.	.	.
Minimum	0.988	0.45	0.823	2	1.84	7.66	1.84	3.27	4.34	7.38	4.9
Maximum	1.92	2.13	1.92	2.13	2.87	7.66	2.62	3.27	4.34	7.38	4.9
n	0	0	0	0	0	0	0	0	0	0	0
Median	.	.	.	.	.	.	.	.	.	.	.
Geo. Mean	.	.	.	.	.	.	.	.	.	.	.
Lower	.	.	.	.	.	.	.	.	.	.	.
Upper	.	.	.	.	.	.	.	.	.	.	.
Mean	.	.	.	.	.	.	.	.	.	.	.
SD	.	.	.	.	.	.	.	.	.	.	.
CV(%)	.	.	.	.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.	.	.	.	.

Source: Supportive Tables ST-5.9 to ST-5.12 and Appendix I.

. Not determined, or not reported due to insufficient data for reliable estimate

(Source: complete report available at m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain-pediatric\5352-stud-rep-uncontr\en3319-302-pk; p.75-76/642)

Repeated with columns removed: AUC0-2 – AUC0-6

Reference ID: 4499855

Summary 6-OH-oxymorphone pharmacokinetic parameters following single-dose administration of 0.05, 0.1, and 0.2 mg/kg oxymorphone HCL oral solution in children aged 2 years to ≤12 years in the single-dose phase

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.05 mg/kg – Children Aged 6 years to ≤12 years					
n	6	5	6	1	1
Median	0.119	2.02	0.399	1.83	20.5
Geo. Mean	0.123	2.68	0.451	1.83	20.5
Lower 95%CI	0.0953	1.64	0.181	.	.
Upper 95%CI	0.158	4.39	1.12	.	.
Mean	0.104	2.86	0.459	1.83	20.5
SD	0.0555	1.17	0.396	.	.
CV(%)	53.4	41	86.3	.	.
Minimum	0	2	0	1.83	20.5
Maximum	0.155	4.25	1.09	1.83	20.5
0.05 mg/kg – Children Aged 2 years to <6 years					
n	7	7	7	1	1
Median	0.0632	2.05	0.205	1.11	4.48
Geo. Mean	0.0838	2.74	0.265	1.11	4.48
Lower 95%CI	0.0475	1.93	0.0845	.	.
Upper 95%CI	0.148	3.88	0.833	.	.
Mean	0.1	2.91	0.467	1.11	4.48
SD	0.073	1.11	0.473	.	.
CV(%)	72.7	38.1	101.4	.	.
Minimum	0.0425	2	0.0425	1.11	4.48
Maximum	0.248	4.28	1.25	1.11	4.48
0.1 mg/kg – Children Aged 6 years to ≤12 years					
n	6	6	6	1	1
Median	0.386	1.04	1.13	0.535	2.31
Geo. Mean	0.346	1.06	1.04	0.535	2.31
Lower 95%CI	0.202	0.491	0.537	.	.
Upper 95%CI	0.593	2.28	2.02	.	.
Mean	0.384	1.38	1.22	0.535	2.31
SD	0.177	1.3	0.761	.	.
CV(%)	46.3	94.6	62.2	.	.
Minimum	0.183	0.5	0.444	0.535	2.31
Maximum	0.62	3.98	2.57	0.535	2.31

0.1 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	4	4
Median	0.292	1.07	1.14	1.65	7.41
Geo. Mean	0.333	1.29	1.15	1.63	5.39
Lower 95%CI	0.153	0.479	0.693	0.809	0.758
Upper 95%CI	0.726	3.48	1.9	3.3	38.3
Mean	0.437	1.86	1.27	1.76	8.67
SD	0.419	1.69	0.637	0.762	8.06
CV(%)	95.7	90.8	50.3	43.4	92.9
Minimum	0.171	0.5	0.598	0.944	1.28
Maximum	1.27	4.07	2.4	2.78	18.6
0.2 mg/kg – Children Aged 6 years to ≤12 years					
n	7	7	7	2	2
Median	0.431	1.45	2.42	7.58	18.7
Geo. Mean	0.428	1.76	1.32	6.65	9.75
Lower 95%CI	0.18	0.608	0.308	.	.
Upper 95%CI	1.02	5.1	5.64	.	.
Mean	0.603	3.08	2.64	7.58	18.7
SD	0.513	3.42	2.52	5.12	22.5
CV(%)	85	110.8	95.2	67.6	120.6
Minimum	0.131	0.5	0.138	3.95	2.75
Maximum	1.51	8.05	7.45	11.2	34.6
0.2 mg/kg – Children Aged 2 years to <6 years					
n	6	6	6	2	2
Median	0.568	1.29	2.32	2.76	5.18
Geo. Mean	0.562	1.28	1.84	2.74	4.85
Lower 95%CI	0.4	0.435	0.746	.	.
Upper 95%CI	0.791	3.78	4.55	.	.
Mean	0.587	1.93	2.26	2.76	5.18
SD	0.182	1.71	1.07	0.399	2.55
CV(%)	31.1	88.6	47.5	14.5	49.3
Minimum	0.353	0.483	0.33	2.47	3.37
Maximum	0.797	4.02	3.58	3.04	6.98

Reference ID: 4499855

Summary 6OH-oxymorphone pharmacokinetic parameters following multiple-dose administration of 0.2 mg/kg oxymorphone HCl immediate-release oral liquid in children aged 2 years to ≤12 years in the multiple-dose phase from dose 1 and dose 7

	Cmax	Tmax	AUC0-t	AUC0-inf	T1/2
	(ng/mL)	(h)	(h*ng/mL)	(h*ng/mL)	(h)
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 1					
n	10	10	10	3	3
Median	0.441	1.58	1.07	2.29	3.88
Geo. Mean	0.325	1.39	0.636	2.05	3.31
Lower 95%CI	0.125	0.862	0.168	0.769	0.874
Upper 95%CI	0.841	2.26	2.41	5.46	12.5
Mean	0.547	1.67	1.35	2.15	3.61
SD	0.472	1.01	1.27	0.769	1.67
CV(%)	86.2	60.5	93.8	35.7	46.2
Minimum	0.0204	0.433	0.0068	1.32	1.82
Maximum	1.59	4.02	4.23	2.84	5.12
0.2 mg/kg – Children Aged 2 years to <6 years – Dose 1					
n	5	5	5	3	3
Median	0.962	0.867	0.962	1.16	1.24
Geo. Mean	0.658	0.96	1.24	1.26	1.29
Lower 95%CI	0.238	0.327	0.431	0.0915	0.357
Upper 95%CI	1.82	2.82	3.54	17.2	4.69
Mean	0.829	1.37	1.61	1.79	1.42
SD	0.541	1.5	1.19	1.73	0.73
CV(%)	65.2	109.6	74.2	96.7	51.6
Minimum	0.24	0.467	0.396	0.455	0.788
Maximum	1.5	4.03	3.09	3.74	2.22
0.2 mg/kg – Children Aged 6 years to ≤12 years – Dose 7					
n	3	3	3	1	1
Median	1.31	1.5	2.04	7.66	4.9
Geo. Mean	1.35	1.13	2.21	7.66	4.9
Lower 95%CI	0.592	0.149	1.24	.	.
Upper 95%CI	3.1	8.57	3.94	.	.
Mean	1.41	1.36	2.25	7.66	4.9
SD	0.473	0.85	0.547	.	.
CV(%)	33.7	62.5	24.3	.	.
Minimum	0.988	0.45	1.84	7.66	4.9
Maximum	1.92	2.13	2.87	7.66	4.9

0.2 mg/kg – Children Aged 2 years to <6 years – Dose 7					
n	0	0	0	0	0
Median	.	.	.	.	.
Geo. Mean	.	.	.	.	.
Lower 95%CI	.	.	.	.	.
Upper 95%CI	.	.	.	.	.
Mean	.	.	.	.	.
SD	.	.	.	.	.
CV(%)	.	.	.	.	.
Minimum	.	.	.	.	.
Maximum	.	.	.	.	.

Additional information:

1. Table ST-2.1. Individual and Summary Oxymorphone Concentrations (ng/mL) Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Single-Dose Phase

For 0.05, 0.1 and 0.2 mg/kg for 2-12 y old single and multiple doses-

Table ST-2.1. Individual and Summary Oxymorphone Concentrations (ng/mL) Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Single-Dose Phase

	Time (hours)										
Subject	0	0.25	0.5	1	1.5	2	4	6	8	12	24
(b) (6)	0	.	.	.	.	0.295	0.098	.	0.097	0.058	0
	0.447	.	.	.	.	0.429	0.215	.	0.047	0.051	0
	0	.	.	.	.	0.135	0.157	.	0.094	0.044	0.037
	0	.	.	.	.	0.138	0.284	.	0.059	0	0
	0.041	.	.	.	.	0.579	0.233	.	0.079	0.03	0
	0.034	.	.	.	.	0.607	0.727	.	0.272	0.08	0.221
n	6	0	0	0	0	6	6	0	6	6	6
Median	0.017	.	.	.	.	0.362	0.224	.	0.087	0.047	0
Mean	0.087	.	.	.	.	0.364	0.285	.	0.108	0.044	0.043
SD	0.177	.	.	.	.	0.209	0.226	.	0.083	0.027	0.088
CV(%)	203.5	.	.	.	.	57.4	79	.	76.5	61.9	205.8
Minimum	0	.	.	.	.	0.135	0.098	.	0.047	0	0
Maximum	0.447	.	.	.	.	0.607	0.727	.	0.272	0.08	0.221

. No sample or not determined.
Source: Study files.

2. Table ST-2.9. Individual and Summary Oxymorphone Concentrations (ng/mL) Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Multiple-Dose Phase from Dose 7

Reference ID: 4499855

Table ST-2.9. Individual and Summary Oxymorphone Concentrations (ng/mL) Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Multiple-Dose Phase from Dose 7

	Time (hours)										
Subject	0	0.25	0.5	1	1.5	2	4	6	8	12	24
(b) (6)	1.26	.	.	.	2.34	3.03	.	.	.	.	.
	1.46	.	1.54	2.8	3.22	2.33	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.
	1.74	.	1.67	1.72	1.5	1.54	.	.	.	.	.
	0.785	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.
	1.58	.	.	.	.	.	.	.	.	.	.
n	5	0	2	2	3	3	0	0	0	0	0
Median	1.46	.	1.61	2.26	2.34	2.33	.	.	.	.	.
Mean	1.37	.	1.61	2.26	2.35	2.3	.	.	.	.	.
SD	0.369	.	0.092	0.764	0.86	0.745	.	.	.	.	.
CV(%)	27	.	5.7	33.8	36.5	32.4	.	.	.	.	.
Minimum	0.785	.	1.54	1.72	1.5	1.54	.	.	.	.	.
Maximum	1.74	.	1.67	2.8	3.22	3.03	.	.	.	.	.

. No sample or not determined.
Source: Study files.

Source: en3319-302-pk.pdf; p. 112- /642

3. Table ST-4.1. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to #12 years in the Single-Dose Phase

Reference ID: 4499855

Table ST-4.1. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.295	2	0.0577	12	1.38	.	.	0.295	0.687	0.882	.	.	.	.
	0.447	0	0.0507	11.9	2.24	2.46	8.98	0.876	1.52	1.87	2.43	3.03	20.3	88.7
	0.157	3.88	0.0369	23.9	1.69	.	.	0.14	0.433	0.712	.	.	.	.
	0.284	4.03	0.0592	8.02	1.25	.	.	0.137	0.555	1.01	.	.	.	.
	0.579	2.02	0.0299	12	2.28	2.39	4.87	0.616	1.43	1.82	2.39	2.7	20.9	81.5
	0.727	4.25	0.221	24.6	6.56	.	.	0.578	1.88	3.15	6.43	.	.	.
n	6	6	6	6	6	2	2	6	6	6	3	2	2	2
Median	0.371	2.95	0.0542	12	1.96	2.43	6.93	0.436	1.06	1.42	2.43	2.87	20.6	85.1
Geo. Mean	0.367	3.06	0.059	14.2	2.14	2.43	6.61	0.347	0.937	1.38	3.34	2.86	20.6	85
Lower 95%CI	0.205	1.9	0.0283	8.89	1.14	2.01	0.135	0.151	0.493	0.763	0.817	1.38	17	49.7
Upper 95%CI	0.659	4.94	0.123	22.6	4.02	2.94	324	0.801	1.78	2.49	13.7	5.93	24.9	146
Mean	0.415	2.7	0.0759	15.4	2.56	2.43	6.93	0.44	1.08	1.57	3.75	2.87	20.6	85.1
SD	0.211	1.66	0.072	7.01	2	0.0516	2.91	0.298	0.601	0.912	2.32	0.232	0.438	5.09
CV(%)	51	61.7	94.9	45.5	78	2.1	42	67.7	55.4	57.9	61.9	8.1	2.1	6
Minimum	0.157	0	0.0299	8.02	1.25	2.39	4.87	0.137	0.433	0.712	2.39	2.7	20.3	81.5
Maximum	0.727	4.25	0.221	24.6	6.56	2.46	8.98	0.876	1.88	3.15	6.43	3.03	20.9	88.7

. No sample or not determined.

Source: Study files.

Table ST-4.2. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.1 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.741	1.08	0.0516	24.1	2.67	.	.	0.877	1.48	1.76	2.66	.	.	.
	0.783	1	0.0359	12.1	2.22	2.34	5.12	1.03	1.72	1.99	2.32	2.32	42.7	143
	1.17	0.583	0.224	12	2.64	.	.	1.34	1.74	1.9	.	.	.	.
	0.837	1.12	0.21	12.1	3.44	.	.	1.26	2.14	2.49	.	.	.	.
	0.494	3.98	0.052	23.9	2.73	3.68	25.9	0.0397	0.58	1.23	2.73	12.7	27.2	497
	2.81	0.5	0.0846	24.1	4.35	.	.	2.47	3.12	3.41	4.35	.	.	.
n	6	6	6	6	6	2	2	6	6	6	4	2	2	2
Median	0.81	1.04	0.0683	18	2.7	3.01	15.5	1.15	1.73	1.95	2.7	7.5	34.9	320
Geo. Mean	0.961	1.06	0.0852	17	2.93	2.93	11.5	0.729	1.61	2.03	2.93	5.42	34.1	266
Lower 95%CI	0.516	0.491	0.0379	11.4	2.28	0.166	0.0004	0.156	0.89	1.42	1.89	0.0001	1.93	0.0955
Upper 95%CI	1.79	2.28	0.192	25.3	3.77	51.8	337958	3.4	2.9	2.9	4.52	267033	602	743125
Mean	1.14	1.38	0.11	18	3.01	3.01	15.5	1.17	1.8	2.13	3.01	7.5	34.9	320
SD	0.847	1.3	0.0847	6.55	0.766	0.946	14.7	0.787	0.833	0.744	0.905	7.33	11	251
CV(%)	74.3	94.6	77.3	36.3	25.5	31.4	94.7	67.3	46.3	34.9	30	97.8	31.4	78.4
Minimum	0.494	0.5	0.0359	12	2.22	2.34	5.12	0.0397	0.58	1.23	2.32	2.32	27.2	143
Maximum	2.81	3.98	0.224	24.1	4.35	3.68	25.9	2.47	3.12	3.41	4.35	12.7	42.7	497

. No sample or not determined.

Source: Study files.

Reference ID: 4499855

Table ST-4.3. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged years 6 to ≤12 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.455	1.05	0.455	1.05	0.137	.	.	.	.	.	.	.	.	.
	2.43	0.5	0.17	18.2	9.41	11.4	17.6	2.54	4.65	5.6	10.2	8.21	17.5	207
	0.944	1	0.387	2	1.05	.	.	1.05	.	.	.	.	.	.
	1.99	8	0.524	12.6	12.9	.	.	1.41	2.4	4.1	.	.	.	.
	1.89	0.533	0.167	6.07	3.24	3.69	12.4	2.14	2.83	3.23	3.68	1.9	54.1	148
	0.54	6.08	0.0549	24.1	5.23	5.65	7.42	0.451	0.692	1.28	5.23	5.3	35.4	270
	1.05	0.283	0.128	24	5.33	.	.	1.6	2.96	3.37	5.33	.	.	.
n	7	7	7	7	7	3	3	6	5	5	4	3	3	3
Median	1.05	1	0.17	12.6	5.23	5.65	12.4	1.51	2.83	3.37	5.28	5.3	35.4	207
Geo. Mean	1.12	1.21	0.211	7.75	2.86	6.2	11.7	1.34	2.3	3.17	5.69	4.35	32.3	203
Lower 95%CI	0.611	0.372	0.0995	2.43	0.672	1.5	3.99	0.701	0.948	1.6	2.89	0.673	7.83	95.8
Upper 95%CI	2.06	3.95	0.446	24.7	12.2	25.6	34.6	2.57	5.6	6.28	11.2	28.2	133	428
Mean	1.33	2.49	0.269	12.6	5.32	6.92	12.5	1.53	2.71	3.52	6.11	5.13	35.7	209
SD	0.772	3.17	0.182	9.85	4.53	4.02	5.1	0.75	1.41	1.56	2.83	3.16	18.3	61.1
CV(%)	58.1	127.1	67.7	78.3	85.1	58	40.9	48.9	52.3	44.4	46.3	61.5	51.3	29.3
Minimum	0.455	0.283	0.0549	1.05	0.137	3.69	7.42	0.451	0.692	1.28	3.68	1.9	17.5	148
Maximum	2.43	8	0.524	24.1	12.9	11.4	17.6	2.54	4.65	5.6	10.2	8.21	54.1	270

. No sample or not determined.
Source: Study files.

Ages 2-6 years old:

Reference ID: 4499855

Table ST-4.4. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 2 years to <6 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.598	2.05	0.109	12	3.69	4.32	14.7	0.583	1.62	2.39	4.25	4.02	11.6	67.2
	0.429	2	0.0893	12	1.48	.	.	0.429	0.971	1.15	.	.	.	.
	0.106	2	0.0255	11.9	0.759	.	.	0.106	0.302	0.465	.	.	.	.
	0.154	2.08	0.0277	24.1	1.67	.	.	0.148	0.401	0.59	1.66	.	.	.
	0.622	2.05	0.0367	11.9	1.8	2.12	15	0.607	1.35	1.51	2.04	6	23.6	204
	0.167	4.28	0.11	12.1	1.32	.	.	0.0829	0.323	0.632	.	.	.	.
	0.234	4	0.0351	8	1.14	.	.	0.185	0.603	0.971	.	.	.	.
n	7	7	7	7	7	2	2	7	7	7	3	2	2	2
Median	0.234	2.05	0.0367	12	1.48	3.22	14.8	0.185	0.603	0.971	2.04	5.01	17.6	136
Geo. Mean	0.269	2.49	0.0516	12.5	1.52	3.02	14.8	0.232	0.652	0.95	2.43	4.91	16.5	117
Lower 95%CI	0.14	1.81	0.0281	9.25	0.972	0.0328	12.8	0.108	0.345	0.556	0.713	0.387	0.179	0.0999
Upper 95%CI	0.516	3.44	0.0945	16.9	2.38	279	17.2	0.498	1.23	1.62	8.28	62.4	1526	137477
Mean	0.33	2.64	0.0618	13.2	1.69	3.22	14.8	0.306	0.795	1.1	2.65	5.01	17.6	136
SD	0.217	1.03	0.0389	5.06	0.943	1.56	0.243	0.228	0.528	0.676	1.4	1.4	8.5	97
CV(%)	65.9	39.1	62.9	38.4	55.7	48.3	1.6	74.6	66.4	61.4	52.7	27.9	48.3	71.4
Minimum	0.106	2	0.0255	8	0.759	2.12	14.7	0.0829	0.302	0.465	1.66	4.02	11.6	67.2
Maximum	0.622	4.28	0.11	24.1	3.69	4.32	15	0.607	1.62	2.39	4.25	6	23.6	204

. No sample or not determined.
Source: Study files.

Reference ID: 4499855

Table ST-4.5. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.1 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 2 years to <6 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrp} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.64	3.98	0.054	24.2	4.05	.	.	0.847	2.04	2.81	4.04	.	.	.
	0.953	0.533	0.126	3.97	1.63	1.83	10.8	1.26	1.63	1.76	1.82	1.09	54.8	86
	0.417	1.07	0.0381	12	1.64	1.94	15.5	0.653	1.17	1.35	1.87	5.49	51.5	408
	4.52	0.5	0.0303	24	7.01	7.29	3.94	4.16	4.88	5.26	7.01	6.57	13.7	130
	1.13	2.1	0.0544	20	4.42	.	.	0.598	2.41	3.28	.	.	.	.
	2.92	0.5	0.1	12	5.22	.	.	2.75	3.84	4.18	.	.	.	.
n	6	6	6	6	6	3	3	6	6	6	4	3	3	3
Median	1.04	0.8	0.0542	16	4.24	1.94	10.8	1.05	2.23	3.05	2.96	5.49	51.5	130
Geo. Mean	1.25	1.03	0.0591	13.7	3.47	2.96	8.72	1.3	2.37	2.8	3.13	3.4	33.8	166
Lower 95%CI	0.482	0.412	0.0333	6.67	1.83	0.424	1.49	0.562	1.36	1.63	1.11	0.29	4.84	22.4
Upper 95%CI	3.23	2.57	0.105	28.1	6.6	20.6	51.1	3	4.14	4.81	8.83	39.8	236	1229
Mean	1.76	1.45	0.0671	16	3.99	3.69	10.1	1.71	2.66	3.11	3.69	4.38	40	208
SD	1.62	1.39	0.0376	8.04	2.09	3.12	5.83	1.44	1.42	1.47	2.44	2.9	22.8	175
CV(%)	91.7	95.9	56.1	50.2	52.4	84.7	57.8	84.2	53.2	47.3	66.3	66.2	57	83.9
Minimum	0.417	0.5	0.0303	3.97	1.63	1.83	3.94	0.598	1.17	1.35	1.82	1.09	13.7	86
Maximum	4.52	3.98	0.126	24.2	7.01	7.29	15.5	4.16	4.88	5.26	7.01	6.57	54.8	408

. No sample or not determined.

Source: Study files.

Table ST-4.6. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 2 years to <6 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	2.02	4	0.216	23.7	13.9	.	.	1.85	5.41	7.86	.	.	.	.
	1.18	0.483	0.0569	24	3.15	.	.	1.51	2.08	2.31	.	.	.	.
	3.95	0.5	3.3	1.07	2.69	.	.	.	.	.	.	.	.	.
	2.13	1.95	0.0953	16.4	10.3	10.8	4.55	3.02	6.44	8.35	10.7	3.57	18.5	95.5
	5.6	2.02	0.0727	24.1	17.3	17.9	3.06	4.18	11.1	13	17.3	5.21	11.2	84.1
	4.06	0.567	0.129	21	8.77	.	.	3.98	5.59	6.53	.	.	.	.
n	6	6	6	6	6	2	2	5	5	5	2	2	2	2
Median	3.04	1.26	0.112	22.3	9.54	14.3	3.8	3.02	5.59	7.86	14	4.39	14.9	89.8
Geo. Mean	2.77	1.14	0.182	13.1	7.55	13.9	3.73	2.69	5.38	6.63	13.6	4.32	14.4	89.6
Lower 95%CI	1.51	0.44	0.0379	3.57	3.34	0.563	0.298	1.52	2.54	2.99	0.618	0.392	0.583	39.9
Upper 95%CI	5.08	2.94	0.872	47.9	17.1	343	46.7	4.74	11.4	14.7	299	47.5	355	201
Mean	3.16	1.59	0.645	18.4	9.37	14.3	3.8	2.91	6.14	7.6	14	4.39	14.9	89.8
SD	1.65	1.38	1.3	8.97	5.81	5.01	1.06	1.21	3.26	3.82	4.72	1.16	5.19	8.06
CV(%)	52.4	87.3	201.9	48.9	62.1	35	27.8	41.6	53.1	50.3	33.7	26.4	35	9
Minimum	1.18	0.483	0.0569	1.07	2.69	10.8	3.06	1.51	2.08	2.31	10.7	3.57	11.2	84.1
Maximum	5.6	4	3.3	24.1	17.3	17.9	4.55	4.18	11.1	13	17.3	5.21	18.5	95.5

. No sample or not determined.
Source: Study files.

4. Multiple dose

Table ST-4.9. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to #12 years in the Multiple-Dose Phase from Dose 1

Reference ID: 4499855

Table ST-4.9. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Multiple-Dose Phase from Dose 1

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	1.5	2.05	0.763	3.77	3.78	.	.	1.76	.	.	.	.	.	.
	1.38	1.03	0.642	3.67	3.07	5.56	44.8	1.68	3.27	4.2	5.55	2.69	36	140
	0.068	1.58	0.0515	1.88	0.0548	.	.	.	.	.	.	.	.	.
	0.0904	1	0.0575	4.02	0.211	.	.	0.103	0.21	.	.	.	.	.
	4.23	1.53	0.827	4.53	11	.	.	5.23	10.4	.	.	.	.	.
	1.89	1.97	0.397	5.87	6.72	.	.	2.32	5.31	.	.	.	.	.
	1.87	0.433	0.194	4.02	2.25	2.75	18.3	1.63	2.24	2.51	2.75	1.8	72.8	189
	1.4	2.02	0.541	4.02	3.01	.	.	1.04	3	.	.	.	.	.
	1.12	1.57	0.696	4.27	2.19	.	.	0.733	2.01	.	.	.	.	.
	1.01	0.5	0.35	4	2.67	3.71	28.1	1.57	2.67	3.19	3.72	2.06	53.9	160
n	10	10	10	10	10	3	3	9	8	3	3	3	3	3
Median	1.39	1.55	0.469	4.02	2.84	3.71	28.1	1.63	2.84	3.19	3.72	2.06	53.9	160
Geo. Mean	0.887	1.21	0.323	3.88	1.82	3.84	28.4	1.25	2.47	3.23	3.84	2.15	52	162
Lower 95%CI	0.34	0.81	0.154	3.16	0.577	1.6	9.34	0.544	0.962	1.71	1.6	1.29	21.6	111
Upper 95%CI	2.31	1.82	0.675	4.76	5.72	9.25	86.6	2.85	6.33	6.11	9.23	3.59	125	235
Mean	1.46	1.37	0.452	4	3.49	4.01	30.4	1.79	3.64	3.3	4.01	2.18	54.2	163
SD	1.16	0.599	0.286	0.971	3.22	1.43	13.4	1.45	3.07	0.848	1.42	0.459	18.4	24.6
CV(%)	79.9	43.8	63.3	24.3	92.2	35.7	44.1	81	84.4	25.7	35.5	21	34	15.1
Minimum	0.068	0.433	0.0515	1.88	0.0548	2.75	18.3	0.103	0.21	2.51	2.75	1.8	36	140
Maximum	4.23	2.05	0.827	5.87	11	5.56	44.8	5.23	10.4	4.2	5.55	2.69	72.8	189

. No sample or not determined.
Source: Study files.

Table ST-4.10. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 2 years to <6 years in the Multiple-Dose Phase from Dose 1

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	1.99	0.5	0.699	6.2	4.31	.	.	2.05	2.96	4.17	.	.	.	.
	3.88	0.467	0.47	1.97	3.07	3.53	13.2	3.08	3.48	3.53	3.53	0.687	56.6	56.1
	2	1	0.135	4.37	2.81	2.99	6.1	1.86	2.75	2.94	2.99	0.937	66.8	90.3
	1.14	2	0.941	4.03	2.97	.	.	0.855	2.94	.	.	.	.	.
	3.9	0.867	0.297	5.8	6.25	7.06	11.4	3.85	5.43	6.31	7.06	1.88	28.3	77
n	5	5	5	5	5	3	3	5	5	4	3	3	3	3
Median	2	0.867	0.47	4.37	3.07	3.53	11.4	2.05	2.96	3.85	3.53	0.937	56.6	77
Geo. Mean	2.33	0.834	0.416	4.16	3.7	4.21	9.72	2.08	3.39	4.06	4.21	1.07	47.5	73.1
Lower 95%CI	1.22	0.4	0.161	2.36	2.43	1.36	3.51	1.01	2.41	2.42	1.36	0.295	15.3	40
Upper 95%CI	4.45	1.74	1.07	7.33	5.62	13	27	4.26	4.79	6.83	13	3.85	147	133
Mean	2.58	0.967	0.508	4.47	3.88	4.53	10.2	2.34	3.51	4.24	4.53	1.17	50.6	74.5
SD	1.24	0.622	0.32	1.68	1.45	2.21	3.69	1.16	1.11	1.47	2.21	0.632	19.9	17.2
CV(%)	48.2	64.3	62.9	37.5	37.4	48.8	36.1	49.5	31.6	34.7	48.7	54	39.4	23.2
Minimum	1.14	0.467	0.135	1.97	2.81	2.99	6.1	0.855	2.75	2.94	2.99	0.687	28.3	56.1
Maximum	3.9	2	0.941	6.2	6.25	7.06	13.2	3.85	5.43	6.31	7.06	1.88	66.8	90.3

. No sample or not determined.

Source: Study files.

Table ST-4.11. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Multiple-Dose Phase from Dose 7

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	3.03	2.13	3.03	2.13	4.4	.	.	4.01	.	.	.	.	.	.
	3.22	1.5	2.33	2.13	5.05	.	.	4.72	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	1.74	0	1.54	2	3.27	.	.	3.27	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
n	3	3	3	3	3	0	0	3	0	0	0	0	0	0
Median	3.03	1.5	2.33	2.13	4.4	.	.	4.01	.	.	.	.	.	.
Geo. Mean	2.57	1.79	2.22	2.09	4.17	.	.	3.96	.	.	.	.	.	.
Lower 95%CI	1.11	0.191	0.949	1.9	2.4	.	.	2.5	.	.	.	.	.	.
Upper 95%CI	5.97	16.8	5.17	2.29	7.24	.	.	6.25	.	.	.	.	.	.
Mean	2.66	1.21	2.3	2.09	4.24	.	.	4	.	.	.	.	.	.
SD	0.805	1.1	0.745	0.077	0.9	.	.	0.728	.	.	.	.	.	.
CV(%)	30.2	90.5	32.4	3.7	21.2	.	.	18.2	.	.	.	.	.	.
Minimum	1.74	0	1.54	2	3.27	.	.	3.27	.	.	.	.	.	.
Maximum	3.22	2.13	3.03	2.13	5.05	.	.	4.72	.	.	.	.	.	.

. No sample or not determined.
Source: Study files.

Reference ID: 4499855

Table ST-4.12. Individual and Summary Oxymorphone Pharmacokinetic Parameters Following Multiple-Dose Administration of 0.2 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 2 years to <6 years in the Multiple-Dose Phase from Dose 7

Subject (b) (6)	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	.	.	.	.	.	.	.	.	.	.	.	.	.	.
n	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Median	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Geo. Mean	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Lower 95%CI	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Upper 95%CI	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Mean	.	.	.	.	.	.	.	.	.	.	.	.	.	.
SD	.	.	.	.	.	.	.	.	.	.	.	.	.	.
CV(%)	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Minimum	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Maximum	.	.	.	.	.	.	.	.	.	.	.	.	.	.

. No sample or not determined.
Source: Study files.

5. 6-OH-oxymorphone

Table ST-5.1. Individual and Summary 6-OH-oxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to #12 years in the Single-Dose Phase. and…others

Reference ID: 4499855

Table ST-5.1. Individual and Summary 6β-Hydroxyoxymorphone Pharmacokinetic Parameters Following Single-Dose Administration of 0.05 mg/kg Oxymorphone HCl Immediate-Release Oral Liquid to Children Aged 6 years to ≤12 years in the Single-Dose Phase

Subject	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{extrap} (%)	AUC_{0-2} (h*ng/mL)	AUC_{0-4} (h*ng/mL)	AUC_{0-6} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h/kg)	V/F (L/kg)
(b) (6)	0.139	2	0.0251	24	1.09	1.83	40.7	0.139	0.343	0.463	1.09	20.5	27.3	809
	0.155	2	0.0327	8	0.691	.	.	0.155	0.415	0.589	.	.	.	.
	0	.	.	.	0	.	.	.	.	.	.	.	.	.
	0.129	4.03	0.0328	8.02	0.537	.	.	0.0416	0.21	0.422	.	.	.	.
	0.109	2.02	0.0434	4.02	0.261	.	.	0.108	0.261	.	.	.	.	.
	0.0926	4.25	0.0926	4.25	0.177	.	.	0.0352	0.155	.	.	.	.	.
n	6	5	5	5	6	1	1	5	5	3	1	1	1	1
Median	0.119	2.02	0.0328	8	0.399	1.83	40.7	0.108	0.261	0.463	1.09	20.5	27.3	809
Geo. Mean	0.123	2.68	0.0404	7.65	0.451	1.83	40.7	0.0805	0.261	0.486	1.09	20.5	27.3	809
Lower 95%CI	0.0953	1.64	0.0217	3.13	0.181	.	.	0.034	0.16	0.317	.	.	.	.
Upper 95%CI	0.158	4.39	0.0754	18.7	1.12	.	.	0.191	0.424	0.747	.	.	.	.
Mean	0.104	2.86	0.0453	9.66	0.459	1.83	40.7	0.0956	0.277	0.491	1.09	20.5	27.3	809
SD	0.0555	1.17	0.0272	8.25	0.396	.	.	0.055	0.104	0.0873	.	.	.	.
CV(%)	53.4	41	60.1	85.4	86.3	.	.	57.5	37.5	17.8	.	.	.	.
Minimum	0	2	0.0251	4.02	0	1.83	40.7	0.0352	0.155	0.422	1.09	20.5	27.3	809
Maximum	0.155	4.25	0.0926	24	1.09	1.83	40.7	0.155	0.415	0.589	1.09	20.5	27.3	809

. No sample or not determined.
Source: Study files.

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