Combined Clinical, CDTL and Summary Division Director Review

Application Type	Supplement NDA (pediatric efficacy supplement)
Application Number(s)	201194/S-009, 200534/S-010, and 200535/S-017
Priority or Standard	Standard
Submit Date(s)	January 3, 2020 (NDA 201194) January 17, 2020 (NDA 200534 and NDA 200535)
Received Date(s)	January 3, 2020 (NDA 201194) January 17, 2020 (NDA 200534 and NDA 200535)
PDUFA Goal Date	November 3, 2020
Division/Office	DAAP/Office of Neuroscience/CDER
From	Robert A. Levin, MD, Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Ning Hu, MD MS, Clinical team leader, DAAP Rigoberto A Roca, MD, Division Director, DAAP
Established/Proper Name	Oxycodone HCL oral solution 5 mg/5 mL (NDA 201194) Oxycodone HCL capsules for oral use 5 mg (NDA 200534) Oxycodone HCl oral solution 100 mg/5 mL and 5 mg/5 mL (NDA 200535)
Trade Name	Oxycodone HCL Oral Solution 5 mg/5 mL (NDA 201194) Oxycodone HCL Capsules 5 mg (NDA 200534) Oxycodone HCL Oral Solution 100 mg/5 mL and 5 mg/5 mL (NDA 200535)
Applicant	VistaPharm (NDA 201194) Genus Lifesciences Inc. (Genus), formerly Lehigh Valley Technologies, Inc. (NDA 200534 and 200535)
Dosage Form	Oral Solution
	(b) (4)
Regulatory Action	Complete Response

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RRR	remote record review
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

Material Reviewed/Consulted

OND Action Package, including:	
Clinical Review	Robert Levin, MD; Ning Hu, MD, MS
Nonclinical	Elizabeth A. Bolan, PhD; R. Daniel Mellon, PhD
Clinical	Qiu Wei, PhD; Yun Xu, PhD
DPMH	Heather Buck; Elizabeth Durmowicz, MD; Mona Khurana, MD
OSIS/OTS	Brian Folian, PharmD; Nicola M Fenty-Stewart

OND: Office of New Drugs; DPMH: Division of Pediatrics and Maternal Health; OSIS: Office of Study Integrity & Surveillance; OTS: Office of Translational Sciences.

2. Executive Summary

2.1. Product Introduction

VistaPharm's Oxycodone Hydrochloride Oral Solution 5 mg/5 mL, Genus' Oxycodone Oral Capsule 5 mg and Oxycodone Oral Solutions 100 mg/5 mL and 5 mg/5 mL are approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Both Oxycodone Hydrochloride Oral Solution and Oxycodone Hydrochloride Capsules were previously marketed unapproved products. Oxycodone Hydrochloride Oral Solution 5 mg/5 mL was approved under NDA 201194 (VistaPharm) on January 12, 2012 and under NDA 200535 (Lehigh Valley Technologies [now Genus Life Sciences]) on August 22, 2013. Oxycodone Hydrochloride Capsules 5 mg and Oxycodone Hydrochloride Oral Solution 100 mg/5 mL were approved under NDA 200534 and NDA 200535, respectively on October 20, 2010. At the time of approval, a post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) was issued for these NDAs to study the pharmacokinetics (PK) and safety of oxycodone oral solution in the pediatric population 2 to <17 years of age, and a separate PMR was issued for a safety, efficacy and pharmacokinetic study in subjects 0 to <2 years. VistaPharm and Genus are working in collaboration to fulfill their PMRs. The purpose of this supplement is to fulfill the PMR for the 2 to <17 year old population. The Applicants conducted one pediatric PK and safety study (2012O004) to fulfill this requirement. Efficacy data were not required or collected because FDA allows extrapolation of efficacy from adults to pediatric patients two years of age and older for opioid analgesics when there is comparable exposure between the two populations. (b) (4)

2.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy data were not required or collected for the 2-17 years age group because FDA allows extrapolation of efficacy from adults to pediatric patients two years of age and older for opioid analgesics when there is similar exposure between the two populations. Expert opinion (Berde 2012[1]) supports that the efficacy of opioids can be extrapolated from adults to children down to 2 years of age, based on the similarity of the underlying disease process and assuming the exposure response to the pediatric age group is similar to adults. The submitted data established that similar exposures were achieved between pediatric dosing and a single dose of 5 mg in adults (lower end of the approved initial dose range), allowing extrapolation of efficacy to pediatric patients. On average, the AUC0-inf values in pediatric patients age 2 to 6 years, 7 to 12 years, and 13 to < 17 years following a single dose of 0.10 mg/kg, 0.08 mg/kg, and 0.07 mg/kg, respectively, are 65% to 79% of that in adults following a single dose of 5 mg. The study results showed 21% to 35% lower mean oxycodone AUC0-inf values in pediatric patients at the studied doses than adults at a dose of 5 mg. The approved dosing regimen in adults is to initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain and then titrate to a dose that provides adequate analgesia and minimizes adverse reactions. Thus, (b) (4)

The study design precluded the ability to clinically confirm that efficacy extrapolated by PK was actually achieved with the administered doses. The analgesic effect could not be assessed because of several factors including no pain scores were collected for subjects 2 to 17 years, frequent concomitant use of rescue medication, lack of a control group, and direct switch from intravenous opioids to study medication without requiring certain levels of baseline pain intensity. All patients received only a single-dose of oxycodone and there was no titration to efficacy based on pain or repeat dosing. However, we expect the same titration-to-effect treatment strategy used in adults will be effective in pediatric patients given the comparable exposure between the starting doses in adults and pediatric patients.

2.3. Benefit-Risk Assessment

[1] Berde, C. B., Walco, G. A., Krane, E. J., Anand, K. J. S., Aranda, J. V., Craig, K. D., Dampier, C. D., Finkel, J. C., Grabois, M., Johnston, C., Lantos, J., Lebel, A., Maxwell, L. G., McGrath, P., Oberlander, T. F., Schanberg, L. E., Stevens, B., Taddio, A., Von Baeyer, C. L., ... Zempsky, W. T. (2012). Pediatric analgesic clinical trial designs, measures, and extrapolation: Report of an FDA Scientific Workshop. Pediatrics, 129(2), 354-364. https://doi.org/10.1542/peds.2010-3591

Benefit-Risk Integrated Assessment

The Division recommends a complete response for the application because onsite inspection or a remote record review (RRR) of the study site for Study 2012O004 were not able to be completed.

The benefits of using Oral Oxycodone Solution in treating pain severe enough to require an opioid analgesic when alternative treatments are inadequate, have been established in the adult population. The Division believes efficacy can be extrapolated from adults to pediatric patients two years of age and older for opioid analgesics when there is a demonstration of comparable exposures between the two populations (Berde 2012). The submitted data established that comparable exposures were achieved between pediatric patients two years of age and older and adults with the starting doses, allowing extrapolation of efficacy to pediatric patients. Based on single-dose PK comparison, a dose of 0.07 mg/kg for patients aged 13 to <17 years, 0.08 mg/kg for patients aged 7 to 12 years, and 0.10 mg/kg for patients aged 2 to 6 years and for patients aged 6 months and <2 years will provide similar oxycodone exposure to that of a 5 mg single-dose in adults. We expect the same titration-to-effect treatment strategy used in adults will be effective in pediatric patients considering the comparable exposure between the starting doses in both populations.

Known risks associated with the use of an opioid such as Oxycodone Hydrochloride Oral Solution in adults are described in the product labeling. Some of the serious risks associated with the use of an opioid include life-threatening respiratory depression, severe hypotension, addiction, abuse, and misuse. In the study conducted by the Applicants, there were no serious or unexpected adverse events, or deaths. Safety findings were generally consistent with post-operative experiences and with the known safety profile of opioid analgesics. However, the study had several limitations in assessing safety, including open-label study design without a control group, single-dose administration of only the starting dose, and small sample size. There were no data to support that the administered doses were efficacious except for PK extrapolation of the starting dose. Because risks associated with use of a drug are often dose-dependent, to adequately assess safety, multiple-doses and doses that are efficacious should be studied. Specifically, the risk of opioid-related respiratory depression is known to be dose-dependent and therefore cannot be fully evaluated by the limited safety data obtained from the study. (b) (4)

Respiratory depression is a known risk of an opioid analgesic and has been included in the boxed warning in the product labeling. It is important to note that several patients had oxygen desaturation with a decrease of up to 10% in Study 2012O004. Although it is difficult to determine the cause of oxygen desaturation in postoperative patients, it is impossible to exclude oxycodone as the cause or a contributing factor in some of

the patients. This raises the serious safety concern of whether higher doses and/or multiple-doses of Oxycodone Hydrochloride Oral Solution, could result in more frequent and severe respiratory depression.

A total of 16 patients had a decrease in pulse oximetry of 4% or greater from pre-dose baseline. Excluding the six patients that received hydromorphone at the same time as oxycodone, leaves 10 patients with the following pulse oximetry changes in decreasing order: 1 patient 10% decrease at 60 minutes, 1 patient 7% at 2 hours, 1 patient 6% at 30 min and again at 2 hours, 2 patients 5% (1 at 4 hours and 1 at 60 minutes) and 5 patients 4% (1 at 10 minutes, 2 at 8 hours, 1 each at 30 minutes and 60 minutes). Although it is impossible to determine from this open-label study in post-operative patients the cause of the oxygen desaturation, Oxycodone Oral Solution cannot be excluded as a contributing factor or cause in some patients.

From the safety information submitted, it is impossible to predict what effect multiple-therapeutic doses of oxycodone would have on safety in general and specifically on respiratory depression. (b) (4) .

However, if the studies were appropriately conducted, then the Division believes that the Applicant has fulfilled their PMR because the requirement for assessing safety with clinically-relevant doses was not included in the previous communications. With respect to the single-dose study conducted, the Division said that if the Applicant believes that adequate safety information exists in the literature on multiple doses, they could submit the final study report and the literature. The Applicant decided to choose this approach, but the Division after reviewing the literature concluded that it was not adequate to support the safety evaluation. It should be noted that even if the Applicant had conducted a multiple-dose study but did not provide evidence that the doses were clinically effective, the safety data would still not have been adequate to support the safety evaluation.

The Division determined that satisfactory inspection of the Cincinnati Children's Hospital Medical Center clinical study site is required before this application may be approved. The Office of Study Integrity and Surveillance (OSIS) is unable to complete an inspection or remote record review of this study site for the reasons described in section 5.1 of this review. As a result, the action date for this application was extended and the Division subsequently recommends complete response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is a serious medical condition which can cause suffering and negatively affect function and quality of life. • Pain can occur in a variety of medical illnesses, post-operatively, or following trauma. • Untreated pain not only can cause suffering and negatively impacts quality of life but can also progress to chronic pain. • The goal of treatment is to control pain with minimal drug-related side effects. • A variety of treatments options are available for the management of pain (described below).	Pain is a serious medical condition in pediatric patients that needs to be managed effectively to minimize suffering and impact on day-to-day functioning, and potential long-term negative consequences. There are many therapeutic options to manage pain.
Current Treatment Options	• Non-pharmacologic management of pain includes physical therapy, acupuncture, relaxation techniques, and massage. Also, a variety of treatment modalities are available including heat, cold, electrical stimulation, and ultrasound. • Pharmacologic options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids. Prescription medications are often a component of a multimodal analgesic approach. • The two major pharmacologic classes of analgesics for treating pain include opioid and non-opioid analgesics. Opioid analgesics or opioid-containing combination products are indicated for the management of severe pain when alternative treatments are inadequate.	Multiple treatment options are available for the management of pain including nonopioid analgesics and opioid analgesics for the management of severe pain. In a hospital setting, the management of pain may initially require intravenous analgesics followed by oral analgesic therapy. All opioids have potential risks that include respiratory depression, which may result in death, and other known opioid-related adverse effects, such as constipation, nausea, and vomiting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Availability of opioid-containing analgesics with pediatric labeling or indications is limited to certain opioid or opioid combination products such as: <u>Opioids</u> o Fentanyl transdermal (≥2 y) o Buprenorphine injection o Fentanyl citrate injection o Meperidine o OxyContin (>11 y) Combination Products o Codeine/APAP (≥3 y) o Hydrocodone/APAP (≥2 y) o Pentazocine/APAP o Dihydrocodeine/ASA/Caffeine o Codeine/ASA/Butalbital/Caffeine o Oxycodone/Ibuprofen o Pentazocine/Naloxone o Carisoprodol/ASA/Codeine o Butalbital/APAP o Butalbital/APAP/Caffeine <u>Non-opioid analgesics</u> o Acetaminophen (oral and IV) o Nonsteroidal anti-inflammatory drugs (NSAIDs [oral and IV])	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Off-label use of opioids in the pediatric population is commonly recognized and raises questions and concerns about effectiveness and safety of such practice.	
Benefit	• Oxycodone Hydrochloride Oral Solution was studied in one open-label, PK, and safety study in pediatric patients. • PK data showed comparable exposures between the adult starting dose of 5 mg and the following starting doses in pediatric patients: o 0.07 mg/kg for patients aged 13 to <17 years o 0.08 mg/kg for patients aged 7 to 12 years o 0.10 mg/kg for patients aged 2 to 6 years	Extrapolation of efficacy from adults to the pediatric populations was based on comparable pharmacokinetic profiles. Most opioids in adults are titrated-to-effect based on severity of pain, response to pain relief and adverse reactions, and titration-to-effect is anticipated similar in pediatric patients.
Risk and Risk Management	• The safety of single-dose Oxycodone Hydrochloride Oral Solution was evaluated in 97 patients (89 subjects 2 to < 17 years of age and 8 subjects under the age of 2) who received a single-dose of Oxycodone Oral Solution for the treatment of postoperative pain. • Repeat dosing and titration to higher doses were not studied. • There were no serious or unexpected adverse events, or deaths • Treatment-emergent AEs (TEAEs) occurred in 37% of patients. The most common AEs included nausea (13%), vomiting (12%), and itching (9%). • There were no adverse events of respiratory depression, but 16 patients had a decrease in pulse oximetry of 4% or greater from pre-dose. It is impossible to exclude oxycodone as either the cause or a contributing factor in some of the patients.	• The safety profile of oral oxycodone product is well characterized in adult population. • The safety findings were generally consistent with known postoperative complications and the safety profile of opioid analgesics, such as nausea, vomiting, itching, and respiratory depression. There were cases of oxygen desaturation which are not unexpected in postoperative patients, but oxycodone could not be excluded as the cause or a contributing factor of the desaturation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• The safety database did not include multiple-dose administration or titration to higher doses. The sponsor did not perform any pain scale assessment to support that the safety data obtained was with a therapeutic dose. The doses studied are reasonable starting doses for the different pediatric age groups based on PK comparison. Pediatric patients may require the same titration-to-effect treatment strategy used in adults. Although efficacy may be established with a single-dose PK study, safety needs to be evaluated with multiple therapeutic doses. Therefore, it is impossible to adequately assess the safety of Oxycodone Hydrochloride Oral Solution based on the safety data obtained in this single-dose study.

3. Therapeutic Context

3.1. Analysis of Condition

Pain is a serious medical condition in pediatric patients that needs to be managed effectively to minimize suffering and the impact on day-to-day functioning, and the potential for long-term negative consequences. There are many therapeutic options available to manage pain including non-pharmacologic and pharmacologic options. The two major pharmacologic classes of analgesics for treating pain include opioid and non-opioid analgesics. Opioid analgesics or opioid-containing combination products are indicated for the management of severe pain when alternative treatments are inadequate. Prescription medications are often a component of a multimodal analgesic approach. Opioid type analgesics are important in treating severe pain conditions such as post-operative pain after major surgery, sickle cell pain crisis, extensive trauma, etc. Opioid-containing analgesics with pediatric labeling or indications and opioid analgesics without pediatric labeling are summarized in the table below.

Table 1: Opioid Analgesics with and without Pediatric Labeling

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

Source: Clinical and Division Director Summary Review for NDA 21611 S-16 on October 25, 2019.

4. Regulatory Background

4.1. Summary of Regulatory History

Oxycodone Hydrochloride Oral Solution is an opioid agonist approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The approved label states that the safety and efficacy of Oxycodone Hydrochloride Oral Solution in pediatric patients below the age of 18 have not been established.

Oxycodone hydrochloride oral solution and oxycodone capsules were previously marketed unapproved products. Oxycodone Hydrochloride Oral Solution 5 mg/5 mL was approved under NDA 201194 by VistaPharm on January 12, 2012 and under NDA 200535 by Lehigh Valley Technologies (now Genus Life Sciences) on August 22, 2013. Oxycodone Hydrochloride Capsules 5 mg and Oxycodone Hydrochloride Oral Solution 100 mg/5 mL were approved on

October 20, 2010 under NDA 200534 and NDA 200535, respectively by Lehigh Valley Technologies. At the time of approval, a PMR was issued for NDAs 201194, 20034 and 200535 to study the pharmacokinetics (PK) and safety of oxycodone oral solution in the pediatric population 2 to <17 years of age. In addition, a PMR was issued for a safety, efficacy and pharmacokinetic study in subjects 0 to <2 years. VistaPharm and Genus are working in collaboration to fulfill their PMRs. The Applicants conducted pediatric Study 2012O004 to fulfill the PMR for the 2 to <17 years population. The PMR in the 0 to <2 years population is still pending and not the subject of this review. At the time of approval, the following pediatric PMRs were required for NDAs 201194, 200534 an 200535:

NDA 201194 Oxycodone Hydrochloride Oral Solution, 5 mg/5mL, by VistaPharm approved January 12, 2012:

1863-1 Pharmacokinetic and safety study in subjects >2 years to <17 years of age.

Final Protocol Submission: June 30, 2012
Study/Trial Completion: May 31, 2014
Final Report Submission: January 31, 2015

1863-2 Pharmacokinetic, safety, and efficacy study in subjects from birth to 2 years of age.

Final Protocol Submission: June 30, 2012
Study/Trial Completion: May 31, 2014
Final Report Submission: January 31, 2015

NDA 200534 Oxycodone Hydrochloride Capsules, 5mg, by Genus approved October 20, 2010

1698-1 Pharmacokinetic, safety, and efficacy study in subjects from birth to 2 years of age.

Final Protocol Submission: August 2011
Trial Completion: November 2014
Final Report Submission: November 2015

1698-2 Pharmacokinetic and safety study in subjects >2 years to <17 years of age.

Final Protocol Submission: May 2011
Trial Completion: November 2013
Final Report Submission: May 2014

NDA 200535 Oxycodone Hydrochloride Oral Solution, 100 mg/5mL [20 mg/mL], by Genus approved October 20, 2010
Note: Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL approved August 22, 2013 under NDA 200535

1695-1 Pharmacokinetic, safety, and efficacy study in subjects from birth to 2 years of age.

Final Protocol Submission: August 2011
Trial Completion: November 2014
Final Report Submission: November 2015

1695-2 Pharmacokinetic and safety study in subjects >2 years to <17 years of age.

Final Protocol Submission: May 2011
Trial Completion: November 2013
Final Report Submission: May 2014

The development program for Oxycodone Hydrochloride Oral Solution was conducted under IND 105754 (VistaPharm) and IND 78623 (Genus) Oxycodone Hydrochloride Capsule 5 mg, and IND 78624 (Genus) Oxycodone Hydrochloride Oral Solution. Key regulatory interactions between the FDA and the Applicants are listed below by date.

October 20, 2010: NDA 200534 (Genus) Approval of Oxycodone Capsule, 5 mg, and NDA 200535 (Genus) Approval of Oxycodone Oral Solution 100 mg per 5 mL.
The Oxycodone Hydrochloride Oral Solution, 5 mg per 5 mL was not be approved at this time. A request for a biowaiver for this concentration oral solution was denied. For approval, the applicant was required to conduct a relative bioavailability study to provide a bridge for this concentration oral solution to the referenced drug product.

January 12, 2012: NDA 201194 (VistaPharm) Approval of Oxycodone Hydrochloride Oral Solution, 5 mg/5mL for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate.

July 18, 2012: VistaPharm submitted a PK and safety study of Oxycodone Oral Solution in adolescent subjects.

August 15, 2012: VistaPharm notified of Full Clinical Hold through a telephone conversation because of the following reasons:

- Insufficient information to assess risks to human subjects. The frequency of safety monitoring was inadequate, and the protocol did not include continuous pulse oximetry.
- Unqualified clinical investigators. The submission did not include information on the investigators, research facilities and Institutional Review Board.

September 5, 2012: Full Clinical Hold Letter
The following is a summary of the Clinical Hold deficiencies.

- The submission did not include information on the investigators, research facilities and Institutional Review Board (IRB).
- Clinically relevant deviations were not adequately defined. The Protocol stated, “any abnormalities or deviations from the acceptable range that might be considered

clinically relevant by the study physician or investigator will be evaluated on a case-by-case basis."

- Frequency of monitoring vital signs was inadequate.
- The protocol did not state that patients will be monitored by continuous pulse oximetry.
- Assessment of adverse events not performed frequently enough.

The following recommendations that were not clinical hold issues were provided including the need for studying multiple doses:

- "Your proposed study is single-dose and limited to enrollment of 15 subjects. From a safety perspective, to fulfill the Pediatric Research Equity Act (PREA) requirements, your pediatric safety database must include approximately 100 children distributed over the entire pediatric age range, with a significant number receiving multiple doses."

March 14, 2013: Letter on collaboration between VistaPharm and Genus submitted to IND 105754.
The Division was notified that VistaPharm and Lehigh Valley Technologies (now Genus) will be collaborating on the required pediatric assessments and will conduct a joint study to satisfy the PREA requirements.

April 12, 2013: Full clinical hold removed.
The Division also provided the following comment:

> The efficacy of your proposed product can be extrapolated from the adult population to pediatric patients ages 2 years and older based on pharmacokinetic data. Therefore, we recommend that, in the proposed study, you choose a dose that will result in a similar oxycodone exposure in pediatric subjects as compared to adults.

August 22, 2013: NDA 200535 (Genus) Approval of the addition of a new strength 5 mg per mL of Oxycodone Hydrochloride Oral Solution to the package insert.

May 2016 to February 2019: Deferral Extensions. During the pediatric development program, three deferral extension requests were granted in the greater than 2 to less than 17 years of age group because of delays involving slower than anticipated enrollment in the study. The first subject in the 2 to 17 years age group was not enrolled until December 2013 and in June 2017 only 76 patients had completed the study.

February 22, 2019: The Division provided advice to VistaPharm on the requirement for multiple-dose safety.

> "… we note that children 2 to <17 years of age received only one dose of oxycodone oral solution. To meet the existing requirement that a significant number of subjects receive multiple doses, you should collect additional repeat dose safety data in the 2 to <17 years age group. Alternatively, if you believe adequate information exists in the literature, submit a review of the literature to inform the safety of multiple doses and to

support the safety findings from your study.
Similar advice was provided to Genus on April 15, 2019

September 18, 2019: Final clinical study report submitted. October 11, 2019 Applicant informed they will need to submit a supplemental New Drug Application (sNDA) to fulfill their PREA requirement. The sNDA should be complete at the time of submission to be accepted for review. The Division noted that from the preliminary review of the Clinical Study Report that the following information was missing:

- (b) (4).
- Module 2.5 (Clinical Overview), 2.7.1 (Summary of Biopharmaceutics and Associated Analytical Methods), 2.7.2 (Summary of Clinical Pharmacology Studies), 2.7.3 (Summary of Clinical Efficacy), and 2.7.4 (Summary of Clinical Safety).
- Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in Module 5. Applicant informed that if they believe that the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) in Module 2 would fulfill the regulatory requirements for an ISE and ISS, they may submit ISE and ISS in Module 5 with a reference and link back to the SCE and SCS in Module 2.
- Complete clinical study reports for all the completed PK studies.
- Benefit-risk analysis.
- Comparison of PK in children obtained from Study 2012O004 with the PK results in adults obtained in the PK studies from the original NDA submission. Provide PK parameters for oxycodone and its metabolites, and summarize all the PK information in Section 2.7.2 (Summary of Clinical Pharmacology Studies).

Jan 3, 2019 VistaPharm submitted NDA 201194/S-009 for a pharmacokinetic and safety study in subjects >2 years to <17 years of age.
Jan 17, 2020 Genus submitted NDA 200534/S-10 and NDA 200535/S-17 for a pharmacokinetic and safety study in subjects >2 years to <17 years of age.

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

5.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) from Office of Translational Sciences (OTS) was consulted to request an inspection of the study sites for Study 2012O004. An alternate to onsite inspection, Remote Record Review (RRR) was considered because of the current COVID-19 public health emergency. However, RRRs were not able to be completed for the following reasons:

Dallas Children's Hospital Medical Center: The Dallas Children's Medical Center clinical investigator stated that the site was unable to participate in the RRR due to limited availability of staff because of restrictions placed on accessing the medical center under the current COVID-19 public health emergency.

Cincinnati Children's Hospital Medical Center: OSIS determined that the Clinical Investigator of record at the Cincinnati Children's Hospital is currently on medical leave. The person identified as the replacement was not authorized to speak or make decisions on behalf of the study.

Therefore, OSIS has determined that RRRs are not able to be completed at these sites. In addition, because of the current COVID-19 public health emergency, inspection of these sites is not possible because the Agency has placed restrictions on domestic travel and onsite inspections.

The Office of Translational Sciences determined that satisfactory inspection or a remote record review will be required before this application may be approved. I concur with this determination.

5.2. Product Quality

No new CMC information was submitted in this application.

5.3. Clinical Microbiology

Not applicable.

5.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology toxicology review team recommend that Oxycodone Oral Solution (5 mg/5 mL), S-009 may be approved.

No nonclinical data were submitted with this supplement. Since the approved formulation of Oxycodone Oral Solution was utilized in the study, the drug substance and drug product impurity/degradant specifications have already been determined to be acceptable by pharmacology toxicology. No pediatric-specific toxicologic concerns were identified for any of the excipients in Oxycodone Oral Solution for this pediatric population (>2 to <17 years). No changes to the product label in the nonclinical sections are proposed.

5.5. Clinical Pharmacology

In Study 2012O004, the single dose PK for oxycodone oral solution 5 mg/5 mL were obtained from sufficient numbers of pediatric patients age 2 to < 17 years (i.e., 22 subjects age 2 to 6 years, 26 subjects age 7 to 12 years, and 31 subjects age 13 to < 17 years) with approximately even distribution in age and gender within each age group using the agency's agreed-upon

doses in each age group (i.e., 0.1 mg/kg in 2 to 6 years, 0.08 mg/kg in 7 to 12 years, and 0.07 mg/kg in 13 to <17 years). The observed mean oxycodone Cmax (5.54 to 5.98 ng/mL), AUC0-t (28.4 to 40.3 ng.h/mL), and AUC0-inf (34.1 to 41.4 ng.hr/mL) values were generally similar. Mean T1/2 values ranging from 2.29 to 3.06 h were also similar across pediatric age groups. The dosages for each age group in the protocol were based on population PK analysis and allometry principle and were agreed upon with the Division before initiation of the pediatric study. These dosing regimens were expected to result in a similar mean concentration time profile as seen after a single dose of 5 mg (i.e., lower end of the approved initial dose range 5 to 15 mg) in a typical adult. On average, the AUC0-inf values in pediatric patients age 2 to 6 years, 7 to 12 years, and 13 to < 17 years following a single dose of 0.10 mg/kg, 0.08 mg/kg, and 0.07 mg/kg, respectively, are 65% to 79% of that in adults following a single dose of 5 mg. Thus, the study results showed 21% to 35% lower mean oxycodone AUC0-inf values in pediatric patients at the studied doses than adults at a dose of 5 mg based on a cross-study comparison (

Table 2). The approved dosing regimen in adults is to initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain and then individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. (b) (4) Systemic safety cannot be extrapolated from adults to pediatrics. From a safety perspective, initiating dosing higher than the studied doses in pediatric subjects, in order to match 100% mean Cmax values or 100% mean AUC0-inf values in adults at a 5 mg dose, may not be supported due to the lack of safety information in pediatrics at doses higher than the studied dose.

Table 2: Mean (%CV) (min, max) Oxycodone PK Parameters Following the Administration of a Single Oral dose of Oxycodone Solution in Pediatric Subjects age 2 to 6 Years, 7 to 12 Years, 13 to < 17 Years (Study 2012O004) and Comparison with Adults via Cross-study Comparison

PK Parameter	2 to 6 Years (0.1 mg/kg) (n = 22)	7 to 12 Years (0.08 mg/kg) (n = 26)	13 to < 17 Years (0.07 mg/kg) (n = 31)	Adults[&] (5 mg) (n = 25)	Relative to Adults (%)
Tmax* (h)	2.05 (0.433, 12.0)	1.44 (0.50, 12.0)	2.07 (0.50, 12.1)	1.00 (0.50, 2.00)	
Cmax (ng/mL)	5.92 (59.63%) (0.411, 15.80)	5.54 (52.53%) (0.106, 9.87)	5.98 (42.47%) (0.357, 9.90)	11.1 (23.45%) (7.88, 16.5)	40% - 54%
AUC0-t (ng.h/mL)	28.4 (53.17%) (3.16, 67.4)[#]	33.5 (48.36%) (0.76, 62.7)	40.3 (44.17%) (2.29, 80.6)	51.6 (22.94%) (34.6, 80.4)	55% - 78%
AUC0-inf (ng.h/mL)	34.1 (37.24%) (23.36, 67.8)[##]	36.2 (41.44%) (0.99, 62.9)[###]	41.4 (44.93%) (2.59, 83.0)[####]	52.4 (22.99%) (35.5, 83.2)	65% - 79%
T1/2 (h)	2.29 (25.15%)	2.81 (29.29%)[###]	3.06 (21.99%)[####]	3.48 (17.02%)	

*Median (min, max); [#]n = 21; [##] n=15; [###]n = 23; [####]n = 28;

[&] Cmax and AUC values were calculated from the exposure of 15 mg in adults (Pivotal BE Study R11-0285) because 'dose proportionality of oxycodone has been established using the Roxicodone 5 mg tablets at doses of 5 mg, 15 mg (three 5 mg tablets) and 30 mg (six 5 mg tablets) based on AUC' per Roxicodone (oxycodone HCl) tablets (NDA 21011) label, the listed drug product for NDA 201194.
Source data: (1) CSR-2-12-Years-PK-Report: Supplemental PK Report Ages 2 to 12: Appendix B Pharmacokinetic Parameter Summary Tables; (2) CSR 13-to-17Y Table 11-5.

5.6. Table of Clinical Studies

The Applicant submitted one clinical study, a Phase IV open-label, pharmacokinetics, and safety study of Oxycodone Hydrochloride Oral Solution to fulfill their PMR requirements for children ages 2 to < 17 years, summarized in the table below.

Table 3: Clinical Study 2012O004

Protocol/NCT Number	Study Title	Design	Treatment	Population	Number of patients	Age range, yrs	Dose
Protocol No. 2012O004 NCT Number 01950204	A Phase IV Study to Evaluate the Pharmacokinetics and Safety of Oxycodone Oral Solution in Pediatric and Adolescent Subjects	Open-label PK and safety study of single-dose oral oxycodone	Oxycodone Oral Solution, 5 mg/mL	Pediatric patients with postoperative pain	8 24 30 35	0.5 to <2 2 to 6 7 to 12 13 to <17	0.1 mg/kg 0.1 mg/kg 0.08 mg/kg 0.07 mg/kg

Source: Clinical Reviewer

5.7. Review Strategy

The NDA contains one open-label, PK and safety study. The study design and results including patient disposition, demographic and baseline characteristics are summarized in Review Section 6. PK findings are summarized in Review Section 4.5 and safety findings are summarized in Review Section 8.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase IV Study to Evaluate the Pharmacokinetics and Safety of Oxycodone Oral Solution in Pediatric and Adolescent Subjects

6.1.1. Study Design

Overview and Objective

Study 2012O004 was an open-label, uncontrolled study conducted to characterize the pharmacokinetics and evaluate the safety of Oxycodone Oral Solution administered in pediatric

and adolescent subjects for postoperative pain. Although the study design allowed for multiple-doses to be administered, all subjects received only a single-dose of Oxycodone Oral Solution.

This was an open-label, nonrandomized, multicenter study conducted at 9 sites. Subjects were enrolled preoperatively or postoperatively with the expectation that they would require intravenous (IV) access after the surgery and postoperative analgesia with an opiate-level medication. Subjects were dosed with Oxycodone Hydrochloride Oral Solution (0.1 mg/kg for children ages 2 to 6 years, 0.08 mg/kg for ages 7 to 12 years, and 0.07 mg/kg for ages 13 to <17 years. Dosing was determined for children under age 2 based on PK modeling from the interim analyses which supported a starting dose of 0.1 mg/kg for children 6 months to < 2 years of age.

Following surgery, subjects received standard of care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that would not interfere with the measurement or metabolism of oxycodone. After subjects had been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution was to be administered at Time Zero of Day 1 in place of the standard analgesic medication. The VistaPharm Oxycodone HCL Oral Solution, 5 mg per 5 mL was utilized for the purposes of conducting this study. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, included in the interim analysis were to receive only one dose of Oxycodone Oral Solution. Subjects enrolled in the study after the interim analysis could then receive additional doses every 4-6 hours as needed. However, no subjects enrolled in the study received repeat doses. If pain control was inadequate with Oxycodone Oral Solution, the investigator could administer IV ketorolac (0.5 mg/kg), IV Morphine Sulfate (0.1 mg/kg), or use other rescue pain medication in accordance with hospital pain management guidelines. Subjects under the age of 2 were studied to obtain PK and safety information to fulfill the PMR requirement for that age group.

Safety was assessed by monitoring adverse events, clinical laboratory test results, vital sign measurements, pulse oximetry, and physical examination findings. No pain scores were collected in patients 2-17 years old. Serial blood samples for PK analysis were collected for the determination of plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone).

Key Inclusion Criteria:

1. Male or female subject 2 to <17 years of age at the time of dosing.
2. In at least the 25% weight group by age and weighs at least 28 lb at the time of dosing. (This inclusion criteria was removed in Amendment 3 dated April 8, 2014)
3. Generally healthy defined as American Society of Anesthesiologists (ASA) Physical Status classification grade I or II (except for the condition for which the procedure was being performed), documented by medical history, physical examination, vital sign assessments, electrocardiogram (ECG), and clinical laboratory assessments.

4. Negative urine pregnancy test pre-dose (for females of childbearing potential).
5. Admitted for a surgical procedure and expected to remain hospitalized for at least 24 hours after dosing with study drug.
6. Anticipated to have postsurgical pain requiring a parenteral analgesic regimen using a short-acting opioid analgesic and anticipated to be switched to an oral opioid for at least one dose.
7. Has an indwelling access catheter for blood sampling.
8. Informed consent and assent (as appropriate) obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively.

Key Exclusion Criteria:

1. History of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease.
2. Clinical laboratory test result documented as “alert”, “critical”, or “panic” per institution laboratory ranges or aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2.0 x the upper limit of normal (ULN); total bilirubin > 1.5 x ULN; serum creatinine > 1.5 x ULN; or blood urea nitrogen > 1.5 x ULN.
3. Clinically significant illness, except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug.
4. Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of all other prescription medications, except required pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for required pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing.
5. Consumed alcohol- or xanthine -containing products within 48 hours before dosing.
6. Consumed grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 5 days of dosing.
7. Is a smoker or has used nicotine or nicotine-containing products within 30 days.
8. Has a history of alcohol or drug addiction or abuse within the last year.
9. Temperature >100°F at time of initial administration of study medication.
10. Donated blood within 28 days or plasma within 14 days of dosing.

11. Has a history of relevant drug allergies or food allergies (i.e., allergy to oxycodone or related drugs, or any significant food allergy).
12. Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.

Assessments

Efficacy was not assessed in the 2 to <17 year age group.

Laboratory assessments included a complete blood count with differential and clinical chemistry performed at Screening and End of Study/Early Discontinuation. Urinalysis was performed at Screening only. The following laboratory tests were collected:

Hematology: hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count.

Serum chemistry: blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, glucose (fasting), albumin, and total protein.

Urinalysis: Included pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive

Urine pregnancy test: conducted for females of childbearing potential only.

Pulse oximetry began minimally 1 hour prior to transition to oral pain medication and continued until 8 hours after the last study dose. The following timepoints were captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last dose of Oxycodone Oral Solution.

Statistical Analysis Plan

No formal statistical testing was performed for this study. Descriptive statistics were provided for all demographic and safety parameters. The safety analysis was based on the safety population defined as all subjects who received study drug.

6.1.2. Study Results

Compliance with Good Clinical Practices

Study O0024 was conducted in accordance with the ethical principles of Good Clinical Practice according to the International Conference on Harmonization (ICH), and applicable Food and Drug Administration requirements regarding IRBs, informed consent, and other statutes or regulations related to the rights and welfare of human subjects participating in biomedical

research.

Financial Disclosure

No financial arrangements were identified that would affect the conduct of Study 2012O004. Financial disclosure forms were submitted for 50 of the 51 investigators certifying that the investigator:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study
- Had no proprietary interest in this product or significant equity interest in the sponsor
- Was not the recipient of significant payments

Financial disclosure information was not submitted for investigator (b) (6) because it could not be retrieved from the site due to office closure due to Covid-19 precautions. In lieu of it, the following statement from Principle Investigator (b) (6) was provided: "Dr. (b) (6) was a pediatric anesthesia fellow for a year with us and he left (b) (6) Hospital about a year ago. I do not know his current contact information. As far as I know, Dr. (b) (6) did not have any financial conflicts."

Patient Disposition

In Study 2012-O004 a total of 97 subjects were enrolled in the study and received a single-dose of oxycodone oral solution. Eight subjects (8%) were reported as discontinued from the study for the reasons, "Subject Requested Withdrawal", "Investigator Decision", and "Other" summarized in Table 4. Review of additional information for the reason of termination provided by the Sponsor from the CRFs for these eight subjects did not reveal any safety concerns. The most common reason for withdrawal was IV stopped working and blood draws. One subject withdrew consent with comment "because she wanted him to receive additional oxycodone doses instead of only one dose."

Table 4: Patient Disposition, Study 2012O004

	6 months to < 2 yrs	2 to 6 yrs	7 to 12 yrs	13 to <17 yrs	Overall
Enrolled	8	24	30	35	97
Completed the Study	7 (88)	23 (96)	26 (87)	33 (94)	89 (92)
Discontinued from Study	1 (13)	1 (4)	4 (13)	2 (6)	8 (8)
Reasons for Discontinuation					
Subject Requested		1 (4)	2 (7)	2 (6)	5 (5)
Investigator Decision	1 (13)	0	1 (3)	0	2 (2)
Other	0	0	1 (3)	0	1 (1)

Source: Table 3 on page 10 of Summary of Clinical Safety

Protocol Violations/Deviations

Two of the four major protocol deviations identified involved an incorrect dose being given to subjects. Subject (b) (6) (15 years old) was dosed at 0.08mg/kg instead of 0.07mg/kg, and subject (b) (6) (16 years old) should have received a calculated dose of 4.319mg, but was given a dose of 4.4mg. Subject (b) (6) (10 years old) was listed as an ASA III but it was confirmed that was only due to the condition being treated and the subject did meet inclusion criteria. Subject (b) (6) (12 years old) did not meet the weight requirement. The subject weighed 30.5kg, which was only in the 5th percentile, although a minimum of 25th percentile was required. These reported major deviations do not appear to affect the interpretation of the study results. There were also minor deviations that involved not collecting required assessments such as vital signs, pulse oximetry and laboratory results.

Demographic Characteristics

Table 5 summarizes the demographics and baseline characteristics of the study population. The population greater than 2 to 17 years consisted of approximately an equal number of male and female subjects and was predominantly White. For the population 6 months to less than 2 years, 63% were male and 38% were female.

Table 5: Demographics and Baseline Characteristics, Study 2012O004

	6 months to < 2 yrs	2 to 6 yrs	7 to 12 yrs	13 to <17 yrs	Overall
Number Patients	8	24	30	35	97
Age (years)					
Mean	1.0	4.5	10.4	15.0	9.9
Min, Max	0.7, 1.9	2.2, 6.8	7.6, 12.5	13.0, 16.8	0.7, 16.8
Gender					
Male Female	5 (63) 3 (38)	12 (50) 12 (50)	15 (50) 15 (50)	20 (57) 15 (43)	52 (54) 45 (46)
Race					
White	5 (63)	19 (79)	28 (93)	35 (100)	87 (90)
African American	2 (25)	4 (17)	2 (7)	0	8 (8)
Other	1 (12)	1 (4)	0	0	2 (2)
Ethnicity					
Hispanic	1 (13)	5 (21)	3 (10)	2(6)	11(11)
Not Hispanic	7 (88)	19 (79)	27 (90)	33 (94)	86 (89)
Height (cm)					
Mean	71.9	105.1	145.9	167.2	137.2
Median	70.6	106.4	146.4	171.5	148.0
Min, Max	67, 78	88, 140	123, 172	144, 179	67, 179
Weight (kg)					

Mean	9.3	17.7	40.8	56.9	38.3
Median	9.5	16.6	36.5	54.2	40.9
Min, Max	6.8, 10.8	11.9, 41.9	20.3, 64.2	41.2, 89.6	6.8, 89.6
BMI (kg/m2)					
Mean	17.9	15.8	19.2	20.4	18.7
Median	18.3	15.5	18.4	19.9	17.9
Min, Max	15.2, 19.7	13.1, 21.3	13.5, 29.2	15.9, 30.2	13.1, 30.2

Source: Table 3 on page 5 Summary of Clinical Efficacy

Rescue Medication Use

More than 90% of subjects used rescue medication at some time during the study which lasted up to 24 hours after the dose of study drug was administered. Table 6 provides a summary of the cumulative number and percent of subjects using rescue medication at different timepoints. A total of 46 subjects (54%) used rescue medication at the same time Oxycodone Oral Solution was administered. In the first hour 63% of subjects used rescue medication and by two hours 74% had used rescue medication. The extensive early use of rescue medication makes it impossible to assess if efficacy was achieved based on rescue medication use.

Table 6: Cumulative Number of Subjects **(≥** 2 years old and < 17 years old) to Time of First Use of Rescue Medication

Time Interval of First time Concomitant Med Use (min)	Cumulative Number of Subjects (%)
Same time as Oxycodone Administration	46 (54.1%)
[0, 30]	51 (60.0%)
(30,60]	54 (63.5%)
(60,120]	63 (74.1%)
(120,180]	66 (77.6%)
(180,240]	77 (90.6%)
(240,300]	83 (97.6%)
(600,	85 (100.0%)

Source: Clinical Reviewer and statistician.

7. Integrated Review of Effectiveness

The open-label study that was conducted was intended to assess only pharmacokinetics and safety. Efficacy was extrapolated from adults to pediatric patients based on similar exposures between pediatric dosing and a single dose of 5 mg in adults (lower end of the approved initial dose range), However, efficacy data, such as pain scores were not collected to support the extrapolation or to confirm the doses administered were effective doses in the 2 to less than 17 years age group.

8. Review of Safety

8.1. Safety Review Approach

The safety of Oxycodone Oral Solution was evaluated in Study 2012O004, an open-label, multicenter, pharmacokinetic and safety study. This review is primarily focused on the safety data submitted from that study, but also includes a review of the literature references provided by the Applicant on the safety of multiple-dose administration of oxycodone.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 97 subjects were exposed to Oxycodone Hydrochloride Oral Solution including eight subjects aged 6 months to less than 2 years, summarized by age group in

Table 7. For the PMR for subjects aged 2 to less than 17 years, currently under review, 89 subjects were exposed to Oxycodone Hydrochloride Oral Solution. All subjects received only a single dose of study drug. Subjects under the age of two were included in the overall safety database because of the relatively small size of the database for children 2 to less than 17 years of age, and because the younger age group may be more sensitive to adverse events.

Table 7: Exposure by Age to Single-dose Oxycodone HCL Oral Solution, Study 2012O004

	6 months to < 2 yrs	2 to 6 yrs	7 to 12 yrs	13 to <17 yrs	Overall
Number Patients	8	24	30	35	97

Source: Clinical Reviewer

8.2.2. Relevant characteristics of the safety population:

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

8.2.3. Adequacy of the safety database:

The safety database was not considered adequate because it did not include patients with repeat-dosing, and doses that were either shown to be clinically relevant or titrated to effect.

8.2.4. Deaths

No deaths occurred during the study.

8.2.5. Serious Adverse Events

No serious Adverse Events (SAEs) were reported during the study.

8.2.6. Dropouts and/or Discontinuations Due to Adverse Effects

No discontinuations due to adverse events were reported during the study.

8.2.7. Significant Adverse Events

There were no deaths, SAEs, or discontinuations due to AEs. Refer to the section below for a discussion of adverse events.

8.2.8. Treatment Emergent Adverse Events and Adverse Reactions

A total of 36 subjects had 55 adverse events (AEs), summarized by age group in Table 8. The number of patients 2 to <17 years old with AEs varied by age group with rates ranging from 33% for the 2 to 6 years age group to 43% for the 7 to 12 years age group. The age group 6 months to less than two had an adverse event rate of 25% but included only 8 patients. Overall, the most common AEs were nausea (13%), vomiting (12%), and itching (9%). Anemia or decreased hematocrit/hemoglobin occurred in 4% of patients and was likely due to postoperative blood loss and not from oxycodone. The AEs of dizziness and decreased oxygen saturation were each reported in one subject. There were three AEs of moderate severity which included two patients with decreased hematocrit/hemoglobin and one patient with headache. The remaining AEs were all of mild severity. The AEs were generally consistent with commonly reported post-operative and opioid-related findings. Because adverse events are often dose related, the adverse events in this single-dose study may not reflect the rates or seriousness of adverse events reported with higher or repeat doses of Oxycodone HCL Oral Solution.

Table 8:Treatment-Emergent Adverse Events

Adverse vents	Age Group (years)				
	0.5 to <2	2 to 6	7 to 12	13 to <17	Total
# patients in age group	N=8	N=24	N=30	N=35	N=97
# patients with any AE	2 (25)	8 (33)	13 (43)	13 (37)	36 (37)
# of AEs	2	10	18	25	55
Blood disorders/decrease Hgb					
Anemia/ ↓Hgb, Hct, RBC	1 (13)	0	1[1] (3.3)	2[2] (5.7)	4 (4)
Gastrointestinal disorders					
Nausea	0	2 (8.3)	6 (20.0)	5 (14.3)	13 (13.4)
Vomiting	0	4 (16.7)	3 (10.0)	5 (14.3)	12 (12.4)
Abdominal pain	0	0	0	1 (2.9)	1 (1.0)
General disorders and administration site conditions					
Application site pruritus	0	0	1[3]	0	1 (1.0)
Chills	0	0	0	1	1 (1.0)
Injection site erythema	0	1 (4.2)	0		1 (1.0)
Pyrexia	0	0	0	1	1 (1.0)
Immune system disorders					
Drug hypersensitivity	0	0	1 (3.3)[4]	0	1 (1.0)

Musculoskeletal disorders					
Neck pain	0	0	0	1 (2.9)	1 (1.0)
Nervous system					
Headache	0	1[5](4.2)	0	1 (2.9)	2 (2.0)
Dizziness	0	1 (4.2)	0	1 (2.9)	2 (2.0)
Psychiatric disorders					
Anxiety	0	0	1 (3.3)	0	1 (1.0)
Skin disorders					
Pruritus	0	1 (4.2)	3(10.0)	5 (14.3)	9 (9.3)
Erythema	1 (12.5)	0	0	0	1 (1.0)
Investigations					
Oxygen saturation ↓	0	0	0	1[6] (2.9)	1 (1.0)
Liver function test	0	0	2[7]	0	2 (2.0)
ALT/AST	0	1[8](4.2)	0	0	1 (1.0)
Phosphorus decreased	0	0	0	1[9] (2.9)	1 (1.0)

[1]Subject (b) (6) reported to have 3 AEs (decreased hematocrit, hemoglobin and red blood cell count), all of moderate severity (counted as 1 AE in table).
[2]Subject (b) (6) reported to have AE of decreased hemoglobin/hematocrit of moderate severity (counted as 1 AE in table).
[3] Itching under bandage (Subject (b) (6))
[4] Subject (b) (6) reported to have drug hypersensitivity to Valium recorded 2 separate times (counted as 1 AE in table), both episodes resolved.
[5] Subjects (b) (6) headache of moderate severity.
[6]Subject (b) (6) 14 year old s/p spinal fusion with AE of oxygen saturation decreased 17 hours after receiving study drug and approximately 3 hours after dose of hydromorphone po 2mg.
[7] Subjects (b) (6) and (b) (6) coded with AE of abnormal liver function test (values listed in table below)
[8]Subject (b) (6) AE of ALT/AST (values listed in table below)
[9]Subject (b) (6) AE of Phosphorus decreased
Source: Listing 16.2.7.1 and Table 5 in Summary of Clinical Safety

Liver Function Adverse Events

The three subjects reported to have adverse events affecting liver function enzymes had normal values at screening for ALT, AST, bilirubin and alkaline phosphatase. At the end of the study all three subjects had isolated increases in ALT and AST (Table 9). For Subject (b) (6) the increase in ALT and AST was less than 2 and 6 times the ULN, respectively and for Subject (b) (6) the increase in ALT and AST was approximately 3 and 8 times the ULN, respectively. Subject (b) (6) had an increase in ALT and AST less than 10 and 20 times the ULN, respectively at the end of study, but the following day ALT was decreased to approximately 5 times the ULN. The limited information provided for these cases makes interpretation difficult, but the findings appear to be consistent with postoperative patients who can have transient increases in liver function tests.

Table 9: Subjects with Liver Function Adverse Events

Subject (b) (6)			
Test	Screening	End of Study	Normal Range
ALT, U/L	17	68	12,49
AST, U/L	12	209	10, 36
Alkaline Phsophatase, U/L	159	117	85, 370
Bilirubin, mg/dL	0.3	0.5	0.1, 1.1
Subject (b) (6)			
Test	Screening	End of Study	Normal Range

ALT, U/L	28	157	12,49
AST, U/L	22	274	10, 36
Alkaline Phsophatase, U/L	261	177	74, 460
Bilirubin, mg/dL	0.4	0.2	0.1, 1.1
Subject (b) (6)			
Test	Screening	End of Study	Normal Range
ALT, U/L	16	451 (day after end of study 250)	12,49
AST, U/L	24	656	10, 36
Alkaline Phsophatase, U/L	172	193	110, 345
Bilirubin, mg/dL	0.1	0.2	0.1, 1.1

Source: Listing 16.2.8.2 CSR

Oxygen Saturation Decreased

Subject (b) (6) was a 14 year old female s/p spinal fusion with an AE of oxygen saturation decreased approximately 17 hours after Oxycodone HCL Oral Solution was administered. The timing of the event makes it unlikely that oxycodone was the cause. It is possible that the AE was related to taking hydromorphone 2mg approximately 3 hours earlier.

Decreased Phosphorus

Subject (b) (6), a 16 year old male, underwent spinal fusion with instrumentation and bone graft. He was coded as having the adverse event of blood phosphorus decreased that was reported as resolved the following day. No additional details were provided.

8.2.9. Laboratory Findings

In general, the changes in laboratory findings are difficult to interpret because laboratory testing was obtained only at Screening and End of Study, and there was no control group. It is expected that many postoperative laboratory findings will change compared to preoperatively. Therefore, no detailed analysis of laboratory values is provided except for laboratory tests resulting in adverse events which are discussed above in Section 7.4.5. The most common laboratory abnormalities resulting in adverse events were due to increased ALT/AST and decreased hemoglobin/hematocrit. For both of these adverse events it is unlikely that oxycodone was the cause. Table 10 summarizes the number of patients with a shift in liver function enzymes from normal to high, and high to normal. As expected in a postoperative patient population, there were many more subjects with a shift from normal at screening to high at end of study. There were only two subjects with an increase in ALT of greater than 100 (451 and 157). For AST there were eight subjects with an increase greater than 100 (5 subjects between 100 and 200, and three subjects with values of 656, 274 and 209). It should be noted that no subjects had an abnormal bilirubin. As noted previously interpretation of these findings is limited but they can often be observed in postoperative patients.

Table 10: Shift in Liver Function Laboratory Tests from Screening to End of Study

Lab Test	**N→H**	**H→N**

ALT	8	2
AST	37	1
Bilirubin	0	0

N→H, normal at Screening to high at End of Study
H→N, high at Screening to normal at End of Study
Source: Listing 16.2.8.2 CSR

8.2.10. Vital Signs

Vital signs, including heart rate, respiratory rate, and blood pressure were measured at pre-dose, every 15 minutes until 4 hours after the dose of Oxycodone Oral Solution, and then every 2 hours until 24 hours after the first dose of oxycodone. The changes in mean systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate by age group compared to pre-dose are summarized through eight hours in Table 14, Table 15, Table 16, and
Table 17, respectively and available in Appendix 13.3. Considering the variability of vital signs in this open-label study of postoperative patients, it is difficult to interpret the vital sign data and attribute any observed changes to oxycodone. In general, there was a decrease observed in mean systolic blood pressure compared to pre-dose in the 2 to 6, 7 to 12, and 13 to < 17 years age groups starting at the first timepoint at 15 minutes. The magnitude of decrease was less in the 13 to < 17 years group. The greatest decrease was 6.8 mm at 3 hours and 15 minutes in the 7 to 12 years group. The reduction in mean diastolic blood pressure was generally in the range of 1-5 mm with the lower end of the range observed in the 13 to < 17 years group. Similar changes were observed for the <2 years group but there was more variability in values between timepoints which may be related to the small sample size. Decrease in mean diastolic blood pressure was observed starting at 15 minutes in the <2 years and 2 to 6 years groups, and starting at 30 minutes in the 7 to 12 and 13 to < 17 years groups. The greatest change was in the <6 months group, 7.8 mm at 2 hours and 45 minutes. In the 2 to <17 years age groups, the greatest change was 5.3 mm in the 2 to 6 years group at 30 minutes. The reduction in mean diastolic blood pressure for subjects 2 to <17 years was generally in the range of 1-3 mm with some higher values in the 2 to 6 years group of 4 and 5 mm.

The greatest decrease in mean heart rate was observed in the under 2 year age group, 15 beats per minute at 15 minutes, but this may have been an artifact related to increased Pre-dose values compared to Screening and Check-in. Mean heart rate was decreased in the 2 to 6 and 7 to 12 year age groups. The mean change was greatest in the 2 to 6 year age group with a maximum decrease of 6.6 beats per minute at 45 minutes. The changes in the 13 to < 17 year age group were variable with small decreases or increases in heart rate at different timepoints. There appeared to be a small decrease in mean respiratory rate in the under 2 age group, generally in the range of 2 to 6 breaths per minute. In the 2 to <17 year age range, reductions in respiratory rate were inconsistent. The greatest decrease in respiratory rate was in the 2 to 6 years age group, 2.3 breaths per minute at 30 minutes.

Change in heart rate was also characterized by variability but there appeared to be a greater decrease in the under 2 year age group compared to the other age groups. Respiratory rate was decreased greater in the under 2 year group compared to the other age groups. In general, review of the vital signs revealed no evidence of clinically significant changes in mean systolic blood pressure, diastolic blood pressure, heart rate, or respiratory rate but there were variations throughout the study limiting interpretation of the data. There are many confounding factors influencing changes in the vital signs including use of concomitant medications, postoperative status, and concurrent medical conditions, which makes it difficult to attribute the observed changes to study drug.

Pulse Oximetry

Continuous pulse oximetry began at least 1 hour prior to transition to oral pain medication and continued until 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints were captured in the CRF: pre-dose, 5, 10, 30 and 60 minutes, 2 hours, and then every 2 hours until 8 hours after the study dose of Oxycodone Oral Solution.

Table 11 Table 11summarizes the mean change in pulse oximetry from pre-dose at different timepoints by age group. All the age groups except for the 6 months to 2 year group had small decreases in mean pulse oximetry. There was no change in mean pulse oximetry in the subjects < 2 years of age, possibly because of the small sample size of eight patients. The greatest decrease overall in mean pulse oximetry was 0.6% at two hours. Given the small changes in mean pulse oximetry, it is difficult to attribute these changes to study drug when a variety of other factors could be the cause.

Table 12 summarizes the 16 patients with a decrease in pulse ox of 4% or greater from pre-dose baseline. Six patients received hydromorphone at the same time as the oxycodone confounding the interpretation of the cause of the decrease in oxygen saturation. The change in pulse ox for the remaining 10 patients in decreasing order was the following: 1 patient 10% at 60 minutes, 1 patient 7% at 2 hours, 1 patient 6% at 30 min and 2 hours, 2 patients 5% (1 at 4 hours and 1 at 60 minutes) and 5 patients 4% (1 at 10 minutes, 2 at 8 hours, 1 each at 30 minutes and 60 minutes). All reported pulse oximetry values remained greater than or equal to 90%. Although it is impossible from this open-label study with no control group in post-operative patients to determine the cause of the desaturation, it is impossible to exclude Oxycodone Oral Solution as either the cause or a contributing factor. Given the variability in the pharmacokinetics of Oxycodone Oral Solution it is also difficult to exclude oxycodone as the cause in many patients based on the timing of the event.

Table 11: Change in Pulse Oximetry by Age Group Through 8 Hours Post-Dose

Timepoint	6 months to <2 years (N=8)	2 to 6 years (N=24)	7 to 12 years (N=30)	13 to <17 years (N=35)	Overall (N=97)
Pre-Dose					
Mean (SD)	97.5 (2.93)	99.2 (1.02)	98.3 (1.63)	98.5 (2.06)	98.5 (1.84)
Median	99.0	99.5	98.5	99.0	99.0

Min, Max	93, 100	97, 100	94, 100	92, 100	92, 100
5 min Post-Dose					
Mean (SD)	98.4 (1.60)	98.9 (1.12)	98.0 (1.67)	98.4 (1.76)	98.4 (1.59)
Change in Mean	0.9 (1.64)	-0.3 (1.01)	-0.4 (0.67)	-0.1 (1.71)	-0.2 (1.31)
10 min Post-Dose					
Mean (SD)	98.1 (2.10)	98.9 (1.21)	98.1 (1.68)	98.5 (1.56)	98.5 (1.58)
Change in Mean	0.6 (2.45)	-0.3 (0.95)	-0.2 (0.85)	0.0 (1.60)	-0.1 (1.35)
30 min Post-Dose					
Mean (SD)	98.0 (2.67)	98.7 (1.37)	97.9 (1.75)	97.9 (2.16)	98.1 (1.91)
Change in Mean	0.5 (2.00)	-0.5 (1.14)	-0.4 (1.09)	-0.8 (1.90)	-0.5 (1.53)
60 min Post-Dose					
Mean (SD)	98.9 (1.89)	98.8 (1.39)	97.9 (1.96)	98.2 (2.02)	98.3 (1.85)
Change in Mean	1.4 (1.51)	-0.5 (1.56)	-0.6 (1.53)	-0.3 (2.35)	-0.3 (1.92)
2 hrs Post-Dose					
Mean (SD)	98.7 (1.70)	98.6 (1.34)	97.7 (2.20)	97.8 (2.23)	98.1 (2.00)
Change in Mean	1.4 (1.51)	-0.6 (1.27)	-0.8 (1.92)	-0.8 (1.80)	-0.6 (1.78)
4 hrs Post-Dose					
Mean (SD)	98.6 (2.30)	98.7 (1.33)	98.1 (1.81)	98.1 (1.75)	98.3 (1.71)
Change in Mean	1.3 (1.38)	-0.5 (1.59)	-0.3 (1.06)	-0.8 (1.79)	-0.4 (1.59)
6 hrs Post-Dose					
Mean (SD)	99.0 (1.15)	99.0 (1.22)	98.1 (1.67)	98.8 (1.12)	98.7 (1.36)
Change in Mean	1.7 (2.21)	-0.2 (1.57)	-0.3 (1.57)	-0.1 (1.46)	-0.0 (1.65)
8 hrs Post-Dose					
Mean (SD)	99.3 (1.25)	98.4 (1.62)	98.1 (1.65)	98.1 (1.67)	98.3 (1.63)
Change in Mean	2.0 (2.00)	-0.8 (1.24)	-0.3 (1.62)	-0.7 (1.52)	-0.4 (1.66)

Source: Table 14.3.7 Pulse Oximetry, Clinical Study Report 2-12 Year Population-Protocol 2012O004

Table 12: Patients with Decrease in Pulse Ox **≥4** from Baseline

Subject Number	Age	Surgical Procedure	Time Point	Time (Hr/Min) after Oxycodone to Rescue Medication[1]	Pulse Ox	Change from Baseline
(b) (6)	14.1	PECTUS REPAIR NUSS PROCEDURE	60 min Post-Dose	3:54 Ketorolac	90	-10
	11.8	PECTUS EXCAVATUM REPAIR	2 hr Post-Dose	0:00 Ropivacaine epidural	91	-7
	16.2	SPINE POSTERIOR FUSION WITH INSTRUMENTATION & BONE GRAFT	4 hr Post-Dose	0:00 Hydromorphone 0.2 mg IV	94	-6
	9.8	SPINE POSTERIOR FUSION WITH INSTRUMENTATION & BONE GRAFT	60 min Post-Dose	0:00 Hydromorphone 0.2 mg IV	94	-6
	9.8		2 hr Post-Dose		94	-6
	9.8		6 hr Post-Dose	6:45 hydromorphone 0.2 mg IV	95	-5
	14.7	SPINE POSTERIOR FUSION WITH INSTRUMENTATION & BONE GRAFT	5 min Post-Dose	0:00 Hydromorphone 0.2 mg IV	94	-6

(b) (6)						
	13.6	PECTUS REPAIR NUSS PROCEDURE	30 min Post-Dose	60 min pulse ox 99%	92	-6
	2.2	BILATERAL URETERAL REIMPLANT	4 hrs Post-Dose	3:21 Ketorolac IV	95	-5
	5.6	LAPAROTOMY, CONTINENT RECONSTRUCTION	60 min Post-Dose	17:57 Oxycodone po	95	-5
	0.7	URETERAL REIMPLANT & URETEROSTOMY (LEFT) CYSTOSCOPY	10 min Post-Dose	5:12 Acetaminophen	95	-4
	3.5	CRANIOTOMY, LOBECTOMY	8 hrs Post-Dose	1:30 Acetaminophen	95	-4
	14.9	SPINE POSTERIOR FUSION & BONE GRAFT & COSTOPLASTY T2 - L1	30 min Post-Dose	0:00 Hydromorphone IV 0.3 mg From dataset	96	-4
	16.2	SPINE POSTERIOR FUSION WITH INSTRUMENTATION & BONE GRAFT	30 min Post-Dose 4 hrs Post-Dose	0:00 Hydromorphone IV	96 94	-4 -6
	11.3	PECTUS EXCAVATUM	8 hrs Post-Dose	0:00 Clonidine epidural	96	-4
	14.7	SPINE POSTERIOR FUSION WITH INSTRUMENTATION & BONE GRAFT	5 min Post Dose 10 min Post-Dose	0:00 Hydromorphone IV	94 96	-6 -4
	15.6	PECTUS REPAIR NUSS PROCEDURE	30 min Post-Dose	0:50 Ketorolac IV	94	-4
			2 hrs Post-Dose	2:57 Hydromorphone po 2 mg	94	-4
	6.2	CRANIOPLASTY FOR SKULL DEFECT	60 min Post-Dose	[2]	95	-4

[1] only first rescue medication listed after study drug administered
[2]Subject not listed in rescue medication dataset
Source: FDA statistician and Listing 16.2.4.4 CSR

Subject (b) (6), a 14 year old male, underwent pectus repair and was reported to have an oxygen saturation of 90% occurring 60 minutes after receiving Oxycodone Oral Solution. Table 13 provides a summary of pulse oximetry and vital signs at different timepoints. At the time of the oxygen desaturation there was a minimal decrease in respiratory rate, but respirations were still well maintained at 20 per minute. No rescue medication was administered prior to the episode of oxygen desaturation. Although oxygen desaturation can occur in postoperative patients, it is impossible to exclude oxycodone as the cause or a contributing factor.

Table 13: Subject (b) (6): Summary of Pulse Oximetry and Vital Signs at Different Timepoints

Time Point	Pulse	RR	Change	Systolic	Diastolic	Heart	Rescue

	Ox		RR	BP	BP	Rate	Medication
Screening		22		106	66	71	
Pre-Dose	100	21		123	77	62	
10 min Post-Dose	100						
15 min Post-Dose	-	26	5	124	81	79	
30 min Post-Dose	100	27	6	118	77	89	
45 min Post-Dose	-	24	3	129	81	84	
60 min Post-Dose	90	20	-1	112	76	88	
1 hr 15 min Post-Dose	-	27	6	114	72	71	
1 hr 30 min Post-Dose	-	28	7	122	76	67	
1 hr 45 min Post-Dose	-	22	1	120	75	71	
2 hrs Post-Dose	100	27	6	122	76	67	
2 hrs 15 min Post-Dose		17	-4	116	72	64	
2 hrs 30 min Post-Dose		17	-4	119	74	69	
2 hrs 45 min Post-Dose		18	-3	120	77	69	
3 hrs Post-Dose		17	-4	114	70	75	
3 hrs 15 min Post-Dose		16	-5	115	71	80	
3 hrs 30 min Post-Dose		16	-5	119	71	81	
3 hrs 45 min Post-Dose		15	-6	115	70	76	
4 hrs Post-Dose	100	26	5	124	70	80	Ketorolac
6 hrs Post-Dose	100	30	9	116	69	67	
8 hrs Post-Dose	99						

Source: Listing 16.2.8.8 and 16.2.8.9 CSR

8.2.11. Electrocardiograms (ECGs)

An ECG was performed at Screening or any time pre-dose.

8.3. Safety Analyses by Demographic Subgroups

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

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

Warnings and precautions about misuse, abuse, and diversion of opioids and statements describing drug abuse, dependence and drug overdose are all included in the product labeling.

8.4. Integrated Assessment of Safety

The pediatric safety database supporting the current pediatric supplement consists of 97 pediatric patients (89 subjects 2 to < 17 years of age and 8 subjects under the age of 2) who received a single-dose of Oxycodone Oral Solution for the treatment of postoperative pain. Safety findings included no cases of death, serious AEs, or discontinuation due to AEs.

Treatment-emergent AEs (TEAEs) occurred in 37% of patients and were generally consistent with commonly reported post-operative and opioid-related findings. The most common AEs included nausea (13%), vomiting (12%), and itching (9%).

There were no adverse events of respiratory depression, but 16 patients had a decrease in pulse oximetry of 4% or greater from pre-dose. Excluding the six patients that received hydromorphone at the same time as oxycodone, leaves 10 patients with a decrease of pulse oximetry of at least 4%. The greatest decrease was 10% occurring at 60 minutes. Although it is difficult to determine the cause of oxygen desaturation in this case or any of the others and notwithstanding the fact that these findings may be observed in postoperative patients, it is impossible to exclude oxycodone as either the cause or a contributing factor in some of the patients. This raises the serious concern that higher doses and/or multiple-doses of Oxycodone Oral Solution could result in more frequent or severe respiratory depression.

The submitted data established that comparable exposures were achieved between pediatric patients two years of age and older and adults with the starting doses. From an efficacy perspective, to initiate dosing in each pediatric age group at the studied doses, which provide 21% to 35% lower mean AUC0-inf values than that for the lowest starting dose in adult (5 mg), is reasonable. The dose may be titrated up based on the patient's response. The same titration-to-effect treatment strategy used in adults may also be required in pediatric patients to achieve a therapeutic dose. The study design precluded the ability to clinically confirm that efficacy extrapolated by PK was actually achieved with the administered doses. The analgesic effect could not be assessed due to limitations of the study such as open-label design, lack of a control group, direct switch from intravenous opioids to study medication without requiring certain levels of baseline pain intensity, no pain scores collected for subjects 2 to 17 years, and frequent concomitant use of rescue medication. The lack of repeat dosing and demonstration of efficacious doses or titration to higher doses, limits the ability of the safety database to support the safety of this product with higher oxycodone exposures. Because adverse events are often dose related, and specifically respiratory depression the safety database is not sufficient to support the safety of the product.

The Applicants submitted literature to help support the safety of multiple-dosing with oxycodone. However, the references which included 3 multiple dose studies of 104 subjects and additional single-dose studies did not provide sufficient safety data to support the safety of multiple-doses. The multiple-dose studies were with buccally and intravenous administered oxycodone, and a controlled release formulation of oxycodone. Only one of the studies was a randomized, controlled study, the other two studies were either an open-label study or a retrospective chart review. In general, the literature lacked sufficient details to adequately assess safety.

Olkkola studied the ventilatory effects of intravenous oxycodone in postoperative children and described mean ETCO2 values appeared to be higher and mean ventilatory rates lower than

observed earlier with morphine, buprenorphine, meperidine and methadone when given postoperatively to pediatric patients. The authors concluded that oxycodone (0.1 mg per kg) appears to cause greater ventilatory depression than comparable analgesic doses of other opioids and it should be used with care in children emerging from anesthesia. It should be noted that in the study oxycodone was administered IV and at higher doses than administered in the study under review. Although no other article was found that supports the finding of greater ventilatory depression with oxycodone, the article by Olkkola does support the need for collecting adequate safety data to assess the risk of respiratory depression. From the safety information submitted, it is impossible to predict what effect multiple-therapeutic doses of oxycodone would have on safety in general and specifically on respiratory depression.

(b) (4)

9. Division of Pediatric and Maternal Health (DPMH)/ Pediatric Review Committee (PeRC)

Division of Pediatric and Maternal Health (DPMH) was consulted to assist the review of this application and determine whether the Applicants fulfilled their PREA requirements for patients 2 years to less than 17 years of age. DPMH representatives participated in the team meetings and provided comments on labeling this supplement. The application was discussed with the Pediatric Review Committee (PeRC) on October 6, 2020. DPMH and PeRC agreed that that the PREA PMRs for these products for pediatric patients 2 years of age and older should be considered fulfilled.

However, the PREA PMR cannot be considered fulfilled due to the pending inspection status.

10. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this product.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

(b) (4)

If approved, the following language will be added to Section 8.4 Pediatric Use:

> The safety and effectiveness of Oxycodone Hydrochloride Oral Solution have not been established in pediatric patients. The safety and pharmacokinetics of a single-dose of Oxycodone Hydrochloride Oral Solution were evaluated in an open-label clinical trial in 89 pediatric patients 2 years to less than 17 years of age with postoperative pain. However, definitive conclusions were not possible because of insufficient information.

12. Risk Evaluation and Mitigation Strategies (REMS)

Oxycodone oral products are part of opioid analgesic REMS. This supplement does not affect or change any aspects of the REMS.

13. Postmarketing Requirements and Commitments

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

14. Recommended Comments to the Applicant

The Division determined that satisfactory inspection or a remote record review will be required before this application may be approved. The Division provided the following comments in the CR letter:

> *There is an inability to ensure the reliability of the clinical study data of the Phase IV Study to Evaluate the Pharmacokinetics and Safety of Oxycodone Oral Solution in Pediatric and Adolescent Subjects. The Office of Study Integrity and Surveillance (OSIS) is unable to complete an inspection or remote record review of the Cincinnati Children's Hospital Medical Center clinical study site. Specifically, the Clinical Investigator for the study was unavailable, and the person identified as the replacement was not authorized to speak or make decisions on behalf of the study.*
>
> *<u>Information needed to resolve Deficiency:</u>*
> *Satisfactory inspection or a remote record review is required before this application may be approved. Please notify us in writing when this facility is ready for an inspection or remote record review.*

15. Appendices

15.1. Literature

The Applicants conducted a literature search to identify published clinical studies that could support the pharmacokinetics and safety of oxycodone hydrochloride in pediatric patients. The Division previously advised the Applicants to submit a review of the literature to support the safety of multiple doses and the safety findings from the conducted study. The search was conducted using PubMed as the search engine. A stop date of Jun 15, 2019, and the terms "Oxycodone" with added terms, "multiple dose", "neonates", and "infants" were searched. All nonclinical and foreign (non-English written) publications were deemed as not relevant. A total of 246 publications were identified during the literature search. Of the 246 publications identified, 117 were found to be potentially relevant and 93 publications were obtained and reviewed. There were 13 studies of special interest identified in the literature search that included five efficacy and safety studies (3 multiple-dose studies), six pharmacokinetic and safety studies (safety data in 5 studies), and two population pharmacokinetic studies which contained no safety data.

The multiple-dose studies were with buccally and intravenous administered oxycodone, and a controlled release formulation of oxycodone. Only one of the multiple-dose studies was a randomized, controlled study, the other two studies were an open-label study and a retrospective chart review. In general, the literature lacked detailed patient safety information to adequately assess safety. Brief individual study summaries are provided below.

Individual Study Summaries

Multiple Dose Studies

The following are summaries of the three multiple-dose studies.

1. Kokki H, et al. Oxycodone vs Placebo in Children with Undifferentiated Abdominal Pain. Arch Pediatr Adolesc Med. 2005; 159:320-325.

   Multiple-dose, 0.1 mg/kg buccally

   Study design
   In this randomized, double-blind, placebo-controlled study, 32 children received oxycodone 0.1 mg/kg buccally and 31 children received placebo for acute abdominal pain. Children ranged in age from 4 to 15 years and received a total of up to three doses at 0, 1 and 3.5 hours. The average number of doses administered was 2.1.

   Safety
   The safety information provided was limited to the following description:
   > "One child experienced headaches and another developed urticaria after receiving oxycodone. No sedation, hypoxia, or hypotension was observed."

Discussion
The authors concluded that early administration of buccal oxycodone provides significant pain relief to children with acute abdominal pain and that results of this trial support a large-scale trial to further evaluate whether this approach is safe. This article provides no patient level safety data and minimal details on safety.

2. Kokki H, et al. Interpleural bupivacaine and intravenous oxycodone for pain treatment after thoracotomy in children. J Opioid Manag. 2006 Sept-Oct;2(5):290-294.

   Multiple dose 0.1 mg/kg IV (OL study)

   Study design
   This was an open-label study of 10 children ages 10 months to 12 years who received interpleural bupivacaine and IV oxycodone 0.1 mg/kg as rescue analgesia for pain following thoracotomy for patent ductus arteriosus. The aim of the study was to evaluate whether pain treatment with interpleural bupivacaine and ibuprofen would provide sufficient analgesia. After surgery all children were given ibuprofen 10 mg/kg rectally every 6 hours and bupivacaine every two hours as needed. If pain was not relieved sufficiently with ibuprofen and bupivacaine children were administered oxycodone 0.1 mg/kg IV. The number of doses of oxycodone ranged from 1 to 12 (mean =6.0).

   Safety
   Vital signs, oxygen saturation, and adverse events were monitored. Oxygen saturation remained greater than 90% in all of the subjects, but six subjects had oxygen saturation values less than 95% (one patient each with values of 91%, 92%, and 93% and 3 patients with 94%). No serious adverse events were recorded. One 13-month old boy developed brief apnea (duration 15 seconds) two minutes after his tenth oxycodone injection. His respiratory rate was 23 breaths/min before the incident and 14 breaths/min after the dose. The lowest respiratory rate reported was 12 breaths/minute. Adverse reactions included one patient each with apnea, urinary retention, vomiting, and nausea.

   Discussion
   The authors concluded that IV oxycodone performed well, and no serious adverse reactions were observed in this small patient population. There was one adverse event of apnea that was likely related to oxycodone. It is unclear whether the mild decrease in oxygen saturation and adverse events in the other patients were related to oxycodone.

3. Czarnecki M, et al. Controlled-Release Oxycodone for the Management of Pediatric Postoperative Pain. J Pain Symptom Manage. 2004 April;27(4):379-386.

   Multiple-dose study with Oxycodone CR (Retrospective chart review)

   Study design

The data from this study was obtained from a retrospective chart review of 62 postoperative spinal fusion patients, ages 10-19 years, evaluating the analgesic efficacy and safety of switching patients from morphine PCA to oral CR oxycodone. The mean duration of oxycodone use was 13.3 days on every 12 hour dosing regimen. The mean initial oxycodone CR dose was 1.24 mg/kg/day. The analgesia produced by oxycodone was essentially comparable to that experienced with the IV morphine.

Safety
Common side effects were dizziness, constipation, sedation, nausea, vomiting, and pruritus which were seen during both treatment periods but were less frequent while on oxycodone compared to morphine. Overall the number of patients with side effects of any kind decreased from 56.5% with PCA to 43.9% 48 hours after transitioning to oxycodone-CR. Respiratory depression was one of the least frequently reported side effects, with both PCA and oxycodone-CR use, and no patient required aggressive intervention.

Discussion
The authors concluded that this study demonstrated safe and effective use of oxycodone-CR in the pediatric post-operative spinal fusion population. It is noted that patients were treated with a controlled release oxycodone and no details of monitoring oxygen saturation or respiratory depression were provided.

Single-dose Studies

4. Sharar S, et al. A Comparison of Oral Transmucosal Fentanyl Citrate and Oral Oxycodone for Pediatric Outpatient Wound Care. J Burn Care Rehabil 2002; 23:27-31.

Single dose, 0.2mg/kg

Study design
This was a randomized, double-blind, active-control study in 10 children ages 5-14 years who received 0.2mg/kg of oral oxycodone elixir as a single dose or 10 children who received oral transmucosal fentanyl citrate (OTFC) approximately10mcg/kg. Drug was administered 30 minutes prior to burn related wound care. Pain assessment was measured 4 times using the Oucher pain scale.

Safety
Vital signs and scores for sedation and anxiety were measured every 15 minutes. Pulse oximetry (room air) was measured continuously and recorded every 15 minutes. There were no significant differences in systolic blood pressure, heart rate, or respiratory rate between subjects receiving oxycodone and those receiving OTFC. Oxygen saturation also was not different between treatment groups, with all individual pulse oximetry measurements between 97 and 99%. No adverse side effects including respiratory, desaturation, nausea, or itching were reported or observed in either treatment group.

Discussion

The authors concluded that both OTFC (10 mcg/kg) and oral oxycodone (0.2 mg/kg) provide comparable analgesia, anxiolysis, and lack of side effects, including nausea or excessive sedation. Oxygen saturation remained above 96% for both groups.

5. Koller D, et al. Effectiveness of Oxycodone, Ibuprofen, or the Combination in the Initial Management of Orthopedic Injury-Related Pain in Children. 2007 Pediatric Emergency Care; 3(9): 627-633.

   Single dose 0.1 mg/kg (active-control study)

   Study design
   This was a randomized, double-blind trial designed to compare the effectiveness of oxycodone, ibuprofen, or the combination in 66 children (22 per treatment group) 6-18 years in pain from suspected orthopedic injury. The oxycodone group received 0.1mg/kg of the drug orally as a single dose. Pain was measured using the Face Pain Scale (FPS) and Visual Analogue Scale (VAS) at 30, 60, 90, and 120-minute intervals. All 3 regimens provided effective analgesia for mild to moderate orthopedic injuries.

   Safety
   The oxycodone group had one adverse event of drowsiness for an overall incidence of adverse events of 4.6% compared to ibuprofen and combination with an incidence of adverse events of 8.2% and 42.9%, respectively. Drowsiness was the most common adverse effect seen in all three treatment groups. All the adverse effects were minor, and none required any intervention. One subject in the oxycodone group reported vomiting after discharge. This subject received procedural sedation with ketamine and midazolam which could account for the emesis. Subjects had decreases in systolic blood pressure and oxygen saturation over the 120-minute observation period but there were no differences between the 3 treatment groups. These changes were reported as statistically significant but without clinical significance. Subjects never had an oxygen saturation below 94%.

   Discussion
   This single-dose study showed that oxycodone appeared to be well tolerated. Safety findings were summarized but no individual patient information was provided

Pharmacokinetics and Safety Studies
The following are brief summaries of the six PK and safety studies.

6. Kokki H, et al. Pharmacokinetics of Oxycodone After Intravenous, Buccal, Intramuscular and Gastric Administration. Clin Pharmacokinet 2004;43(9): 613-622.

   Single dose 0.1 mg/kg PK study

   Study design: Open-label pharmacokinetic study of 4 routes of administration of oxycodone: IV (n=9), IM (n=10), buccally (n=11) and orally (n=10). The forty children aged 6-93

months were given 0.1mg/kg as a single dose after induction of anesthesia for inpatient surgery.

Results: Mean Cmax (mcg/L) for each route of administration: IV 82.2, IM 33.6, Buccal 9.8, Gastric 9.2. Mean tmax (min) IV 2, IM 16 Buccal 221, Gastric 193. Mean terminal half-life (min): IV 163, IM 150, Buccal 150, Gastric 147.

Safety: Limited safety information was provided. There were four adverse events: 3 vomiting and 1 nausea.

Discussion: The authors concluded that buccal and gastric administration of oxycodone in young children provides a relatively slow rate of oxycodone absorption. The estimated bioavailability of buccal oxycodone was acceptable, 55%, when compared with IV administration. However, the inter-individual variation was large and therefore the authors concluded that in the management of acute severe pain, oxycodone should be administered intravenously. Only limited safety information was provided.

7. Kokki H, et al. Comparison of Oxycodone Pharmacokinetics after Buccal and Sublingual Administration in Children. Clin Pharmacokinet 2006;45(7):745-754.

   Single dose, 0.2 mg/kg (PK study)

   Study design
   The objective of this study was to compare the pharmacokinetics of two different oral administration routes of oxycodone, either buccally or sublingually in 30 children ages 6-91 months administered 0.2mg/kg oxycodone as a single-dose prior to surgery.

   Results
   Bioavailability was similar for both routes. Twelve of the 15 children in both groups reached the oxycodone concentration of 12 ng/mL, which was sustained for 43–209 minutes (median 160 minutes) in the children with buccal oxycodone and for 32–262 minutes (median 175 minutes) in the children with sublingual oxycodone.

   Safety
   Five children developed adverse events: 3 emesis, 1 dizziness and 1 nasal itching. Limited safety information was provided.

   Discussion
   The authors concluded that in children aged ≥1 the absorption of oxycodone is similar after buccal and sublingual administration. Safety data was limited to reporting the adverse events that occurred during the study.

8. Pokela M et al. Marked variation in oxycodone pharmacokinetics in infants. Pediatric Anesthesia 2005; 15:560-565.

Single dose 0.1 mg/kg (PK study)

Study design
The aim of this study was to evaluate the pharmacokinetics of oxycodone in infants from ages 0-6 months. Twenty-two infants undergoing surgery were given postoperatively an IV bolus of 0.1mg/kg of oxycodone hydrochloride. Ten of the patients were younger than one week, six from 1 week to 2 months, and six from 2 to 6 months.

Results
The median (range) values for clearance (Cl), youngest to oldest, were 9.9 (2.3-17.2), 20.1 (3.7-40.4), 15.4 (14.8-80.2) ml/min/kg. Values for elimination half-life were: 4.4 (2.4-14.1), 3.6 (1.6-11.6) and 2.0 (0.8-3.9) hours respectively. Both clearance and half-life were correlated to the age of the patient.

Safety
At the time of oxycodone administration 13 patients needed mechanical ventilation. None of the spontaneously breathing infants had apnea or hypoventilation that required assistance during the study. Alanine aminotransferase was slightly elevated in two patients, but no clinically significant liver or renal dysfunction was observed in any of the patients.

Discussion
The authors concluded that since the values for clearance and half-life varied greatly between the subjects in the 2 youngest groups, dosing of very young infants may be dangerous and should be titrated individually. Minimal safety information was provided, and the subjects were all 6 months or younger.

9. Kokki M, et al. Maturation of Oxycodone Pharmacokinetics in Neonates and Infants: Oxycodone and its Metabolites in Plasma and Urine.Br J Clin Pharmacol 2017;83:791-800

Single dose 0.1 mg/kg (PK study)

Study design
This was a pharmacokinetic study of oxycodone and its major metabolites in infants ranging between preterm neonates to 2-year-old infants. A total of 79 infants (gestational age 23-42 weeks; postnatal age 0-650 days) received IV oxycodone at a dose of 0.1mg/kg during or after surgery.

Results
Oxycodone pharmacokinetics changed markedly with patient age. Preterm neonates were found to have the highest pharmacokinetic variability out of the study population. In extremely preterm neonates (n = 6) median of elimination half-life was 8.8 h (range 6.8–12.5), in preterm 7.4 h (4.2–11.6), and in older neonates 4.1 h (2.4–5.8), all of which were significantly longer than that in infants aged 6–24 months 2.0 h (1.7–2.6). Median renal clearance was fairly constant in all age groups, whereas non-renal clearance markedly increased with age. Noroxycodone was the major metabolite in plasma and urine.

Safety
One boy who had surgery due to pyloric stenosis had postoperative nausea and vomiting, and urinary retention. One preterm underwent surgery for patent ductus arteriosus, and died at the first postoperative morning. The death was considered not related to the study drug. No other adverse events were recorded.

Discussion
The authors concluded that since oxycodone elimination is slower and pharmacokinetic variability more pronounced in neonates when compared to older infants, it is important to carefully dose titrate for neonates. Minimal safety information was provided, and the subjects were all under the age of two.

10. Olkkola K, et al. Pharmacokinetics and Ventilatory effects of Intravenous Oxycodone in Postoperative Children. Br J Clin Pharmacol 1994; 38:71-76.

Single dose 0.1 mg/kg (PK study)

Study design
A single dose of oxycodone hydrochloride (0.1 mg/kg) was given by intravenous bolus to 18 children, ages 2-10 years, after ophthalmic surgery. Blood was drawn for pharmacokinetic analysis, and blood pressure, heart rate, peripheral arteriolar oxygen saturation, end-tidal carbon dioxide ($ETCO_2$) and ventilatory rate were monitored.

Results
After the administration of oxycodone, the ventilatory variables were characterized by remarkably rapid and steep changes. Major increases in ETCO2 and decreases in ventilatory rate occurred in all patients. Mean ETCO2 values appeared to be higher and mean ventilatory rates lower than observed earlier with morphine, buprenorphine, meperidine and methadone when given postoperatively to pediatric patients who had undergone eye surgery. Mean values of drug clearance was 15.2+ 4.2 ml /min /kg. Maximum mean end-tidal carbon dioxide concentration and minimum mean ventilatory rate occurred 8 min after administration of oxycodone but the minimum mean peripheral arteriolar oxygen saturation occurred at 4 min.

Safety
Four patients had to be ventilated manually but one patient received a higher dose of oxycodone (10 mg [0.5mg/kg]). Eight patients had nausea or vomiting, and one patient did not urinate during the operation day.

Discussion
The authors concluded that oxycodone (0.1mg/kg) appears to cause greater ventilatory depression than comparable analgesic doses of other opioids and it should be used with care in children emerging from anesthesia. After the administration of oxycodone, the ventilatory variables were characterized by remarkably rapid and steep changes. Major increases in

ETCO2 and decreases in ventilatory rate occurred in all patients. Mean ETCO2 values appeared to be higher and mean ventilatory rates lower than observed earlier with morphine, buprenorphine, meperidine and methadone when given postoperatively.

11. Balyan R, et al. CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients. Pharmacogenomics 2017;18(4):337-348
Single dose (PK study)

Study design
This was a pharmacokinetic/pharmacogenetic study in 30 pediatric postoperative patients (n=5 2-6 years; n=8 7-12 years; n=17 13-18 years) given a single dose of oral oxycodone to compare the pharmacokinetics of oxycodone based on different CYP2D6 genotypes. The metabolism phenotypes were divided into 3 groups, poor metabolizer (PM), intermediate metabolizer (IM), and extensive metabolizer (EM). The dose of oxycodone was 0.1 mg/kg for children aged 2–6 years, 0.08 mg/kg for ages 7–12 years and 0.07 mg/kg for ages 13–17 years. Oxycodone is metabolized to the active and potent metabolite oxymorphone by hepatic CYP2D6.

Results
Compared to PM/IM patients, EM patients had a significantly greater oxymorphone exposure.

Safety
No safety results were reported in the study.

Discussion
The authors concluded that CYP2D6 genotypes play a significant role in the pharmacokinetics of oxycodone and its metabolite, oxymorphone. Specifically, children identified as being extensive metabolizers of oxycodone had greater exposure to oxymorphone, an active and potent metabolite of oxycodone compared with poor metabolizers. No safety information on the subjects in the study was provided.

Population PK Studies (no safety information)

12. El-Tahtawy A, et al. Population Pharmacokinetics of Oxycodone in Children 6 Months to 7 Years Old. J Clin Pharmacology 2006; 46:433-442.

No Safety information was provided in this study.

A total of 382 plasma concentrations from 39 patients aged 6 to 88 months in four separate studies were included in the population pharmacokinetic analysis. A single population model that described the observed pharmacokinetics was developed. Weight was found to significantly influence both clearance and volume of distribution. The authors concluded that

this model confirms using a weight-based dose for oxycodone without adjustment for age between 6 months and 7 years.

13. Valitalo P, et al. Maturation of Oxycodone Pharmacokinetics in Neonates and Infants: A Population Pharmacokinetic Model of Three Clinical Trials. Pharm Res 2017;34: 1125-133.

No Safety information was provided in this study.
The aim of this population pharmacokinetic study was to quantify oxycodone pharmacokinetics in children ranging from preterm neonates up to 7 years of age. This population pharmacokinetic study was used to develop a model for dosing very young infants with 0.1 mg/kg IV oxycodone every hour or every fourth hour. The study used data on intravenous or intramuscular oxycodone administration obtained from three previously published data studies. The authors concluded that oxycodone clearance matures rapidly after birth, and between-subject variability is pronounced in neonates. The pharmacokinetic model developed may be used to evaluate different multiple dosing regimens, but the safety of repeated doses should be ensured.

15.2. Financial Disclosure

Refer to Section 5.1.2 Study Results for additional details on financial disclosure.

Covered Clinical Study: Study 2012O0024

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 51		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 Note: The financial disclosure form was not submitted for one investigator because it could not be retrieved from the site due to office closure due to Covid-19 precautions. In lieu of it, the Principle Investigator Dr. (b) (6) provided the following statement, "Dr. (b) (6) was a pediatric anesthesia fellow for a year with us and he left (b) (6) Hospital about a year ago. I do not know his current contact information. As far as I know, Dr. (b) (6) did not have any financial conflicts."		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

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

15.3. Vital Sign Tables

Table 14: Change in Systolic Blood Pressure by Age Group Through 8 Hours Post-Dose

Timepoint	6 months to <2 years (N=8)	2 to 6 years (N=24)	7 to 12 years (N=30)	13 to <17 years (N=35)	Overall (N=97)
Screening					
Mean (SD)	103.9	106.0	114.9	118.0	113.0
Check-in					
Mean (SD)	95.5	102.3	108.6	111.4	107.3
Pre-Dose					
Mean (SD)	101.3 (14.98)	103.9 (14.96)	108.4 (17.38)	114.0 (15.52)	108.7 (16.34)
Median	99.0	101.0	106.5	116.5	108.0
Min, Max	85, 125	77, 135	83, 147	86, 142	77, 147
15 min Post-Dose					
Mean (SD)	98.9 (11.15)	101.0 (11.83)	105.5 (19.87)	112.9 (14.40)	106.5 (16.16)
Change in Mean	-2.4 (8.63)	-2.1 (13.03)	-1.8 (7.89)	-1.1 (8.37)	-1.7 (9.48)
30 min Post-Dose					
Mean (SD)	101.9 (13.56)	97.7 (11.72)	107.0 (18.68)	112.3 (12.98)	106.1 (15.62)
Change in Mean	0.6 (20.93)	-5.3 (10.58)	-2.7 (8.82)	-1.5 (7.28)	-2.7 (10.28)
45 min Post-Dose					
Mean (SD)	95.5 (6.57)	99.5 (14.61)	106.7 (16.78)	114.1 (14.88)	106.7 (16.13)
Change in Mean	-5.8 (11.95)	-3.1 (15.85)	-3.1 (9.19)	0.1 (7.38)	-2.1 (10.85)
60 min Post-Dose					
Mean (SD)	98.7 (9.60)	101.7 (10.66)	106.2 (15.84)	114.8 (13.61)	107.6 (14.46)
Change in Mean	-3.0 (13.90)	-2.3 (10.49)	-3.6 (9.05)	0.9 (9.41)	-1.6 (9.99)
1hr 30 min PD					
Mean (SD)	99.4 (5.59)	100.0 (12.52)	103.3 (16.25)	113.0 (15.87)	105.9 (15.54)
Change in Mean	-2.0 (14.20)	-3.0 (11.27)	-5.6 (8.98)	-1.0 (7.58)	-2.9 (9.63)
1 hr 45 min PD					
Mean (SD)	99.0 (6.73)	99.6 (12.83)	103.5 (15.81)	113.5 (14.71)	105.9 (15.20)
Change in Mean	-2.4 (12.27)	-3.9 (12.81)	-5.4 (11.47)	-1.2 (7.34)	-3.2 (10.54)
2 hr Post-Dose					
Mean (SD)	106.4 (15.88)	99.4 (12.36)	106.3 (16.23)	112.7 (16.81)	106.9 (16.14)
Change in Mean	5.0 (5.86)	-3.6 (12.45)	-2.1 (10.31)	-1.2 (9.14)	-1.6 (10.31)
2 hrs 15 min PD					
Mean (SD)	103.9 (7.67)	102.0 (14.44)	106.8 (17.65)	112.1 (15.96)	107.3 (15.94)
Change in Mean	2.4 (15.46)	-1.5 (15.12)	-4.3 (13.58)	-1.5 (9.37)	-2.0 (12.69)
2 hrs 30 min PD					
Mean (SD)	102.0 (3.32)	100.1 (13.49)	106.0 (16.86)	112.9 (16.43)	106.8 (15.91)
Change in Mean	0.6 (17.09)	-3.4 (14.93)	-5.0 (9.33)	-0.4 (9.33)	-2.5 (11.64)
2 hrs 45 mins PD					
Mean (SD)	100.5 (5.01)	101.7 (16.45)	106.7 (15.37)	112.6 (16.49)	107.3 (16.09)
Change in Mean	-1.0 (21.87)	-1.7 (16.76)	-3.9 (11.30)	-0.7 (9.89)	-1.9 (13.04)
3 hrs Post-Dose					
Mean (SD)	99.1 (7.22)	102.4 (15.24)	105.8 (16.81)	111.9 (15.17)	106.6 (15.66)
Change in Mean	-2.3 (16.48)	-1.5 (14.92)	-6.1 (13.49)	-1.4 (9.67)	-2.8 (12.83)

3 hrs 15 min PD					
Mean (SD)	105.0 (7.16)	100.9 (13.31)	103.9 (16.73)	112.2 (13.80)	106.3 (14.80)
Change in Mean	3.6 (17.56)	-3.5 (14.75)	-6.8 (13.43)	-1.1 (11.12)	-3.0 (13.45)
3 hrs 30 min PD					
Mean (SD)	100.6 (8.94)	99.7 (12.51)	106.8 (16.91)	113.3 (15.73)	107.1 (15.78)
Change in Mean	-0.9 (16.78)	-3.8 (13.22)	-3.9 (12.62)	0.0 (12.13)	-2.1 (12.84)
3 hrs 45 mins PD					
Mean (SD)	103.9 (7.27)	99.0 (14.33)	107.0 (15.59)	113.9 (17.92)	107.5 (16.63)
Change in Mean	2.4 (17.88)	-4.6 (15.61)	-4.4 (14.28)	0.6 (13.16)	-1.9 (14.48)
4 hrs Post-Dose					
Mean (SD)	105.7 (16.35)	101.9 (15.72)	107.4 (16.31)	111.7 (16.20)	107.5 (16.30)
Change in Mean	4.3 (16.18)	-3.5 (15.07)	-3.3 (13.29)	-1.6 (12.35)	-2.1 (13.56)
6 hrs Post-Dose					
Mean (SD)	101.0 (6.61)	100.0 (17.30)	106.0 (14.59)	113.8 (15.49)	107.1 (16.05)
Change in Mean	-0.4 (19.54)	-3.8 (13.85)	-2.6 (9.96)	0.5 (9.94)	-1.5 (11.86)
8 hrs Post-Dose					
Mean (SD)	104.4 (7.02)	98.9 (11.65)	106.4 (15.16)	111.6 (12.79)	106.4 (13.65)
Change in Mean	3.0 (16.64)	-2.3 (13.90)	-3.4 (13.50)	-1.7 (10.47)	-2.0 (12.66)

Source: Table 14.3.6.2 Vital Sign Change, Clinical Study Report 2-12 Year Population-Protocol 2012O004

Table 15: Change in Diastolic Blood Pressure by Age Group Through 8 Hours Post-Dose

Timepoint	6 months to <2 years (N=8)	2 to 6 years (N=24)	7 to 12 years (N=30)	13 to <17 years (N=35)	Overall (N=97)
Screening					
Mean (SD)	62.7 (17.80)	60.3 (8.84)	67.1 (9.85)	69.3 (8.25)	65.9 (10.30)
Check-in					
Mean (SD)	56.0 (12.55)	59.7 (13.13)	59.9 (10.80)	62.3 (9.60)	60.5 (11.02)
Pre-Dose					
Mean (SD)	59.8 (15.80)	61.7 (13.91)	59.3 (11.84)	63.5 (11.14)	61.4 (12.43)
Median	54.0	56.0	55.5	61.0	57.5
Min, Max	43, 89	41, 97	43, 94	48, 92	41, 97
15 min Post-Dose					
Mean (SD)	59.4 (14.02)	59.2 (9.34)	59.0 (13.50)	63.6 (11.15)	60.8 (11.77)
Change in Mean	-0.4 (16.53)	-2.2 (9.81)	0.3 (5.48)	0.0 (6.19)	-0.5 (8.21)
30 min Post-Dose					
Mean (SD)	58.6 (12.81)	56.0 (8.10)	58.4 (13.05)	62.5 (10.78)	59.3 (11.25)
Change in Mean	-1.1 (16.41)	-5.3 (14.12)	-1.5 (4.00)	-1.3 (5.27)	-2.4 (9.30)
45 min Post-Dose					
Mean (SD)	54.5 (7.07)	57.0 (11.09)	59.1 (13.99)	63.1 (10.44)	59.7 (11.73)
Change in Mean	-5.3 (12.33)	-4.0 (13.18)	-0.9 (5.48)	-0.5 (6.23)	-1.9 (8.86)
60 min Post-Dose					
Mean (SD)	54.9 (7.80)	61.4 (12.30)	57.7 (12.78)	62.7 (9.70)	60.3 (11.39)
Change in Mean	-7.3 (15.25)	-0.3 (11.43)	-2.3 (4.40)	-0.8 (7.37)	-1.6 (8.77)
1hr 15 min PD					
Mean (SD)	53.6 (2.76)	59.6 (10.10)	58.6 (13.08)	62.4 (9.94)	59.9 (10.79)
Change in Mean	-7.0 (17.28)	-1.7 (9.07)	-0.9 (5.23)	-1.1 (6.03)	-1.7 (8.01)
1hr 30 min PD					
Mean (SD)	56.4 (6.68)	59.4 (10.75)	57.2 (12.61)	61.9 (10.84)	59.5 (11.12)
Change in Mean	-4.1 (19.65)	-1.9 (10.62)	-2.6 (5.01)	-1.7 (6.69)	-2.2 (8.87)

1 hr 45 min PD					
Mean (SD)	56.6 (4.65)	57.0 (8.37)	57.7 (13.02)	62.7 (9.40)	59.3 (10.30)
Change in Mean	-4.0 (15.79)	-4.9 (14.97)	-2.1 (7.46)	-1.5 (6.41)	-2.8 (10.28)
2 hr Post-Dose					
Mean (SD)	61.7 (14.87)	59.3 (10.87)	59.8 (13.26)	61.2 (9.87)	60.4 (11.44)
Change in Mean	1.1 (10.61)	-2.0 (14.99)	0.6 (7.62)	-2.5 (7.69)	-1.2 (10.20)
2 hrs 15 min PD					
Mean (SD)	57.3 (5.22)	58.0 (11.63)	59.1 (12.43)	62.2 (10.50)	59.8 (11.10)
Change in Mean	-3.3 (13.66)	-2.7 (17.17)	-1.7 (8.16)	-2.0 (6.60)	-2.2 (10.97)
2 hrs 30 min PD					
Mean (SD)	54.6 (4.83)	58.0 (11.21)	60.9 (12.59)	61.5 (10.58)	59.9 (11.10)
Change in Mean	-6.0 (16.08)	-2.7 (16.37)	0.1 (7.88)	-2.5 (5.69)	-2.1 (10.72)
2 hrs 45 mins PD					
Mean (SD)	53.8 (8.28)	58.9 (13.16)	58.4 (12.03)	61.5 (11.34)	59.4 (11.84)
Change in Mean	-7.8 (22.89)	-1.6 (17.54)	-1.8 (5.96)	-2.5 (6.13)	-2.4 (11.36)
3 hrs Post-Dose					
Mean (SD)	57.4 (11.30)	58.9 (11.40)	58.5 (13.31)	62.1 (10.82)	59.9 (11.69)
Change in Mean	-3.1 (17.27)	-2.8 (15.71)	-2.7 (6.89)	-1.9 (7.66)	-2.5 (10.92)
3 hrs 15 min PD					
Mean (SD)	59.9 (10.16)	59.1 (10.96)	57.3 (13.07)	61.9 (10.83)	59.7 (11.48)
Change in Mean	-0.7 (16.08)	-2.0 (13.69)	-3.1 (6.47)	-2.1 (7.27)	-2.3 (9.80)
3 hrs 30 min PD					
Mean (SD)	55.1 (9.03)	57.8 (8.86)	59.0 (12.20)	62.5 (12.47)	59.7 (11.44)
Change in Mean	-5.4 (17.38)	-2.8 (13.69)	-1.4 (6.26)	-1.5 (9.01)	-2.1 (10.37)
3 hrs 45 mins PD					
Mean (SD)	58.0 (11.20)	59.9 (10.87)	59.0 (10.64)	61.8 (10.31)	60.2 (10.51)
Change in Mean	-2.6 (20.02)	-1.1 (14.60)	-2.1 (6.47)	-2.2 (7.55)	-1.9 (10.53)
4 hrs Post-Dose					
Mean (SD)	65.0 (17.03)	59.3 (11.26)	60.9 (13.02)	60.9 (11.07)	60.8 (12.10)
Change in Mean	4.4 (19.32)	-3.8 (12.69)	0.5 (7.19)	-3.2 (8.13)	-1.6 (10.49)
6 hrs Post-Dose					
Mean (SD)	56.3 (3.04)	57.8 (12.36)	59.6 (13.19)	63.1 (11.13)	60.2 (11.76)
Change in Mean	-4.3 (18.75)	-4.5 (13.57)	0.2 (6.89)	-1.0 (6.77)	-1.8 (10.13)
8 hrs Post-Dose					
Mean (SD)	57.3 (5.77)	57.0 (8.85)	58.0 (11.47)	63.5 (10.42)	59.8 (10.36)
Change in Mean	-3.3 (15.14)	-3.0 (10.94)	-1.0 (7.32)	-0.5 (8.71)	-1.5 (9.45)

Source: Table 14.3.6.2 Vital Sign Change, Clinical Study Report 2-12 Year Population-Protocol 2012O004

Table 16: Change in Heart Rate by Age Group Through 8 Hours Post-Dose

Timepoint	6 months to <2 years (N=8)	2 to 6 years (N=24)	7 to 12 years (N=30)	13 to <17 years (N=35)	Overall (N=97)
Screening					
Mean (SD)	124.5 (19.40)	96.6 (18.92)	89.6 (13.95)	82.2 (14.30)	91.5 (19.35)
Check-in					
Mean (SD)	130.2 (25.42)	107.5 (23.78)	92.7 (18.47)	84.9 (21.15)	95.7 (24.40)
Pre-Dose					
Mean (SD)	139.6 (21.30)	111.6 (21.83)	95.6 (18.39)	85.7 (20.26)	99.6 (25.29)
Median	148.0	107.0	95.5	87.0	98.0
Min, Max	97, 160	67, 156	55, 134	52, 129	52, 160
15 min Post-Dose					
Mean (SD)	128.0 (20.80)	110.5 (19.74)	93.1 (18.30)	84.9 (19.80)	96.3 (23.17)
Change in Mean	-15.3 (21.57)	-1.6 (19.60)	-1.5 (8.81)	-0.8 (10.04)	-2.2 (13.68)
30 min Post-Dose					
Mean (SD)	136.6 (25.67)	106.9 (18.81)	94.5 (21.17)	84.6 (20.04)	97.8 (25.03)
Change in Mean	-3.0 (36.29)	-4.7 (18.35)	0.3 (13.92)	-1.5 (10.10)	-1.9 (16.72)
45 min Post-Dose					
Mean (SD)	121.1 (15.31)	105.0 (17.33)	90.7 (16.45)	85.9 (20.70)	95.2 (21.10)
Change in Mean	-18.5 (14.53)	-6.6 (21.70)	-2.9 (8.93)	-0.3 (11.13)	-4.2 (15.04)
60 min Post-Dose					
Mean (SD)	122.0 (15.46)	107.7 (17.21)	90.4 (19.28)	85.4 (18.97)	95.8 (21.71)
Change in Mean	-17.6 (19.15)	-4.0 (20.07)	-3.3 (13.31)	-0.7 (11.70)	-3.8 (15.75)
1hr 15 min PD					
Mean (SD)	124.4 (9.68)	109.0 (17.71)	89.5 (18.18)	86.7 (18.52)	96.0 (21.31)
Change in Mean	-12.9 (24.63)	-2.7 (20.63)	-3.6 (12.47)	1.0 (11.27)	-2.4 (15.78)
1hr 30 min PD					
Mean (SD)	132.3 (25.08)	112.6 (18.03)	90.0 (21.14)	88.6 (18.86)	98.6 (24.06)
Change in Mean	-5.0 (33.77)	1.0 (19.38)	-2.8 (10.52)	2.5 (10.75)	-0.0 (15.83)
1 hr 45 min PD					
Mean (SD)	124.0 (17.90)	108.8 (16.07)	88.5 (20.73)	87.4 (19.55)	96.3 (22.28)
Change in Mean	-13.3 (27.87)	-2.8 (17.57)	-4.8 (10.91)	1.3 (9.23)	-2.7 (14.57)
2 hr Post-Dose					
Mean (SD)	135.6 (25.22)	108.0 (16.38)	91.8 (21.15)	86.3 (21.05)	97.4 (24.48)
Change in Mean	-1.7 (20.02)	-3.7 (18.50)	-1.6 (10.18)	0.2 (10.22)	-1.4 (13.52)
2 hrs 15 min PD					
Mean (SD)	132.6 (15.53)	107.2 (16.15)	90.4 (21.47)	87.5 (20.75)	97.3 (23.23)
Change in Mean	-4.7 (28.59)	-4.6 (20.81)	-3.0 (12.34)	2.1 (11.80)	-1.8 (16.49)
2 hrs 30 min PD					
Mean (SD)	130.6 (21.05)	108.3 (16.14)	91.5 (22.51)	84.2 (19.74)	96.2 (23.95)
Change in Mean	-6.7 (24.94)	-3.2 (18.92)	-1.9 (16.34)	-0.3 (9.61)	-2.0 (15.64)
2 hrs 45 mins PD					
Mean (SD)	131.0 (15.49)	111.6 (14.67)	90.7 (19.89)	83.2 (20.93)	96.6 (23.88)
Change in Mean	-6.3 (22.95)	0.0 (20.41)	-2.0 (14.94)	-1.4 (8.28)	-1.6 (15.26)
3 hrs Post-Dose					
Mean (SD)	132.4 (25.20)	113.6 (13.32)	91.4 (20.68)	84.8 (21.82)	98.2 (24.85)
Change in Mean	-4.9 (25.27)	2.0 (19.50)	-1.9 (13.85)	0.3 (11.16)	-0.3 (15.64)
3 hrs 15 min PD					
Mean (SD)	133.9 (21.43)	108.3 (12.34)	88.3 (18.85)	86.3 (21.10)	96.5 (23.13)

Change in Mean	-3.4 (17.61)	-3.4 (16.84)	-3.5 (14.54)	1.8 (11.10)	-1.5 (14.29)
3 hrs 30 min PD					
Mean (SD)	134.0 (32.29)	108.8 (14.46)	89.2 (20.19)	86.7 (23.43)	97.0 (25.27)
Change in Mean	-3.3 (23.87)	-2.9 (18.84)	-2.6 (15.90)	2.2 (12.41)	-1.0 (16.20)
3 hrs 45 mins PD					
Mean (SD)	141.3 (39.32)	106.6 (12.83)	89.5 (17.60)	83.0 (21.29)	95.7 (25.90)
Change in Mean	4.0 (29.60)	-4.4 (20.29)	-3.0 (10.33)	-1.5 (9.33)	-2.2 (15.19)
4 hrs Post-Dose					
Mean (SD)	131.9 (19.77)	107.3 (16.34)	87.7 (18.24)	84.3 (19.82)	95.1 (23.14)
Change in Mean	-5.4 (12.47)	-4.3 (22.07)	-4.2 (13.25)	-0.2 (10.57)	-2.8 (15.17)
6 hrs Post-Dose					
Mean (SD)	136.9 (20.98)	109.9 (15.09)	89.7 (21.05)	87.2 (21.61)	97.7 (24.57)
Change in Mean	-0.4 (19.65)	-2.0 (22.96)	-2.1 (17.73)	2.7 (9.98)	-0.2 (16.99)
8 hrs Post-Dose					
Mean (SD)	133.9 (12.35)	111.3 (17.08)	90.4 (20.20)	86.2 (18.90)	97.6 (23.39)
Change in Mean	-3.4 (26.78)	-0.6 (17.27)	-1.4 (16.10)	1.6 (12.49)	-0.2 (16.01)

Source: Table 14.3.6.2 Vital Sign Change, Clinical Study Report 2-12 Year Population-Protocol 2012O004

Table 17: Change in Respiratory Rate by Age Group Through 8 Hours Post-Dose

Timepoint	6 months to <2 years (N=8)	2 to 6 years (N=24)	7 to 12 years (N=30)	13 to <17 years (N=35)	Overall (N=97)
Screening					
Mean (SD)	26.7 (7.67)	21.8 (3.03)	20.1 (3.09)	19.4 (2.55)	20.8 (3.85)
Check-in					
Mean (SD)	26.5 (5.92)	25.5 (6.12)	20.8 (4.74)	21.2 (5.45)	22.5 (5.77)
Pre-Dose					
Mean (SD)	31.4 (8.85)	25.3 (7.80)	20.8 (5.01)	20.0 (6.16)	22.5 (7.28)
Median	29.5	23.5	20.0	20.0	22.0
Min, Max	22, 49	11, 44	12, 32	11, 35	11, 49
15 min Post-Dose					
Mean (SD)	27.1 (8.71)	25.6 (9.07)	20.2 (4.60)	20.2 (5.93)	22.1 (7.23)
Change in Mean	-4.3 (10.87)	0.3 (5.44)	-0.5 (4.54)	0.2 (6.68)	-0.4 (6.30)
30 min Post-Dose					
Mean (SD)	28.3 (9.53)	23.0 (5.42)	21.6 (6.97)	18.8 (5.96)	21.5 (6.94
Change in Mean	-3.1 (9.98)	-2.3 (7.04)	0.7 (6.76)	-1.5 (7.37)	-1.1 (7.34)
45 min Post-Dose					
Mean (SD)	25.3 (4.80)	25.1 (7.68)	20.6 (6.39)	19.3 (6.31)	21.7 (7.00)
Change in Mean	-6.1 (8.27)	-0.2 (7.33)	-0.0 (5.83)	-1.0 (8.72)	-0.9 (7.63)
60 min Post-Dose					
Mean (SD)	23.8 (4.06)	23.0 (5.95)	20.8 (6.43)	18.5 (5.42)	20.8 (6.03)
Change in Mean	-7.6 (7.60)	-2.3 (6.34)	-0.1 (6.64)	-1.7 (6.72)	-1.9 (6.85)
1hr 15 min PD					
Mean (SD)	24.6 (4.16)	23.6 (6.38)	21.5 (6.80)	19.8 (4.93)	21.6 (6.04)
Change in Mean	-6.7 (8.48)	-1.7 (7.41)	0.9 (5.61)	-0.2 (7.12)	-0.7 (7.05)
1hr 30 min PD					

Mean (SD)	25.9 (6.62)	22.5 (6.07)	20.6 (4.72)	19.0 (4.89)	20.9 (5.59)
Change in Mean	-5.4 (6.45)	-2.8 (6.60)	0.4 (4.71)	-1.3 (6.93)	-1.5 (6.33)
1 hr 45 min PD					
Mean (SD)	27.0 (4.97)	25.9 (6.87)	21.0 (5.96)	18.6 (5.17)	21.9 (6.63)
Change in Mean	-4.3 (6.24)	0.6 (5.86)	0.5 (6.79)	-1.6 (7.82)	-0.6 (6.97)
2 hr Post-Dose					
Mean (SD)	29.3 (10.92)	24.7 (6.30)	20.7 (4.07)	19.1 (5.89)	21.8 (6.73)
Change in Mean	-2.0 (6.27)	-0.7 (7.85)	0.3 (4.97)	-1.2 (7.34)	-0.7 (6.72)
2 hrs 15 min PD					
Mean (SD)	28.4 (7.04)	24.8 (6.74)	20.0 (5.44)	19.3 (6.08)	21.7 (6.78)
Change in Mean	-2.9 (7.36)	-0.5 (7.68)	-0.6 (6.47)	-0.8 (7.26)	-0.8 (7.07)
2 hrs 30 min PD					
Mean (SD)	27.6 (5.65)	24.6 (4.84)	20.9 (5.28)	18.8 (5.33)	21.6 (5.88)
Change in Mean	-3.7 (5.74)	-0.7 (8.44)	0.4 (5.72)	-1.0 (6.87)	-0.7 (6.92)
2 hrs 45 mins PD					
Mean (SD)	28.0 (6.11)	23.7 (5.78)	20.6 (4.66)	18.3 (5.22)	21.2 (5.94)
Change in Mean	-3.3 (6.78)	-1.6 (7.15)	0.4 (6.32)	-1.4 (7.10)	-1.1 (6.84)
3 hrs Post-Dose					
Mean (SD)	28.3 (7.32)	25.0 (5.21)	19.8 (5.11)	18.4 (5.18)	21.4 (6.24)
Change in Mean	-3.0 (8.41)	-0.3 (8.52)	-0.6 (6.45)	-1.3 (7.88)	-1.0 (7.63)
3 hrs 15 min PD					
Mean (SD)	31.7 (16.29)	24.5 (5.07)	21.2 (5.47)	17.5 (3.71)	21.6 (7.38)
Change in Mean	0.4 (9.34)	-0.8 (7.10)	1.0 (6.53)	-2.2 (7.29)	-0.7 (7.20)
3 hrs 30 min PD					
Mean (SD)	27.0 (6.06)	24.9 (4.63)	21.3 (5.58)	19.7 (6.69)	22.1 (6.26)
Change in Mean	-4.3 (5.88)	-0.4 (7.80)	1.1 (6.40)	-0.1 (8.09)	-0.1 (7.41)
3 hrs 45 mins PD					
Mean (SD)	26.1 (7.24)	24.9 (4.82)	19.8 (4.25)	19.3 (5.85)	21.5 (5.87)
Change in Mean	-5.1 (4.98)	-0.4 (8.57)	-0.8 (5.19)	-0.4 (8.49)	-0.9 (7.47)
4 hrs Post-Dose					
Mean (SD)	29.9 (12.36)	24.5 (5.19)	20.0 (5.21)	18.4 (4.32)	21.4 (6.61)
Change in Mean	-1.4 (6.37)	-0.8 (7.03)	-0.2 (5.91)	-1.3 (6.95)	-0.9 (6.55)
6 hrs Post-Dose					
Mean (SD)	29.7 (7.41)	24.5 (4.34)	19.7 (4.99)	19.5 (4.75)	21.6 (5.83)
Change in Mean	-1.6 (5.22)	-0.3 (5.72)	-0.6 (5.78)	-0.3 (7.62)	-0.5 (6.39)
8 hrs Post-Dose					
Mean (SD)	26.6 (9.29)	25.2 (5.10)	20.7 (3.47)	19.6 (6.13)	21.9 (6.04)
Change in Mean	-4.7 (4.35)	0.3 (7.51)	0.5 (5.06)	-0.2 (8.87)	-0.2 (7.29)

Source: Table 14.3.6.2 Vital Sign Change, Clinical Study Report 2-12 Year Population-Protocol 2012O004

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