

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205777Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

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| Application Type | NDA |
| Application Number(s) | 205-777 |
| Priority or Standard | Standard |
| Submit Date(s) | September 23, 2013 |
| Received Date(s) | September 23, 2013 |
| PDUFA Goal Date | July 23, 2014 |
| Division / Office | Anesthesia, Analgesia and Addiction Products (DAAAP) |
| Reviewer Name(s) | Elizabeth Kilgore, MD |
| Review Completion Date | June 18, 2014 |
| Established Name | Oxycodone/Naloxone |
| (Proposed) Trade Name | Targiniq ER |
| Therapeutic Class | Combination Opioid Analgesic and Opioid Antagonist (Abuse Deterrent Formulation) |
| Applicant | Purdue Pharma L.P. |
| Formulation(s) | Oral tablet |
| Dosing Regimen | Every 12 hours |
| Indication(s) | Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate |
| Intended Population(s) | Adults aged ≥18 years |

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Throughout this review, study drug may be referred to as OXN (oxycodone naloxone), OXN PR, Targiniq or Targiniq ER interchangeably. Oxycodone may be referred to as Oxy, OxyCR, OxyPR, or OxyContin.

This 505(b)(2) NDA references the listed drug Narcan (naloxone hydrochloride [NDA 16-636]) approved April 13, 1971 and cross-references original OxyContin (oxycodone hydrochloride [NDA 20-553]) and reformulated OxyContin (oxycodone hydrochloride [NDA 22-272]), approved April 5, 2010.

The proposed Tradename for this product is Targiniq ER (extended-release) tablets. Approval is recommended for Targiniq ER for the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, based upon the efficacy and safety information included in the submission. However, there are currently two unresolved issues which may affect the approvability of this product : 1) Insufficient exploration by the Applicant to determine the maximum total daily dose and 2) Inadequate DMF support for naloxone. The status of both of these issues is pending at the time of this review and will be addressed in the CDTL memo.

The product is unique because it is a combination product which contains an extended-release opioid analgesic (oxycodone ER) and an opioid antagonist (naloxone) in a 2:1 ratio. The intent of the addition of naloxone is to provide abuse deterrent properties. The dosage units studied included oxycodone/naloxone 10/5 mg, 20/10 mg, 30/15 mg and 40/20 mg. The Applicant is seeking abuse deterrent claims for the IV and nasal routes of administration for dosage strengths of 10, 20 and 40 mg.

Efficacy was established based on findings of pain improvement in Targiniq ER-treated patients compared to placebo-treated patients in one adequate and well controlled clinical trial. There was adequate exposure during clinical trials to inform as to the safety of Targiniq ER and the adverse event profile appeared acceptable in the intended to-be-marketed dosage of up to 40 mg oxycodone/20 mg naloxone every 12 hours. There were some study subjects who exhibited adverse events related to opioid withdrawal, possibly due to systemic exposure to naloxone. The profile of adverse events was, otherwise, generally consistent with a mu-opioid agonist. The dosing recommendations are acceptable based on the data from the clinical development program, however the determination regarding the acceptability of the maximum total daily dose of 80/40 mg per day is pending.

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1.2 Risk Benefit Assessment

The efficacy of Targiniq ER (OXN) was demonstrated in a single, adequate and well-controlled clinical trial, Study ONU3701. This key efficacy clinical trial was conducted as a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm enriched design study in opioid-experienced patients with chronic low back pain who required around the clock opioids in a range of 20 mg to 160 mg morphine equivalents. Patients were converted from their incoming opioid to OXN during the open-label titration period of the study and then randomized to placebo or OXN in fixed doses of 10, 20, 30, or 40 mg every 12 hours for 12 weeks. Dose titrations were allowed but could not exceed a maximum total daily dose of OXN 80/40 mg.

The primary endpoint was the average pain score over the last 24 hours at week 12 of the double-blind period. Statistical significance of the primary endpoint was shown using acceptable imputation methods. In general, the secondary endpoints supported the primary endpoint. Therefore, Targiniq ER was found to be efficacious in the population studied.

From the perspective of risk, the safety data submitted were, overall, consistent with those of the opioid class of drugs. There were no deaths definitely or probably attributable to Targiniq ER and no unexpected or unusual adverse events of special interest were identified. In the investigator-identified cases of opioid withdrawal, there was a slightly higher incidence of "Drug withdrawal syndrome" in the Targiniq ER-treated subjects in the double-blind period compared to placebo being 3% and 2%, respectively. When the adjudicated cases of opioid withdrawal are included, there are 4% of Targiniq ER treated subjects with possible opioid withdrawal compared with 2% in placebo. It is not definitive, however, whether the increased incidence of withdrawal in Targiniq ER-treated subjects is due to the inclusion of naloxone. Most cases identified as drug withdrawal syndrome or possible drug withdrawal (determined by an independent Adjudication Committee) were mild to moderate in severity, resolved spontaneously, and did not require intervention other than dose adjustment or discontinuation of Targiniq ER.

All opioids pose the risk of abuse and misuse. Targiniq ER was formulated with abuse-deterrent properties. At this time, Dr. Jim Tolliver's Controlled Substances Staff (CSS) review is ongoing. However, Dr. Tolliver's preliminary findings are as follows:

Overall, the in vitro physical and chemical manipulation studies and human abuse potential studies indicate that Targiniq ER tablets display resistance to abuse by intravenous and intranasal administration, but not to oral administration. Due to the very low (< 2%) absolute bioavailability of naloxone and to the susceptibility of Targiniq ER tablets to physical and chemical manipulation, Targiniq ER tablets may be susceptible to oral abuse particularly by non-dependent recreational opioid users. In the case of individuals physically dependent upon opioids, oral abuse, including abuse by chewing, of Targiniq ER

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tablets may be reduced due to both tolerance development and the emergence of a withdrawal syndrome, usually mild in intensity.

As an extended-release Schedule II opioid analgesic, the risks (including overdose, misuse and abuse) associated with this product appear similar to other opioids in this class. These risks, however, appear to be manageable with the labeling and REMS and should not preclude approval. The presence of abuse deterrent features may provide an incremental improvement regarding abuse liability.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This product will be under the existing Extended Release/Long-Acting (ER/LA) class-wide opioid Risk Evaluation and Mitigation Strategy (REMS).

The NDA was originally submitted prior to the Agency announcement on September 10, 2013 for class-wide safety labeling changes for all extended-release and long-acting (ER/LA) opioid analgesics. The Applicant subsequently revised pertinent sections of the proposed label following approval of the updated label for OxyContin approved April 15, 2014 as agreed upon with the Agency.

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric plan.

The proposed pediatric plan was discussed at a PeRC (Pediatric Review Committee) meeting on May 28, 2014. The Committee was in agreement with the Applicant's proposal for a partial waiver for ages birth to 6 years as studies are impossible or highly impractical because of the small number of patients in this age group treated with long-term, around-the-clock opioid analgesics and a deferral for PK and safety studies in ages 7 to 17 years (inclusive) with extrapolation for efficacy as adult studies are completed and ready for approval. The proposed timeline to submit the PK/safety protocol to the FDA by December, 2014, initiate the study December, 2015 and submit the final study report by December, 2019 was also acceptable.

2 Introduction and Regulatory Background

2.1 Product Information

The drug product is manufactured using two active pharmaceutical ingredients, oxycodone HCL USP and naloxone HCL USP as OXN (oxycodone/naloxone) in a 2:1 ratio.

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Oxycodone naloxone has been developed in three dosage strengths as OXN 10/5 mg, OXN 20/10 mg and OXN 40/20 mg. Each OXN tablet contains two parts oxycodone HCl (for analgesia) and one part naloxone HCl (for abuse deterrence) on an anhydrous, assay-corrected, mg/mg basis. The upper dose limit for which the Applicant seeks approval is 80/40 mg/day.

The product was developed as a controlled-release oral combination tablet formulated to be dosed daily with one tablet every 12 hours.

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the treatment of moderate-to-severe acute pain, including immediate and extended-release opioids, prescription strength NSAIDs, tramadol, and tapentadol.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients in this combination product are the opioid agonist, oxycodone and the opioid antagonist, naloxone.

Oxycodone: Single-entity oxycodone is available as an extended-release tablet, as immediate-release oral tablets and capsules, and as an oral solution. It is also available in combination with APAP as an immediate-release product.

Naloxone: Naloxone (naloxone HCL) is currently approved in the U.S. under the tradename, Narcan, the listed drug for this NDA as an injection which may be administered intravenously, intramuscularly, or subcutaneously for the “complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids including natural and synthetic narcotics, propoxyphene, methadone and certain narcotic-antagonist analgesics: nalbuphine, pentazocine and butorphanol”. It is also indicated for the diagnosis of suspected acute opioid overdosage. Naloxone injection may also be used as an adjunctive agent to increase blood pressure in the management of septic shock.

Multiple approved drug products containing the active ingredient, naloxone, are available and marketed in the United States (Table 1 below). Most of the approved products are combination products used for maintenance of opioid dependence. The naloxone component of the approved combination drug products is generally included to deter intravenous abuse.

Oral naloxone is available in combination products: 1) Buprenorphine and Naloxone tablet, 2) Pentazocine and naloxone tablet [ANDA]; 3) buprenorphine and naloxone film (soluble) and buprenorphine and naloxone tablet (orally disintegrating).

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Table 1. Brand Name Naloxone Products and Indications

| Drug Product Name | NDA | Approval Date | Dose Form | Indication |
|-----------------------------------|--------|---------------|-----------|---|
| Narcan | 016636 | 4/13/1971 | Injection | Complete or partial reversal of opioid depression, including respiratory depression |
| Talwin NX (pentazocine/naloxone) | 018733 | 12/06/1982 | Tablet | Relief of moderate to severe pain |
| Suboxone (Buprenorphine/naloxone) | 020733 | 10/08/2011 | Tablet | Maintenance treatment of opioid dependence |
| Suboxone (Buprenorphine/naloxone) | 022410 | 8/20/2010 | Film | Maintenance treatment of opioid dependence |
| Zubsolv (Buprenorphine/naloxone) | 204242 | 7/3/2013 | Tablet | Maintenance treatment of opioid dependence |

(Table, Medical Officer Review NDA 205-783, EVZIO [naloxone injection], p. 7)

2.4 Important Safety Issues With Consideration to Related Drugs

Opioids: The risks associated with the use of OXN appear similar to the risks of other immediate-release and extended-release opioids. These risks include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdosage (intended or accidental). The class of opioids, in general, carries label warnings regarding concomitant use with CNS depressants such as alcohol, other opioids, anesthetic agents, sedative hypnotics and skeletal muscle relaxants which can potentiate respiratory depressant effects and increase the risk of adverse outcome.

Naloxone: Naloxone may cause an abrupt and complete reversal of opioid effects leading to withdrawal symptoms (e.g., abdominal cramping, muscle aches, sweating, anxiety, nausea, vomiting, diarrhea). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with use postoperatively and naloxone should be used with caution in patients with pre-existing cardiac disease or who have received potentially cardiotoxic drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were numerous communications between the Agency and the Applicant prior to the NDA submission. The following are key events:

- February 24, 2009 - preIND meeting for IND 70,851
- February 26, 2010 - New IND 70,851 was opened

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- [REDACTED] (b) (4)
- November 18, 2010 – EOP2 meeting
- August 19, 2011 – Written responses were provided to the Applicant from the Agency regarding Study ONU3701
 - Positive results from the phase 3 study ONU3701 could serve as the basis for establishing analgesic efficacy and previously conducted European studies may be supportive
- September 13, 2012– preNDA meeting to support the proposed indication
 - Adequacy of safety database
 - Study ONU3701, the three Phase 3 European studies with open-label extension, and post-marketing experience together with data from Phase 2 and Phase 3 trials appear sufficient to support a safety database for OXN
 - A sufficient number of subjects must be exposed to the highest proposed doses of OXN in order to adequately assess withdrawal
 - A potential safety signal was identified in trials of a peripheral μ-opioid antagonist with possible MACE (Major Adverse Cardiovascular Events). The Sponsor was advised that a premarketing, randomized, controlled trial designed and powered to assess the risk of adverse CV events must be conducted.
 - Inclusion of the dose conversion strategy into the label
 - The Sponsor's approach to data collection for analyzing opioid conversion appeared acceptable and the Sponsor was advised that it was possible that the conversion strategy may be included in the label.
 - The extent to which inclusion of opioid conversion data are included in labeling is currently under discussion within the Agency and the Sponsor's submitted data would be reviewed and considered for inclusion

2.6 Other Relevant Background Information

According to the Oxycodone/Naloxone Company Core Data Sheet dated July 23, 2013, the therapeutic indications of OXN are 1) Pain requiring the use of an opioid analgesic

(b) (4)

[REDACTED]

As of April, 2013, OXN had been approved in a total of 36 countries. It was launched in 20 European Union (EU) and nine non-EU countries prior to December, 2012, the data cut-off date for this NDA. OXN products are marketed in four different strengths at

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present, depending on the specific country, as OXN 5/2.5 mg, OXN 10/5 mg, OXN 20/10 mg and OXN 40/20 mg for twice daily administration.

Per the Applicant, the European approved and marketed OXN product is identical to the US OXN in the following features: (1) active and inactive ingredients; (2) CR formulation; (3) dosage form and strengths; and (4) route of administration.

The Applicant conducted in vitro laboratory studies and clinical human abuse liability studies to support the abuse-deterrent formulation properties of the product. See Dr. Jim Tolliver's CSS review for further discussion regarding these studies.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Although the submission, overall, was of good quality, well organized and easily navigated, there were numerous clinical information requests which were sent to the Applicant during the review process from multiple disciplines. The Applicant responded to these requests in a timely manner.

3.2 Compliance with Good Clinical Practice

All U.S. and non-US clinical studies were conducted in the accordance with applicable regulatory guidances according to the Applicant's statements in the clinical study reports.

According to Dr. Cynthia Kleppinger's June 9, 2014, OSI (Office of Scientific Investigations) Clinical Inspection Summary review, the Division of Scientific Investigations (DSI) conducted three routine inspections [REDACTED] (b) (4). All inspections have been completed [REDACTED] (b) (4).

[REDACTED] Of the remaining three, one site was NAI (no action indicated) and two were VAI (voluntary action indicated) with minor citations. [REDACTED] (b) (4)

[REDACTED] OSI found that, in general, based on the inspection of the three clinical sites, the inspectional findings of these sites support validity of data as reported by the Applicant under this NDA. According to the OSI Inspection Summary Review, observations were based on the preliminary review of the Establishment Inspection Reports and an inspection summary addendum will be generated if conclusions change upon OSI final classification.

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3.3 Financial Disclosures

The Applicant's submission included the completed Form 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators" in compliance with 21CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators, that each clinical investigator had no financial interest to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant for Study ONU3701. See Appendix G of this review for the Clinical Investigator Financial Disclosure Form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Each Targiniq ER tablet contains two parts oxycodone HCL and one part naloxone HCL (2:1 ratio) on an anhydrous, assay-corrected, mg/mg basis.

The oxycodone component of Targiniq ER provides analgesia and the naloxone component is intended to decrease the potential for certain routes of abuse.

Oxycodone, Figure 1, below, is a μ -opioid receptor agonist, with some activity at the κ (kappa) and δ (delta) receptors. Naloxone, Figure 2, is a nonselective, competitive inhibitor of the μ -, κ -, and δ -opioid receptors.

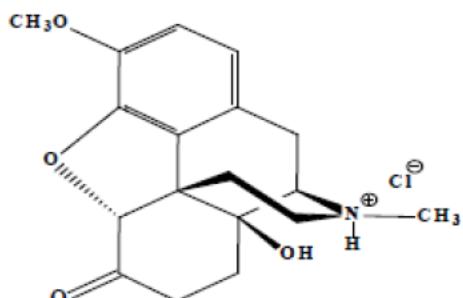
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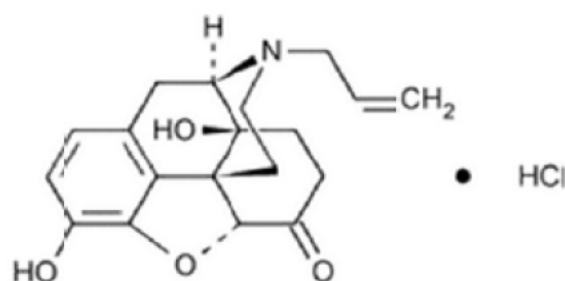
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Figure 1. Pharmacologic Class of Oxycodone HCL (left) and Naloxone HCL (right)



Oxycodone Hydrochloride



Naloxone Hydrochloride

(NDA submission, Introduction, p. 1)

Dr. Eugenia Nashed, CMC reviewer, reported that the controls for inactive ingredients and active ingredient, oxycodone, are acceptable. However, the DMF supporting the active ingredient, naloxone comes from two sources: [REDACTED] (b)(4). A major CMC issue of concern was identified during the review regarding the [REDACTED] (b)(4) DMF ([REDACTED] (b)(4)) supporting naloxone and on June 4, 2014, a General Advice letter was sent to the Applicant informing them that the [REDACTED] (b)(4) DMF for naloxone hydrochloride was found inadequate to support the submission and a deficiency letter was sent to the DMF holder on June 3, 2014. The Applicant's response to this information is pending at the time of this review. Dr. Nashed's CMC review is ongoing at this time.

4.2 Clinical Microbiology

This product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Both oxycodone HCL and Naloxone HCL contain process impurities that are potentially genotoxic, based on substructure alerts. The total intake levels for the potentially genotoxic impurities were calculated based on a maximum daily dose of 80 mg oxycodone and 40 mg naloxone (OXN 40 mg/20 mg q 12 h).

The nonclinical studies indicate that adverse effects in rats and dogs associated with oral administration of OXY/NAL at a 2:1 ratio were attributable to the OXY component and reflected an extension of, or were considered secondary to, the pharmacologic effects of OXY (e.g., hypoactivity and associated reduction in food consumption and/or body weight parameters).

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The sponsor concludes that no specific target organ of toxicity was identified after administration of OXY and NAL as single entities or the OXN combination in the rat or dog. The results of the nonclinical studies performed with the OXY/NAL combination consistently showed that there was no PK interaction (in either direction) between OXY and NAL when they were co-administered at a 2:1 or 12:1 ratio to rats and dogs. The 12:1 ratios were evaluated in the various nonclinical studies to achieve closer alignment with the human plasma concentration data in terms of relative systemic exposure of the two components and to better characterize the safety risk.

Dr. Belinda Hayes's pharmacology/toxicology review is ongoing at this time based on 80 mg/40 mg as the maximum daily dose of Targiniq ER. If additional data is submitted by the Applicant requesting a higher MDD, there may be additional nonclinical issues regarding approvability.

4.4 Clinical Pharmacology

Dr. Srikanth Nallani performed the Agency's Clinical Pharmacology review.

4.4.1 Mechanism of Action

Oxycodone HCL is an opioid agonist, relatively selective for the μ (mu) receptor, although it can interact with κ (kappa) and δ (delta) opioid receptors.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

Naloxone is an antagonist acting on kappa, mu and delta opioid receptors in the brain, spinal cord, and peripheral organs (e.g. intestine, heart, kidney, and lungs). In the CNS, naloxone produces opioid withdrawal effects in opioid-dependent subjects. In opioid receptors located in peripheral organs (e.g. intestine, heart, kidney, and lungs), local competitive antagonism of the opioid receptor mediated oxycodone effect by naloxone can occur.

4.4.2 Pharmacodynamics

The findings were consistent with the known profile of Oxycodone and Naloxone. See Dr. Nallani's review for details.

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4.4.3 Pharmacokinetics

Relative bioavailability study ONU1009 established a PK bridge of each component of oxycodone and naloxone to approved products OxyContin (oxycodone) and Narcan (naloxone). Per Dr. Nallani's review:

Oxycodone from TARGINIQ ER tablets was rapidly absorbed with the median T_{max} 3 to 4 hours following a single oral administration over a range of doses from 10 mg/5 mg to 80 mg/40 mg. About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. Absolute bioavailability of naloxone from OXN tablets was very low ($\leq 2\%$). See Tables 2 and 3 below for details.

Table 2. Pharmacokinetic Parameters for Oxycodone (Mean [SD])

| Regimen | TARGINIQ ER Dose (mg/mg) | AUC (ng•hr/mL)† | C_{max} (ng/mL) | T_{max} (hour) ‡‡ | Trough Conc. (ng/mL) |
|------------------|--------------------------------|-----------------|----------------------|------------------------|-------------------------|
| Single Dose | 10/5 mg | 130 [25.6] | 12.1 [2.67] | 3 [1, 6] | NA |
| | 20/10 mg | 247 [62.7] | 22.2 [4.19] | 3 [1, 6] | NA |
| | 40/20 mg | 506 [128] | 40.9 [9.52] | 3.5 [1, 6] | NA |
| Multiple Dose | 10/5 mg q12h | 129 [33.4] | 15.0 [3.25] | 1.75 [1, 5] | 5.69 [1.78] |
| | 40/20 mg q12h | 507 [100] | 57.0 [10.0] | 2 [0.5, 5] | 24.7 [5.68] |

† for single-dose, AUC = $AUC_{0-\infty}$; for multiple-dose, AUC = AUC_{tau}

‡‡ median (range)

Data obtained from healthy subjects receiving naltrexone.

Table 3. Pharmacokinetic Parameters for Naloxone (Mean [SD])

| Regimen | TARGINIQ ER Dose (mg/mg) | AUC (ng•hr/mL)† | C_{max} (ng/mL) | T_{max} (hour) ‡‡ | Trough Conc. (ng/mL) |
|------------------|--------------------------------|--------------------|----------------------|------------------------|-------------------------|
| Single Dose | 10/5 mg | 0.136 [0.141] | 0.0306 [0.0236] | 5 [1, 12] | NA |
| | 20/10 mg | 0.657 [0.585] | 0.0839 [0.0812] | 1.5 [0.5, 12] | NA |
| | 40/20 mg | 0.833 [0.526] | 0.0845 [0.0834] | 2 [1, 16] | NA |
| Multiple Dose | 10/5 mg q12h | 0.416 [0.367] | 0.0725 [0.0885] | 3.75 [0.5, 8] | 0.0154 [0.00882] |
| | 40/20 mg q12h | 1.55 [1.02] | 0.217 [0.173] | 5 [0.5, 12] | 0.0711 [0.0410] |

† for single-dose, AUC = AUC_{0-t} ; for multiple-dose, AUC = AUC_{tau}

‡‡ median (range)

Data obtained from healthy subjects receiving naltrexone.

(Proposed label and Dr. Srikanth Nallani's Clinical Pharmacology review, p. 50-51)

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant conducted 46 clinical trials and one study (ONU9001) to support this application¹. Throughout this review, the terms clinical trial and study may be used interchangeably as the Applicant did not make a distinction in the submission.

Most of the clinical trials were conducted at non-U.S. sites. The prefix OXN refers to non-U.S. trials and ONU refers to U.S. trials.

Four clinical trials (OXN3001, OXN3006, OXN3401 and OXN2001) had extensions (OXN3001S, OXN3006S, OXN3401S and OXN2001S). In this section of the review, extension trials are counted as separate, individual trials.

The 46 clinical trials in the Integrated Summary of Safety (ISS) are categorized as follows:

- Twenty-two phase 1 studies
 - 15 trials in healthy subjects (single and multiple-dose)
 - Four single-dose, crossover, abuse potential trials: (ONU1003, ONU1004, ONU1007 and ONU1008)
 - Three trials in special groups and situations : OXN1006 (hepatic), OXN1007 (renal) and OXN1017 (Elderly ≥65 years)
- Two phase 2 trials in cancer patients: (OXN2001 + extension OXN2001S)
- Eight Phase 3 trials
 - Two placebo-controlled trials in nonmalignant pain patients (ONU3701 and OXN3401)
 - Three active comparator (OxyCR) controlled trials in nonmalignant pain + OIC (OXN3001, OXN3006, OXN3503). Trial OXN3401 also had an

¹ The Food and Drug Administration Amendments Act of 2007 (FDAAA) distinguishes a study from a clinical trial as follows: *Clinical trials are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Studies are all other investigations, such as investigations with humans that are not clinical trials as previously defined (e.g., observational epidemiologic studies), animal studies and laboratory experiments* ¹.MAPP 6010.3R (12/14/10), p. 9.

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OxyCR arm but was previously included in placebo-controlled trials above and is not counted here again

- Three OxyCR active comparator extension trials OXN3001S, 3006S and 3401S
- One phase 4 codeine/paracetamol active comparator trial (OXN4502)
- One phase 2 dose-finding study (OXN2401) using separate component formulations
- Eight ongoing [as of 12/31/12] Phase 2 or 3 trials (038-002, ONU3704, ONU3705, OXN2503, OXN2504, OXN3504, OXN3505, OXN3506)
- Four postmarketing trials after European approval (038-001, 038-001S, OXN2501, OXN2502)

Study ONU9001, a noninterventional, interview-style study was conducted to determine drug abuse preferences in drug abusers. No drugs were administered during this study and no safety data was obtained. Therefore, Study ONU9001 could not contribute to the ISS, although the CSR was included in the submission.

The ISS consisted of 33 pooled clinical trials and 13 additional clinical trials which were not pooled. The Applicant's pooling strategy is discussed at length in Section 7.1.3 (Review of Safety) of this review.

The 33 clinical trials in the pooled safety database are listed below according to their primary designated pool. The pooled groups which contribute to the ISS are in bold font followed by the studies included in that pool, summarized in Table 4, below.

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Table 4. Clinical Studies in Pooled Safety Database

Phase 3 Group A1A (Placebo-controlled) Clinical Trials

| Study ID | No. of Sites | Design | Population | Endpts ¹ | Treatment Group | Dose | Frequency Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race | | | | |
|---|---|---|---|--|-----------------|--|-----------------|---------------|------------------------------|---|--|--|--|--|--|
| Group A1A Double-blind placebo-controlled studies | | | | | | | | | | | | | | | |
| ONU3701 25-May-2011/ 15-Oct-2012 | 132 US | R, DB, PC, PG, enriched, ph 3 | Inadequately cont M/S, chronic, normalalg NNP, low back pain; opioid experienced, req ATC opioids | AEs, laks, VS, ECG, COWS, mod SOWS | OLT | 10/5, 20/10, 30/15 (20/10+10/5), or 40/20 mg | q12h PO | Up to 28 d | OXY IR | 1924/601/399 DB safety: 600 OXN: 298 PLAC: 302 | M: 262 F: 338 54 (20,85) y W: 77.0% | | | | |
| | | | | | DB | 10/5, 20/10, 30/15 (20/10+10/5), or 40/20 mg | q12h PO | 12 wk | OXY IR | | | | | | |
| A, A1, A1A, C | | | | | | | | | | | | | | | |
| OXN3401 19-Jan-2005/ 10-May-2006 | 100 Austria, Czech Rep., Denmark, Germany, Hungary, Slovakia, Spain | R, DB, PC, AC, DD, PG, enriched, ph 3 | M/S chronic normalalg low back pain req ATC opioids | AEs, laks, VS, PE, ECG, BFI, CSBM, mod SOWS | OLT | 5 mg Titrage to effect (target 20 or 40 mg/d) | q4-6h pm, PO | 14 d | OXY IR | 751/464/402 DB safety: 463 OXN: 154 OXY CR: 151 PLAC: 158 | M: 178 F: 285 56 (22,85) y W: 100% | | | | |
| | | | | | DB | 10/5 &/or 20/10 mg To equal effective OLT dose | q12h PO | 12 wk | OXY IR, lax per invest | | | | | | |
| | | | | | OXN + PLAC | 10 &/or 20 mg To equal effective OLT dose | q12h PO | 12 wk | OXY IR, lax per invest | | | | | | |
| | | | | | DB | 10 &/or 20 mg To equal effective OLT dose | q12h PO | 12 wk | OXY IR, lax per invest | | (31 enrolled (24 R) subjects excluded because of audit findings) | | | | |
| A, A1, A1A, A1B, C | | | | | | | | | | | | | | | |
| Phase 3 Group A1B (Active Comparator-controlled) Clinical Trials | | | | | | | | | | | | | | | |
| Study ID | No. of Sites | Design | Population | Endpts ¹ | Treatment Group | Dose | Frequency Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race | | | | |
| Group A1B Double-blind oxycodone CR-controlled studies | | | | | | | | | | | | | | | |
| OXN3001 05-Jan-2006/ 23-Apr-2007 | 93 Czech Rep., Germany, Spain, UK | R, DB, AC, DD, PG, enriched, ph 3 | M/S chronic normalalg pain req ATC opioids; OIC | AEs, laks, VS, PE, ECG, BFI, mod SOWS, COWS | OLT | 10 &/or 20 mg To achieve 20-50 mg OXY/d | q12h PO | 7-28d | OXY IR, kisacodyl | 525/322/277 DB safety: 322 OXN: 162 OXY CR: 160 | M: 126 F: 196 60 (25,87) y W: 99.4% | | | | |
| | | | | | DB | 10/5 &/or 20/10 mg To achieve OLT dose; allowed titration up to 80 mg OXY/d | q12h PO | 12 wk | OXY IR, kisacodyl | | | | | | |
| A, A1, A1B, C | | | | | | | | | | | | | | | |
| OXN3006 26-May-2006/ 12-Jul-2007 | 86 Czech Rep., Finland, Germany, Hungary, NL, Spain, UK | R, DB, AC, DD, PG, enriched, ph 3 | M/S normalalg chronic pain req ATC opioids; OIC | AEs, laks, VS, PE, ECG, BFI, PACOI, PAC-SYM(b), mod SOWS | OLT | 10, 20, &/or 40 mg To achieve 60-80 mg OXY/day | q12h PO | 7-28 d | OXY IR, kisacodyl | 347/278/222 DB safety: 265 OXN: 130 OXY CR: 135 | M: 84 F: 181 56 (32,84) y W: 100% | | | | |
| | | | | | DB | 10/5, 20/10, &/or 40/20 mg To achieve OLT dose; allowed titration up to 120 mg OXY/d | q12h, PO | 12 wk | OXY IR, kisacodyl | | | | | | |
| | | | | | OXN + PLAC | 10 &/or 20 mg to achieve OLT dose; allowed titration up to 80 mg OXY/d | q12h PO | 12 wk | OXY IR, kisacodyl | | | | | | |
| | | | | | DB | 10, 20, &/or 40 mg To achieve OLT dose; allowed titration up to 120 mg OXY/d | q12h, PO | 12 wk | OXY IR, kisacodyl | | | | | | |

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|--|---|---|--|---|------------------------|--|-------------|--------|----------------------|--|---|
| OXN3503 06-May-2009/ 02-Aug-2010 | 76 Austria, Belgium, Czech Rep., Finland, Germany, Hungary, Israel, Poland, Spain | R, DB, AC, DD, PG, enriched, ph 3 | M/S chronic knee/hip pain due to OA req ATC opioids; OIC | AEs, laks, VS, PE, ECG, BFI, CSBM, lax use, mod SOWS | OLT OXY CR | 5, 10, 20, &/or 40 mg to achieve 20-80 mg OXY/day | q12h, PO | 7-28 d | OXY IR, bisacodyl | 294/210/175 DB safety: 209 OXN: 101 OXY CR: 108 | M: 59 F: 150 63 (29,84) y W: 99.5% |
| | | | | | DB OXN + PLAC | 5/2.5, 10/5, 20/10, &/or 40/20 mg To achieve 60-80 mg OXY/day (max 120 mg/d) | q12h, PO | 12 wk | OXY IR, bisacodyl | | |
| | | | | | DB OXY CR + PLAC | 5, 10, 20, &/or 40 mg To achieve 60-80 mg OXY/day (max 120 mg/d) | q12h, PO | 12 wk | OXY IR, bisacodyl | | |

Additional Clinical Trials in Group A1 (One Codeine/Paracetamol Active Comparator Study (XN4502) +3 OLE Studies for Core Studies 3001, 3006 and 3401

| Study ID | No. of Sites | Design | Population | Endpts ¹ | Treatment Group | Dose | Frequency | Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) |
|--|---|---|--|--|-------------------------|--|-------------|----------------|---|---|--|--------------------------------|
| Additional group A1 studies involving subjects with chronic nonmalignant pain – controlled core/core + open-label extension study (part of groups A, A1, and C; not a separate pool) | | | | | | | | | | | | |
| OXN4502 06-Feb-2009/ 24-Mar-2010 | 36 UK | R, DB, AC, DD, PG, enriched, ph 4 | OA with hip/knee as primary pain site, or M/S chronic low back pain | AEs, laks, VS, PE, ECG, BFI, PAC- SYM(b), lax use | OLT Pre-study med | | | 7-14 d | Bisacodyl | 345/250/135 DB safety: 247 OXN: 124 C/P: 123 | M: 89 F: 158 65 (27,89) y W: 97.6% | |
| | | | | | DB OXN + PLAC | 5/2.5 mg (starting dose), 10/5 mg, &/or 20/10 mg (max dose) | q12h, PO | 12 wk | Ibuprofen with omepraz, bisacodyl | | | |
| | | | | | DB C/P + PLAC | 2 x 15/500 mg (starting dose) &/or 2 x 30/500 mg (max dose) | q6h, PO | 12 wk | Ibuprofen with omepraz, bisacodyl | | | |
| OXN3001S 21 Apr 2006/ 25 Apr 2008 | 93 Czech Rep., Germany, Spain, UK | Uncont, OL, ph 3 Ext | M/S chronic nonmalign pain req continued opioid Rx; completion of OXN3001 DB | AEs, laks, VS, PE, ECG, mod SOWS, BFI | OL OXN | 10/5, 20/10, &/or 40/20 mg Starting dose = OXY dose at end of DB Titration to 20/10-80/40 mg/d | q12h, PO | Up to 52 wk | OXY IR & bisacodyl first 7 d, then per invest | 258/NA/227 Safety: 258 | M: 102 F: 156 60 (26,88) y W: 99.6% | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| OXN3006S 04-Sep-2006/ 14-July-2008 | 57 Czech Rep., Finland, Hungary, Germany, NL, Spain, UK | Uncont, OL, ph 3 Ext | M/S chronic nonmalign pain req continued daily opioid Rx; completion of OXN3006 | AEs, laks, VS, PE, ECG, mod SOWS, BFI | OL OXN | 10/5, 20/10, &/or 40/20 mg Starting dose = OXY CR dose at end of DB Titration up to 120/60 mg/d | q12h PO | Up to 52 wk | OXY IR & bisacodyl first 7 d, then per invest | 216/NA/172 Safety: 216 | M: 73 F: 143 55 (34,84) y W: 100% | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| OXN3401S 17-May-2005/ 27-Apr-2007 | 100 Austria, Czech Rep., Denmark, Germany, Hungary, Slovakia, Spain | Uncont, OL, ph 3 Ext | M/S chronic nonmalign pain req continued daily opioid Rx; completion of OXN3401 | AEs, laks, VS, PE, ECG | OL OXN | 10/5, 20/10, &/or 40/20 mg Starting dose = 20/10 mg/d Titration up to 80/40 mg/d | q12h PO | Up to 52 wk | OXY IR first 7 d, then per invest; lax per invest | 380/NA/296 Safety: 379 | M: 148 F: 231 56 (22,85) y W: 100% | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

Phase 2 Additional Clinical Trials in Group A (Chronic Malignant Pain)

| Study ID | No. of Sites | Country (les) | Design | Population | Endpts ¹ | Treatment Group | Dose | Frequency | Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race |
|----------|--------------|--|---------------------------|--|--|--|--|--|---------|-------------|-------------------------------------|--|---|
| OXN2001 | 64 | Australia, Czech Rep, France, Germany, Hungary, Israel, NL, Poland, UK | R, DB, AC, DD, PG, ph 2/3 | Cancer & M/S chronic cancer pain req ATC opioids; OIC | AEs, labs, VS, PE, ECG, mod SOWS, BFI, lax use | Direct conversion from prestudy opioid to study drug DB OXN + PLAC Titration up to 120 mg OXY/d | DB OXN CR + PLAC Titration up to 120 mg OXY/d | 5/2.5, 10/5, 20/10, &/or 40/20 mg q12h PO Titration up to 120 mg OXY/d | q12h PO | 4 wk | OXY IR & lisacodyl pm or per invest | 224/185/133 DB safety: 184 OXN: 92 OXY CR: 92 | M: 94 F: 90 64 (36,84) y W: 99.5% |
| | | | | | | | | | | | | | |
| OXN2001S | 31 | Czech Rep, France, Germany, Hungary, Israel, NL, Poland, UK | Uncont, OL, ph 2/3 Ext | Cancer & M/S chronic cancer pain req ATC opioids; completion of DB period of OXN2001 or early DC due to constipation | AEs, labs, VS, PE, ECG, mod SOWS, BFI, lax use | OL OXN If on ≤80 mg OXY/d, starting dose = dose at end of DB; otherwise, stepwise conversion Titration up to 120/60 mg/d | OL OXN If on ≤80 mg OXY/d, starting dose = dose at end of DB; otherwise, stepwise conversion Titration up to 120/60 mg/d | 5/2.5, 10/5, &/or 40/20 mg q12h PO Titration up to 120 mg OXY/d | q12h PO | Up to 24 wk | OXY IR & lisacodyl first 7 d | 128/NA/68 Safety: 128 | M: 68 F: 60 64.0 (36, 84) y W: 99.2% |
| | | | | | | | | | | | | | |

15 Clinical Pharmacology Studies in Healthy Subjects

| Study ID | No. of Sites | Country (les) | Design | Population | Endpts ¹ | Treatment Group | Dose | Frequency | Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race |
|----------|--------------|---------------|---|------------------------------|---|--------------------------------------|--|--|--|----------|--|--|--|
| ONU1001 | 1 | US | OL, SD, 2 seq, 2 period, 2-way, R, CO, ph 1 | Healthy vol NTX with each Rx | AEs, labs, VS, PE, ECG, O ₂ sat, | OXN Wilson, NC facility | 10/5 mg | x 1 PO | 2 Rx periods | — | 99/50/48 Safety: 50 Wilson: 25 Bard: 25 | M: 38 F: 12 30 (18,54) y W: 40% | |
| | | | | | | | | | | | | | |
| ONU1002 | 1 | US | OL, SD, R, 2 seq, 2 period, 2-way CO, ph 1 | Healthy vol NTX with each Rx | AEs, labs, VS, PE, ECG, pulse oximetry | OXN from Wilson, NC facility | 40/20 mg | x 1 PO | 2 Rx periods | — | 126/55/48 Safety: 55 Wilson: 29 Bard: 26 | M: 29 F: 26 25 (18,55) y W: 74.5% | |
| | | | | | | | | | | | | | |
| ONU1009 | 1 | US | OL, SD, R, 4 Rx, 4 period, CO, ph 1 | Healthy vol NTX with OXN | AEs, labs, VS, PE, ECG, pulse oximetry | OXN BUP/NAL | 20/10 mg 2/0.5 mg | x 1 PO x 1 SL | 4 Rx periods Min 7-d WO between doses | — | 57/30/27 Safety: 30 OXN: 27 BUP/NAL: 28 | M: 18 F: 12 32 (19,55) y W: 80% | |
| | | | | | | | | | | | | | |
| ONU1003 | 1 | Germany | OL, SD, R, 4 Rx, 4 period, CO, ph 1 | Healthy vol | AEs, labs, VS, PE, ECG | A. OXN B. OXN C. OXN D. OXN | 40/20 mg 10/5 mg 40/20 mg 10/5 mg | x 1 PO, fed x 1 PO, fed x 1 PO, fasted x 1 PO, fasted | 4 Rx periods 7-d WO between doses | — | 59/28/25 Safety: 28 A: 26 B: 26 C: 25 D: 27 | M: 18 F: 10 32 (22,45) y W: 100% | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |

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|---------|---|---|---|---------------------------------|--------------------------|---------------|--------------------|--------------------------------------|---|---|---|
| OXN1004 | 1 | OL, SD, UK (N Ireland) 03-Nov-2004/ 09-Dec-2004 | Healthy vol 4 Rx, 4 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | A. OXN large batch | 4 x 10/5 mg | x 1 PO, fasted | 4 Rx periods | — | 40/40/0 Safety: 40 | M: 31 F: 9 |
| | | | | | B. OXN large batch | 40/20 mg | x 1 PO, fasted | 7-d WO between doses | | A: 10 B: 10 C: 10 D: 10 | 26 (18.48) y W: 100% Note: Study terminated early after 1 Rx period. |
| | | | | | C. OXN small batch | 4 x 10/5 mg | x 1 PO, fasted | | | | |
| | | | | | D. OXN small batch | 40/20 mg | x 1 PO, fasted | | | | |
| OXN1005 | 1 | OL, SD, UK 21-Jun-2007/ 24-Aug-2007 | Healthy vol, M only 5 Rx, 5 period, PC, R, CO, ph 1 | AEs, labs, VS, PE, ECG | A. OXN, radiolabel | 10/5 mg | x 1 PO, fasted | 5 Rx periods | — | 31/15/13 Safety: 15 | M: 15 F: 0 |
| | | | | | B. OXN, radiolabel | 20/10 mg | x 1 PO, fasted | 7-d WO between doses | | A: 14 B: 14 C: 15 | 35 (21.56) y W: 93% |
| | | | | | C. OXY CR, radiolabel | 10 mg | x 1 PO, fasted | | | D: 14 E: 14 | |
| | | | | | D. OXY CR, radiolabel | 20 mg | x 1 PO, fasted | | | | |
| | | | | | E. PLAC, radiolabel | — | x 1, PO, fasted | | | | |
| OXN1008 | 1 | OL, SD, 3 Germany 07-Jul-2005/ 22-Aug-2005 | Healthy vol Rx, 3 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | OXN fasted | 40/20 mg | x 1 PO, fasted | 3 Rx periods | — | 64/29/26 Safety: 29 | M: 18 F: 11 |
| | | | | | OXN fed | 40/20 mg | x 1 PO, fed | 7-d WO between doses | | OXN fast: 27 OXN fed: 26 Liq: 28 | 37 (23.53) y W: 100% |
| | | | | | OXY liq + NAL liq | 20 mg + 10 mg | x 1 PO, fasted | | | | |
| OXN1009 | 1 | OL, SD, 3 UK 09-Jan-2006/ 25-Feb-2006 | Healthy vol Rx, 3 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | OXN fasted | 10/5 mg | x 1 PO, fasted | 3 Rx periods | — | 34/20/18 Safety: 20 | M: 9 F: 11 |
| | | | | | OXN fed | 10/5 mg | x 1 PO, fed | 7-d WO between doses | | OXN fast: 19 OXN fed: 18 Liq: 20 | 30 (21.55) y W: 100% |
| | | | | | OXY liq + NAL liq | 10 mg + 5 mg | x 1 PO, fasted | | | | |
| OXN1011 | 1 | OL, MD, Germany 08-Aug-2005/ 24-Nov-2005 | Healthy vol 3 Rx, 3 period, R, CO, ph 1 NTX with each Rx | AEs, labs, VS, PE, ECG | OXN | 40/20 mg | q12h PO | 3 Rx periods, | — | 76/34/28 Safety: 32 | M: 28 F: 6 |
| | | | | | OXY CR | 40 mg | q12h PO | 3.5 d each | | OXN: 30 OXY CR: 31 | 37 (19.52) y W: 100% |
| | | | | | NAL CR | 2 x 10 mg | q12h PO | 7-d WO between dose periods | | NAL CR: 30 | |
| OXN1013 | 1 | OL, SD, 4 UK 19-Feb-2007/ 24-Apr-2007 | Healthy vol, M only Rx, 4 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | OXN slow dissol | 20/10 mg | x 1 PO, fasted | 4 Rx periods | — | 33/18/17 Safety: 18 | M: 18 F: 0 |
| | | | | | OXN | 20/10 mg | x 1 PO, fasted | 7-d WO between doses | | Slow: 17 Medium: 17 Fast: 18 Liq: 17 | 40 (19.54) y W: 89% |
| | | | | | medium dissol | | | | | | |
| | | | | | OXN fast dissol | 20/10 mg | x 1 PO, fasted | | | | |
| | | | | | OXY liq + NAL liq | 10 mg + 5 mg | x 1 PO, fasted | | | | |

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|----------------|---|--------------------------------|---|---|--|---|--|--|--|--|---|
| OXN1016 | 1 | OL, SD, 5 UK | Healthy vol Rx, 5 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | A. OXN prod scale B. OXN prod scale C. OXN prod scale D. OXN lab scale E. OXN lab scale | 10/5 mg 40/20 mg 10/5 mg 10/5 mg 40/20 mg | x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted | 5 Rx periods 7-d WO between doses — — — — | — A: 30 B: 30 C: 30 D: 30 E: 30 — — | 52/30/30 Safety: 30 A: 30 B: 30 C: 30 D: 30 E: 30 — — | M: 16 F: 14 26 (18,53) y W: 87% |
| | | | B, C | | | | | | | | |
| OXN1018 | 1 | OL, SD, UK (N Ireland) | Healthy vol 4 Rx, 4 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | A. OXN B. OXN C. OXY liq + NAL liq D. OXY CR | 5/2.5 mg 5/2.5 mg 5/2.5 mg 5 mg | x 1 PO, fasted x 1 PO, fed x 1 PO, fasted x 1 PO, fasted | 4 Rx periods 7-d WO between doses — — | — A: 24 B: 24 C: 24 D: 24 | 24/24/24 Safety: 24 A: 24 B: 24 C: 24 D: 24 | M: 10 F: 14 32 (18,54) y W: 100% |
| | | | B, C | | | | | | | | |
| OXN1403 | 1 | OL, SD, 4 Germany | Healthy vol Rx, 4 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG, pulse oximetry | A. OXN B. OXN C. OXN D. OXY CR + NAL CR | 4 x 10/5 mg 2 x 20/10 mg 1 x 40/20 mg 2 x 20 mg + 2 x 10 mg | x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted | 4 Rx periods 7-d WO between doses — — | — A: 25 B: 26 C: 26 D: 24 | 46/28/23 Safety: 28 A: 25 B: 26 C: 26 D: 24 | M: 22 F: 6 32.3 (mean) (24, 42) y W: 100% |
| | | | B, C | | | | | | | | |
| OXN1505 | 1 | OL, SD, 3 UK (N Ireland) | Healthy vol Rx, 3 period, R, CO, ph 1 | AEs, labs, VS, PE, ECG | OXN fasted OXN fed OXY liq + NAL liq | 80/40 mg 80/40 mg 20 mg + 10 mg | x 1 PO, fasted x 1 PO, fed x 1 PO, fasted | 3 Rx periods 7-d WO between doses — — | — A: 24 OXN fast: 24 OXN fed: 23 Liq: 24 | 86/28/23 Safety: 28 A: 24 OXN fast: 24 OXN fed: 23 Liq: 24 | M: 16 F: 12 27 (18,51) y W: 100% |
| | | | B, C | | | | | | | | |
| OXN1506 | 1 | OL, SD, 7 UK (N Ireland) | Healthy vol Rx, 5 period, R, incomp CO, ph 1 | AEs, labs, VS, PE, ECG | A. OXN B. OXN C. OXN D. OXN E. OXN F. OXN (ref) G. OXN (ref) | 2.5/1.25 mg 15/7.5 mg 30/15 mg 60/30 mg 80/40 mg 10/5 mg 40/20 mg | x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted x 1 PO, fasted | 5 Rx periods Min 7-d WO between doses — — — — | — A: 32 B: 32 C: 31 D: 31 E: 31 F: 32 G: 32 | 105/48/40 Safety: 48 A: 32 B: 32 C: 31 D: 31 E: 31 F: 32 G: 32 | M: 33 F: 15 28 (18,54) y W: 100% |
| | | | B, C | | | | | | | | |

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Four Abuse Potential Studies ±PK (Group C Pool)

| Study ID | No. of Sites | Treatment Group | Frequency Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) | | | | |
|---|--|---|--|---|---|--|--------------------------------|--|-----------------|---|--|
| Data Pool | Country (ies) | Design | Population | Endpts ¹ | Dose | | Predom Race | | | | |
| Abuse potential studies ± pharmacokinetics (group C) | | | | | | | | | | | |
| ONU1003 | 1 Canada 08-Sep-2010/ 08-Feb-2011 | DB, PC, 3 PGs, R, CO, ph 1 NAL as part of screen | Healthy vol; moderate experience with non-therapeutic opioids; able to tolerate study drug & discriminate from PLAC | AEs, labs, VS, PE, ECG, telemetry | 1. OXN chewed OXY liq PLAC | 40/20 mg 40 mg — | x 1 PO | 3 Rx periods/group 5- to 7-d WO between doses | — | 1. 65/16/14 Safety: 16 2. 140/27/23 Safety: 27 3. 114/24/22 Safety: 24 | 1. M: 14 F: 2 38 (19,54) y W: 87.5% 2. M: 20 F: 7 31 (20,50) y W: 77.8% 3. M: 21 F: 3 34 (20,54) y W: 87.5% |
| | | | | AEs, labs, VS, PE, ECG | 2. OXN crushed OXY powder PLAC | 40/20 mg 40 mg — | x 1 IN | | | | |
| | | | | | 3. OXY | 0.07 mg/kg | x 1 IV | | | | |
| | | | | | OXY + NAL | 0.07 mg/kg + 0.035 mg/kg | x 1 IV | | | | |
| | | | | | PLAC | — | x 1 IV | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| ONU1004 | 1 Canada 08-Oct-2010/ 14-Mar-2011 | DB, PC, R, block-order CO (2 blocks, 3 Rx per block), ph 1 | Healthy vol with opioid dependence; on stable methadone regimen | AEs, labs, VS, PE, ECG | 1.OXN chewed OXY liq PLAC | 30/15 mg 30 mg — | x 1 PO | 2 Rx blocks, ≥3-d WO between blocks | Methadone | 55/18 & 16/16 Safety: 18 & 16 | 1. M: 9 F: 9 32 (22,46) y W: 94.4% 2. M: 9 F: 7 31 (22,38) y W: 93.8% |
| | | | | | 2.OXN chewed OXY liq PLAC | 60/30 mg 60 mg — | x 1 PO | 3 Rx periods/block, 24-h WO between doses | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| ONU1007 | 1 Canada 09-Jan-2012/ 11-Apr-2012 | DB, 4 Rx, triple dummy, 4 period, R, CO, ph 1 | Healthy vol; moderate experience with non-therapeutic opioids; able to tolerate study drug & discriminate from PLAC | AEs, labs, VS, PE, ECG | OXN OXN chewed OXY liq PLAC | 40/20 mg 40/20 mg 40 mg — | x 1 PO | 4 Rx periods, 5- to 7-d WO between doses | — | 112/37/36 Safety: 36 OXN: 36 OXN chewed: 36 OXY liq: 36 PLAC: 37 | M: 32 F: 5 39 (24, 52) y W: 78.4% |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| ONU1008 | 1 Canada 01-May-2012/ 31-Oct-2012 | DB, triple dummy, 4 Rx, 4 period, R, CO, ph 1 | Healthy vol with opioid dependence; on stable methadone regimen; able to discriminate study drug from PLAC | AEs, labs, VS, PE, ECG, cardiac telemetry, pulse oximetry | OXN intact OXN chewed OXY liq PLAC | 60/30 mg 60/30 mg 60 mg — | x 1 PO | 4 Rx periods, 48-h WO between doses | Daily methadone | 118/33/29 Safety: 33 OXN: 31 OXN chewed: 31 OXY liq: 31 PLAC: 29 | M: 21 F: 12 33 (23,55) y W: 100% |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

Studies Involving Special Groups or Situations (Group C Pool)

| Study ID | No. of Sites | Treatment Group | Frequency Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) | | | | |
|-----------|---|------------------|---|------------------------|-------------------|--|--------------------------------|----|-----|---|---|
| Data Pool | Country (ies) | Design | Population | Endpts ¹ | Dose | | Predom Race | | | | |
| OXN1006 | 3 Czech Rep 15-Aug-2005/ 09-Feb-2006 | OL, SD, PG, ph 1 | Healthy vol or hepatic impairment (mild, moderate, or severe by Child Pugh grading) | AEs, labs, VS, PE, ECG | OXN | 10/5 mg | x 1 PO, fasted | SD | --- | 29/NA/24 Safety: 24 Healthy: 6 Mild: 6 Moderate: 6 Severe: 6 | M: 13 F: 11 52 (38,61) y W: 100% |

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|---------|---|---|---|---------------------------------|-----|---------|-------------------|--------------------|----|---|---|
| OXN1007 | 1 Czech Rep 03-Aug-2005/ 19-Dec-2005 | OL, SD, PG, ph 1 | Healthy vol or renal impairment (mild, moderate, or severe per creatinine clearance) | AEs, laks, VS, PE, ECG | OXN | 10/5 mg | x 1 PO, fasted | SD | -- | 35/NA/24 Safety: 24 Healthy: 6 Mild: 6 Moderate: 6 Severe: 6 | M: 12 F: 12 54 (28,64) y W: 100% |
| OXN1017 | 1 UK 15-May-2006/ 05-Jul-2006 | OL, MD, elderly vs younger subjects, ph 1 | Healthy vol, half elderly (≥ 65 y) & half younger subjects, ph 1 (18-45 y) | AEs, laks, VS, PE, ECG | OXN | 10/5 mg | q12h, PO | 3.5 d (7 doses) | -- | 72/NA/36 Safety: 39 elderly: 18 young: 21 | M: 18 F: 21 43 (19,77) y W: 97% |

Abbreviations: AC = active control; ATC = around-the-clock; AE = adverse event; BFI = Bowel Function Index; BUP = buprenorphine; cont = controlled; CO = crossover; COWS = Clinical Opiate Withdrawal Scale; C/P = codeine/paracetamol; CR = controlled-release; CSBM = complete spontaneous bowel movement; d = day(s); DB = double-blind; DC = discontinuation; DD = double dummy; dissol = dissolution; ECG = electrocardiogram; endpt = endpoints; Ext = extension; F = female subjects; h = hour(s); ID = identification; IN = intranasal(ly); incomp = incomplete; invest = investigator; IR = immediate-release; IV = intravenous(ly); Kg = Kilogram(s); lab = laboratory; labs = clinical laboratory tests; lax = laxative(s); liq = liquid; M = male subjects; max = maximum; MD = multiple dose; med = medication; mg = milligram(s); min = minimum; mod = modified; mo = month; MOR = morphine tablets; M/S = moderate to severe; N = Northerm; NA = not applicable; NAL = naloxone; NC = North Carolina; NL = Netherlands; NNP = non-neuropathic; no. = number; nonmalign = nonmalignant; NR = not reported; NTX = naltrexone; O₂ sat = oxygen saturation; OA = osteoarthritis; OIC = opioid-induced constipation; OL = open-label; OLT = open-label titration; omepraz = omeprazole; OOWS = Objective Opiate Withdrawal Scale; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets; PACOI = patient assessment of opioid-induced constipation summary score; PAC-SYM(b) = Patient Assessment of Constipation Symptoms and Bothersomeness; PC = placebo control; PE = physical examination; PG = parallel group; ph = phase; PLAC = placebo; PO = by mouth (orally); pop = population; predom = predominant; prn = as needed; prod = production; q = every; R = randomized; ref = reference; Rep = Republic; req = requiring; Rx = treatment; SD = single dose; seq = sequence; SL = sublingual; SOWS = Subjective Opiate Withdrawal Scale; UK = United Kingdom; uncont = uncontrolled; US = United States; VS = vital sign(s); W = white; WHO = World Health Organization; wk = week(s); WO = washout; y = year(s).

¹ Whether classified as safety or efficacy endpoints in the actual study, bowel function endpoints were considered safety endpoints in the Integrated Summary of Safety and, therefore, in this table.

(SCS, p. 149-162)

Thirteen studies were not pooled because their study designs differed considerably from the pooled trials, used a formulation different from the pooled trials, or were ongoing. The tables for these studies are provided in Appendix F (Non-pooled Studies) of this review. These non-pooled trials included one dose-finding study, four postmarketing studies after European approval (two studies in nonmalignant LBP (low back pain), one study in OIC (opioid induced constipation) and nonmalignant pain, and one study evaluating the use of OXN with pregabalin vs pregabalin alone in diabetic polyneuropathic pain), and eight ongoing phase 2 and 3 studies assessing OIC and nonmalignant pain and/or malignant pain and one study in Parkinson's disease pain.

The 120-day safety update, submitted to the NDA on January 14, 2014, contained information compiled from January 1, 2013 through April 30, 2013. During that period, two clinical trials (OXN3505 and OXN1507) conducted in the EU were completed and narratives were provided for fatal SAEs, non-fatal SAEs and discontinuation AEs. The results from these two studies were not integrated into the safety database as the Applicant determined that they provided limited additional safety information (i.e., one was a 4-week Phase 3 study and the other a Phase 1 study in healthy volunteers). I agree with the Applicant's determination not to include these studies in the pooled ISS. Eight trials were ongoing during the reporting interval and CIOMS (Council for International Organizations of Medical Sciences) forms corresponding to fatal and non-fatal SAEs reported to the international drug safety database were provided. Postmarketing data was also updated in the 120-day report.

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5.2 Review Strategy

The Phase 1 studies were reviewed primarily for pertinent safety sections. The full protocols and final reports for the key efficacy study ONU3701 and synopses of all Phase 2 and Phase 3 studies included in the submission were read. Data from individual study reports, Summary of Clinical Safety, ISS, ISE, proposed annotated label, consultant reviews, literature, approved labels of OxyContin and naloxone and other pertinent sections of the NDA submission were read and included in the review as appropriate.

Although relevant safety data from all pooled and non-pooled clinical trials were reviewed, safety data from the key efficacy study ONU3701 and data from pooled Group A1A (studies ONU3701 and OXN3401) represent the most clinically important data as these were Phase 3, enriched, randomized-withdrawal, placebo-controlled trials in a pain population (the intended population for the to-be-marketed product). Therefore, the safety and efficacy sections of this review focus on these studies in more detail in most cases. Studies ONU3701 and OXN3401 were designed to test the superiority of OXN compared to placebo with respect to analgesic efficacy in subjects with low back pain.

The other clinically important safety pool was Group A1B (Phase 3, double-blind, enriched design, oxycodone-controlled studies). Studies OXN3001 and OXN3006 were designed to evaluate the efficacy of OXN compared with OxyCR in managing OIC in subjects with moderate to severe nonmalignant pain. Study OXN3503 evaluated the noninferiority of OXN analgesic efficacy compared to OxyCR and its superiority for improving symptoms of constipation in subjects with moderate to severe pain due to osteoarthritis of the knee and/or hip. These studies provide comparative safety data for OXN compared to Oxy CR.

Additional studies in Group A1 which provided key safety information were the extension studies (long-term use of study drug).

Other supporting documents included in the submission which were reviewed include:

- In response to the Agency's concerns about the potential for μ antagonists to precipitate ischemic cardiovascular events, the submission included a document titled, *Evaluation of Cardiovascular Events*. Dr. Preston Dunmon, Division of Cardiovascular and Renal Products, was consulted with regard to the cardiovascular safety.
- A detailed rationale of the conversion tables used to convert subjects from prior opioids to OXN treatment was provided in a document titled, *Strategy for Converting to OXN and OxyCR*. Findings from this document were incorporated into the review as needed.

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- The issue of abuse deterrence was addressed in a report titled, *Evaluation of Drug Abuse Liability*. Dr. Jim Tolliver, CSS, provided the Agency's review regarding abuse liability findings and recommendations.
- Opioid withdrawal and reasons for discontinuation were designated as specific safety concerns prior to NDA submission. Documents pertinent to this issue included 1) *Adjudication Plan* for Study ONU3701 and ISS and 2) *Final Adjudication Report* for Study ONU3701 and ISS. I reviewed the reports from the independent Adjudication Committee included in the Adjudication Plan and Final Adjudication Report for assignment of opioid withdrawal cases and the Discontinuation Reason Adjudication Committee (DRAC) findings for determination of primary and secondary reasons for discontinuation. The key findings from these specific reports are included in this review under the appropriate Safety section 7.
- Postmarketing safety was evaluated based upon the submission data and Periodic Safety Update Reports (PSURS) in a document titled, *Reports of Postmarketing Experience*.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant identified 11 studies which comprise the controlled and open-label extension studies in chronic nonmalignant or malignant pain used to provide primary and supportive efficacy.

The protocol for key efficacy study ONU3701 is described in detail in this section of the review. The efficacy results for study ONU3701 are discussed in Section 6 (Review of Efficacy). The other 10 studies providing supportive efficacy are summarized following key efficacy study ONU3701 in this section of the review.

Key Efficacy Study ONU3701

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Trial with an Enriched Design to Assess the Efficacy and Safety of Oxycodone/Naloxone Controlled-release Tablets (OXN) Compared to Placebo in Opioid-experienced Subjects with Moderate to Severe Pain due to Chronic Low Back Pain who Require Around-the-clock Opioid Therapy

Date Issued: The original protocol was dated March 10, 2011. Protocol Amendments 1, 2 and 3 were dated April 13 and May 11, 2011, and April 5, 2012, respectively. The protocol was submitted to IND 70,851.

Objective: The primary objective was to have been the assessment of efficacy and safety of OXN compared to placebo in opioid-experienced subjects with moderate to severe pain due to chronic low back pain who required around-the-clock opioid therapy.

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Population: A total of 600 males and females aged 18 or older with nonmalignant low back pain for at least three months were to have been randomized (300 in each of the two treatment groups)

Duration: The duration of the study was to have included a Screening period (up to 10 days); an Open-label titration period (up to 28 days); a Double-blind period (84 days); and a 7 day Safety follow-up period

Study Design: This was to have been a double-blind, placebo-controlled, parallel group, randomized, enriched design study

Study Drugs:

- OXN: 10/5, 20/10, 30/15 mg and 40/20 mg tablets every 12 hours taken orally during the open-label titration and double-blind periods
- Matching placebo as above
- OxyIR (oxycodone immediate release) 5mg allowed as rescue medication for breakthrough low back pain

Study Conduct: The study was to have consisted of 3 phases comprising 4 periods (see Figure 2) below:

- Pre-randomization phase included the screening period (up to 14 days) and an open-label titration period (up to 28 days, during which subjects were switched from their incoming opioids to OXN)
- Double-blind phase included the double-blind period (12 weeks post-randomization)
- Safety follow-up phase included the safety follow-up period (1 week after double-blind period completion or early discontinuation)

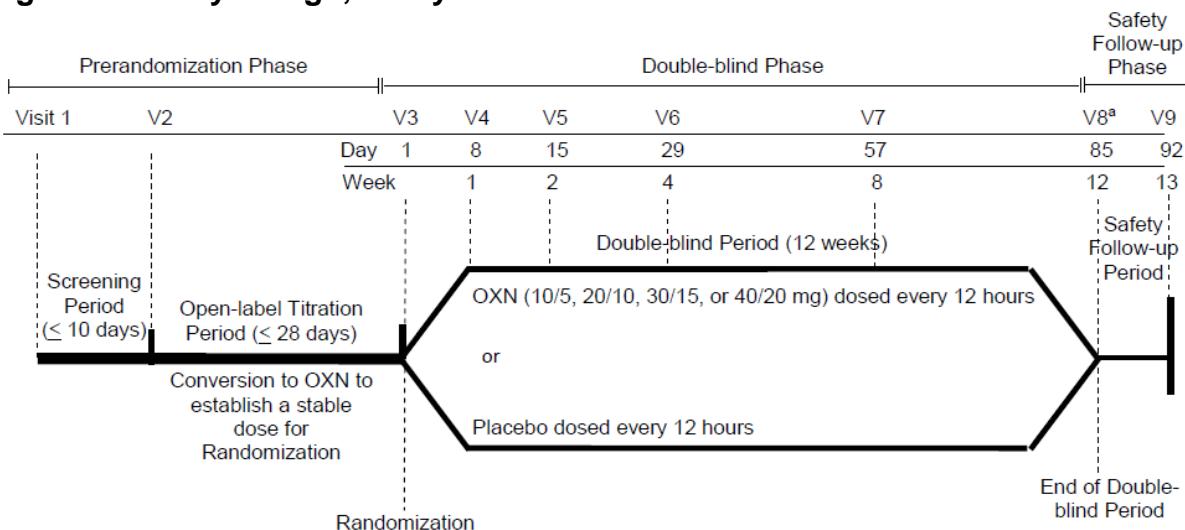
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Figure 2. Study Design, Study ONU3701



a Visit 8 is the end of the double-blind period; procedures associated with this visit will be conducted for subjects who discontinue the study early. Visit 9 will occur approximately 7 days after visit 8 for a follow-up safety assessment. The figure shows scheduled visits. An unscheduled study drug discontinuation visit, unscheduled study drug discontinuation safety follow-up visit, and other unscheduled visits for dose adjustments may occur as necessary.

V=visit.

Note: Durations in the double-blind period are given relative to the date of visit 3. During the first 2 to 10 days of the double-blind period, subjects randomized to placebo group will be tapered off OXN and the OXN group will receive dummy taper tablets to maintain the blinding of the taper. After the first 10 days of the double-blind period, a subject's dose may be down titrated 1 dose level 1 time, and may subsequently be titrated back to the starting dose.

(CSR 3701, p. 23)

Overview: Each subject who entered the 12-week double-blind period must have demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period to be randomized to receive either OXN or matching placebo, based on their OXN dose at the end of the open-label titration period. OxyIR (oxycodone immediate-release) was allowed for breakthrough pain except during the 30 hours preceding study visits 5 through 8 (double-blind).

Key Inclusion Criteria

1. Male and female subjects ≥ 18 years of age with moderate-to-severe, chronic low back pain (LBP) lasting at least several hours daily as their predominant pain condition for at least three months prior to screening period
2. Nonmalignant and nonneuropathic LBP without radiation or with only proximal radiation (above the knee); i.e., meeting Quebec Task Force Classification 1 or 2
3. Must have been on opioid analgesic therapy for low back pain which
 - a. Had been ongoing for at least 4 weeks prior to the screening visit and
 - b. Consisted of a stable opioid regimen at a total average daily dose equivalent to 20 to 160 mg (inclusive) of morphine for the last 2 weeks

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prior to the screen visit. Subjects taking tramadol \geq 100 mg daily on stable regimen for the last 2 weeks prior to the screening visit were also to have met this criterion

4. Must have required continuation of opioid analgesic treatment in the range of 20 to 160 mg (inclusive) of morphine or its equivalent daily and be likely to benefit from chronic opioid therapy for the duration of the study
5. Must have had an average pain over the last 14 days' score \geq 5 on an 11-point NRS at the screening visit on their current opioid analgesic medication

Key Exclusion Criteria

1. Any subjects who, in the opinion of the investigator, exhibited significant opioid withdrawal during the open-label phase such that they should not be in the study
2. Unable or unwilling to agree to completely stop all incoming opioid and nonopioid analgesic medications and other medications used for chronic pain (excluding herbal and neutraceutical medications as per the inclusion criteria). NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen may have been used intermittently during the course of the study for headache, fever, or acute pain other than low back pain; low dose aspirin for cardiovascular disease prophylaxis was allowed. Muscle relaxants may be used intermittently during the course of the study for treatment of acute muscle spasms. Medications such as antiepileptics and antidepressants may be continued only if not used for chronic pain
3. History of malignancy within the past 2 years, with the exception of basal cell carcinoma that had been successfully treated
4. Current uncontrolled depression or other uncontrolled psychiatric disorder (subjects with controlled depression or other psychiatric disorder must have been on stable medication for at least 1 month prior to the screening visit [visit 1] to participate in the study)
5. Evidence of impaired liver/kidney function upon entry into the study defined as aspartate aminotransferase (AST; SGOT) or alanine aminotransferase (ALT; SGPT) $>$ 3 times the upper limit of normal (ULN); alkaline phosphatase levels $>$ 2 times ULN; total bilirubin level $>$ ULN; creatinine 2 mg/dL; or in the investigator's opinion, liver and/or kidney disease to the extent the subject should not participate in this study
6. An average QTcF of $>$ 460 msec at the screening visit

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7. Currently taking, or who had taken naloxone, naltrexone, methylnaltrexone, or alvimopan within 10 days before the screening visit
8. History of opioid, alcohol, medication, or illicit drug abuse or addiction
9. Positive result on urine drug testing for illicit drugs or non-prescribed opioids or with a positive breath alcohol result at visit 1

Schedule of Activities: See Table 5 below which describes the schedule of visits and procedures.

Table 5. Schedule of Visits and Procedures Protocol ONU3701

| Procedure | Prerandomization Phase | | Double-blind Phase | | | | | | | | | Safety Follow-up |
|--|------------------------------------|---|--------------------|----------------|----------------|--------------|--------------|--------------|--------------------|-----------------|---------------------------------------|---------------------------|
| | Screening Period (≤ 10 days) | Open-label Titration Period (≤ 28 days) | Double-blind Phase | | | | | | | | | Safety Follow-up (1 week) |
| | | | V 3 (randomize) | | V 4 (wk 1) | V 5 (wk 2) | V 6 (wk 4) | V 7 (wk 8) | Unscheduled SDD | V 8 ESD (wk 12) | Unscheduled SDD FU Visit ^a | |
| | | | TF | RAND | (± 2 d) | (± 2 d) | (± 3 d) | (± 3 d) | Visit ^b | (± 3 d) | (± 2 d) | |
| ICF | X | | | | | | | | | | | |
| Subject Number assignment | X | | | | | | | | | | | |
| Entry criteria | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Concomitant medications/therapies | X | X | X | X | X | X | X | X | X | X | X | |
| Physical examination | X | | X | | | | | | | X | X | |
| ECG ^c | X | | X | X | | | | X | X | X | X | X ^d |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | |
| Serum pregnancy test ^e | X | | X | X | | | | X | | X | X | |
| Clinical laboratory tests (blood, urine) | X | | X | X | | | | X | | X | X | |
| Urine drug and breath alcohol testing | X | | X | X | | | | X | | X | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X |
| PG (DNA) sample (optional) | X | | | | | | | | | | | |
| PG (RNA and protein) sample (optional) ^f | X | | X | X | | | | | | X | X | |
| Blood Sample for OXN Concentrations | | | X | | ◀→▶ | | X | ◀→▶ | X | X | X | |
| Opioid treatment evaluation | X | X | | | | | | | | | | |
| Conversion to OXN | | | X | | | | | | | | | |
| Drug dispensing and/or accountability ^g | | | X | X | X | X | X | X | X | X | X | |
| OXN and immediate-release oxycodone HCl ^h treatment | | | X | X | X | X | X | X | X | | | |
| Distribution/collection of diary | | | X | X | | | | | | X | X | |
| Review of diary data | | | X | X | X | X | X | X | X | X | X | |
| Randomization | | | | | X | | | | | | | |
| 2 days before visit: remind subject to abstain from pain rescue ⁱ | | | | | | | X | X | X | | X | |
| Confirm subject abstained from pain rescue ^j | | | | | | | X | X | X | | X | |
| Subject Evaluations | | | | | | | | | | | | |
| NRS (average pain over the last 24 hours) ^k | X | X | | X | | X | X | X | X | X | X | |
| NRS (pain right now) ^k | | X | | X | X | X | X | X | X | X | X | |
| NRS (average pain over the last 14 days) ^k | X | | | | | | | | | | | |
| OXN intake | | | X | | X | X | X | X | X | X | X | |
| Immediate-release oxycodone HCl intake | | | X | | X | X | X | X | X | X | X | |
| MOS Sleep Scale | | | X | | X | | | X | X | X | X | |
| BPI-SF | | | X | | X | | X | X | X | X | X | |
| Oswestry Disability Index (ODI) | | | X | | X | | X | X | X | X | X | |
| Modified SOWS | X | X ^m | X | X ^m | X ^m | X | X | X | X | X | X | X |
| PGIC | | | | | | | | | | X | X | |

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| | | | | | | | | | | | |
|---------------------------|----------------|----------------|---|---|---|---|---|---|---|---|---|
| COWS | X | X | X | X | X | X | X | X | X | X | X |
| Abuse and diversion | | | X | X | X | X | X | X | X | X | |
| Final subject disposition | X ^j | X ^j | X | | | | | X | X | | |

V = visit; wk = week; d = days; SDD = study drug discontinuation; ESD = early study discontinuation; FU = follow-up; PG = pharmacogenomic; MOS = Medical Outcomes Survey; BPI-SF = Brief Pain Inventory-Short Form; PGIC = Patient Global Impression of Change. At visit 3, TF= Titration Failure subject procedures; RAND = randomized subject procedures.

- a Three 12 lead ECGs at each time point, with a minimum of 10 minutes between each ECG.
- b For women who are premenopausal or postmenopausal for less than 1 year, and who have not had surgical sterilization. Women will be required to use effective (in the opinion of the investigator) contraception throughout the study.
- c "Average pain over the last 24 hours" will be also recorded daily, using the diary, during the open-label titration and the double-blind periods.
- d "Pain right now" will be recorded before each dose of immediate-release oxycodone HCl supplemental pain medication taken, using the diary, for low back pain during the open-label titration and the double-blind periods.
- e Subjects will also complete the modified SOWS daily during the open-label titration period and from visit 3 until visit 5 of the double-blind period (using the diary).
- f "Unscheduled SDD visit" procedures will be performed for subjects that discontinue study drug for any reason before completing all 84 days of the Double-blind Period and continue in the study and complete all remaining clinic visits and procedures. The "unscheduled SDD visit" procedures should be completed as soon as possible after discontinuing study-drug (within 2 days). Importantly, the subject should record their "pain over last 24 hours" score, using the diary, at the time of discontinuation of study-drug.
- g "Unscheduled SDD FU Visit" procedures will be performed for subjects who discontinue study drug for any reason before completing the double-blind period, and continue in the study and complete all remaining clinic visits and procedures. The "Unscheduled SDD FU Visit" procedures should be completed 1 week after study drug discontinuation. Each subject will only have one safety follow-up visit. The subject who has completed "unscheduled SDD FU visit" will not have safety follow-up visit 9.
- h These assessments are not required for the subsequent regularly scheduled visits after the unscheduled SDD visit for subjects who discontinued study drug early and completed the remaining study visits.
- i Blood samples for OXN (oxycodone HCl and naloxone HCl [and naloxone-3-glucuronide]) concentrations will be collected at visit 3 for all randomized subjects, at visit 6, at any visit during the double-blind period at which a subject is noted to have a COWS score ≥ 13 and/or an adverse event of opioid withdrawal, and at the first visit post the last dose of double-blind study drug (visit 8/early study discontinuation or unscheduled study drug discontinuation visit), see section 9.4.3.
- j Only for screening failures.
- k Only for the subject who has an average QTcF value > 500 msec at the unscheduled study drug discontinuation visit.
- l Only for the subject who has an average QTcF value > 500 msec at the open-label titration failure visit or visit 8/early study discontinuation.

(CSR 3701, p. 35-36)

Key Procedures:

I) Prerandomization Phase

- *Screening [Visit 1]:* Must have met inclusion criteria
- *Open-label Titration/Conversion Period [Visit 2]*
 - Subjects were to have discontinued all incoming long-acting opioid medication and other prohibited medications as per protocol
 - In order to qualify for entry into the open-label titration period, subjects were to have met all the following criteria at visit 2:
 - Average pain over the last 24 hours' score ≥ 5 (on an 11-point NRS)
 - Total average daily opioid dose over the screening period equivalent to 20 to 160 mg (inclusive) morphine. Subjects taking tramadol ≥ 100 mg daily on a stable regimen for the last 2 weeks prior to the screening visit (visit 1) could also have met this criterion.
 - Continued to be an appropriate candidate for the study, in the investigator's opinion
 - Subjects were to have been converted from their current opioid therapy to OXN at an oxycodone dose approximately equivalent to the current therapy based on the conversion chart (see Appendix A and B) and in accordance with the investigator's judgment.
 - Rescue OxyIR (5mg) was to have been available for breakthrough low back pain at a dose of one or two tablets every 4 hours as needed, up to eight pills daily
 - Dose titration was to have been conducted based on individual tolerability and analgesic effectiveness until a stable dose was achieved.
 - The dose of OXN could have been uptitrated every one to two days as needed.
 - Down titrations were to have been made at any time by the investigator for safety and/or tolerability.
 - OXN was never to exceed 40/20 mg every 12 hours.

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- When a stable, effective, and tolerable dose was achieved, the subject was to schedule Visit 3. See Double blind entry criteria (described in Double-blind Phase section below) for the definition of a stable and effective dose.

Randomization [Visit 3]

- If the investigator confirmed that the subject continued to be an appropriate candidate for the study and could be stabilized on one of the four OXN regimens then the subject was to have proceeded to the randomization visit (visit 3), which must have occurred within 28 days after visit 2.
- Subjects were to have been randomized in a 1:1 fashion to either the established stable dose of OXN or matched placebo dosed every 12 hours.
- For any subjects who could not achieve a stable, effective, and tolerable dose within 28 days of visit 2, the Titration Failure procedures were to have been performed at visit 3.

II) Double-blind Phase [Visits 3 through 8]

- Double-blind Period Entry Criteria: In order to enter the double-blind phase, the subject was to have achieved a stable and effective dose of OXN. To be considered as having achieved a stable and effective OXN dose, the subject must have met the following criteria for a period of seven consecutive days, after having discontinued any incoming nonopioid medications requiring tapering:
 - Remained on the same dose of OXN during the seven consecutive days, and
 - Had an average pain over the last 24 hours' score on an 11-point NRS of ≤ 4 and at least two points lower than their screening mean pain score (where screening mean pain is defined as the mean of the average pain over the last 24 hours' score collected at visits 1 and 2) for the last three days out of these seven days, and
 - Not taken more than two OxyIR 5 mg pills on any given day during these seven days
- During the first two to ten days of the double-blind period, subjects randomized to placebo group were to have been tapered off OXN and the OXN group was to have received dummy taper tablets to maintain the blinding of the taper as per Table 6 below.

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Table 6. Blinded Taper for Subjects Randomized to Matching Placebo

| Dose of OXN | Initial Blister Card (sufficient for 10 days) | | | | | | | | | |
|-------------|---|-------|-------|-------|-------|-------|-------|-------|-------|--------|
| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 |
| 10 mg q12h | AM 10 | 10 | x | x | x | x | x | x | x | x |
| | PM | x | x | x | x | x | x | x | x | x |
| 20 mg q12h | AM 20 | 20 | 10 | 10 | 10 | 10 | x | x | x | x |
| | PM | 10 | 10 | 10 | x | x | x | x | x | x |
| 30 mg q12h | AM 20 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | x | x |
| | PM | 20 | 20 | 10 | 10 | 10 | x | x | x | x |
| 40 mg q12h | AM 30 | 30 | 20 | 20 | 20 | 10 | 10 | 10 | 10 | 10 |
| | PM | 30 | 30 | 20 | 20 | 10 | 10 | 10 | x | x |

Doses given in mg oxycodone; all drugs are dispensed as OXN with the appropriate naloxone dose.

Subjects will also have access to supplemental analgesic medication (i.e., 1 immediate-release oxycodone HCl 5-mg pill twice daily) during the taper.

(CSR, p. 75)

- After the first ten days of the double-blind period, a subject's dose may have been downtitrated one dose level one time and may subsequently have been titrated back to the starting dose
- Subjects may have taken one OxyIR 5 mg pill up to two times per day as supplemental (rescue) pain medication but were not to take the OxyIR for 30 hours prior to Visits through 8.

III) Safety Follow-up Phase [7 days post completion/early discontinuation]

- All subjects were to have returned to the study center one week after the open-label titration failure, double-blind completion or early study drug discontinuation

Outcome Measures Assessments

- Efficacy Assessments:
 - The primary efficacy variable was to have been the average pain over the last 24 hours' score obtained at Visits 5 through 8. The primary efficacy outcome was to have been the average pain over the last 24 hours at week 12 of the double-blind period.
 - The secondary efficacy variables were to have been the following:
 - Sleep Disturbance Subscale of MOS (Medical Outcomes Study) Sleep Scale (assessed at Visits 6, 7, and 8)
 - PGIC [Patient Global Impression of Change] (assessed at Visit 8 or at the time of early study discontinuation)

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- Pain Responder Analysis (percentage of reduction from the screening mean pain score to the average pain over the last 24 hours' score week 12)
- Safety Assessments: Safety was to have been assessed using adverse events, Clinical Opioid Withdrawal Scale (COWS), modified Subject Opioid Withdrawal Scale (SOWS), clinical laboratory tests, vital signs and ECGs. (See Schedule of Activities, Table 5) for frequency of assessments.
- PK Assessments
 - OXN (oxycodone HCL and naloxone HCL [and naloxone-3-glucuronide]) plasma concentrations were to have been measured as follow:
 - During the double-bind period at Visit 3 (all randomized subjects); Visit 6 (week 4 of the double-blind period for all subjects); First visit post the last dose of double-blind study (Visit 8 for subjects who completed the study, early discontinuation for subjects who discontinued the double-blind study drug early and discontinued from the study at the same time, or at the unscheduled study drug discontinuation visit)
 - Visits with a COWS score ≥ 13 or an adverse event of opioid withdrawal.
- Pharmacogenomics (optional): Samples of DNA, RNA and protein obtained at visits per protocol (See Schedule of Activities, Table 5)

Efficacy Endpoints

- Primary: Average pain over the last 24 hours score at week 12 of the double-blind period
- Secondary: (1) Supplemental pain medication for low back pain, (2) Sleep Disturbance Subscale of the MOS Sleep Scale , (3) PGIC, and (4) Responder Analysis

Other Efficacy Variables Assessment

- Exploratory efficacy variables: (1) Supplemental pain medication for LBP (average daily number of pills of OxyIR using during the double-blind period after the blinded taper), (2) Oswestry Disability Index (ODI), (3) Pain Right now score on 11-point NRS during the OLT and DB periods before taking OxyIR, (4) Brief Pain Inventory- Short Form (BPI-SF) and (5) Weekly Average of the Average Pain Over the Last 24 hours' score during the double-blind

Statistical Methods

- Sample size determination: The Applicant determined that based on available chronic pain studies with similar designs and comparable study populations, the observed effect size for different extended release opioids ranged from 0.3 to 0.35 if a single imputation method such as LOCF was applied. Based on the Applicant's analysis of statistical software simulations, the estimated sample size was 300 subjects per treatment arm, for an overall number of 600 subjects to be randomized to the double-blind treatment
- Populations analyzed
 - *Enrolled Population:* The enrolled population consisted of all subjects who provided informed consent.
 - *Safety Population:* The safety population consisted of subjects who received at least one dose of open-label study drug.
 - *Randomized Safety Population:* The randomized safety population consisted of subjects who were randomized and received at least one dose of the double-blind study drug.
 - *Full Analysis Population (FAP):* The FAP was the group of subjects who were randomized and received at least one dose of double-blind study drug.
 - *Per Protocol Population:* The per protocol population was a subset of the FAP and consists of all subjects in the FAP who were not considered major protocol violators. Criteria for defining the per protocol set was to have been fully defined in the Statistical Analysis Plan before unblinding the study.
- Primary Efficacy Analyses
 - The planned analysis of the primary efficacy variable was to have used an expansion upon the traditional MMRM analysis. The analysis was to have been an adaptation of a hybrid single imputation approach that accounts for sources of variability introduced by the missing data mechanism.
 - Screening mean pain score was defined as the mean of the "average pain over the last 24 hours' scores recorded at visits 1 and 2. Pre-randomization mean pain score was calculated as the average pain over the last 24 hours' score averaged over the last three days prior to randomization. The primary efficacy analysis,

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the average pain over the last 24 hours' scores during the double-blind period were the ones collected at study visits 5-8 (weeks 2, 4, 8 and 12)

- Descriptive statistics were to have been presented for the average pain over the last 24 hours by treatment and by time point.
- Secondary Efficacy Analyses
 - MOS –Mixed effect linear model with repeated measures
 - PGIC – Descriptive statistics
 - Responder Response – Percent reduction in pain using a Cochran-Mantel-Haenszel (CMH) model
- Interim Analyses: None planned
- AdHoc Analyses: None planned

Protocol Amendments: The original Protocol was dated March 10, 2011, and the study was initiated May, 2011. There were three protocol amendments summarized in Table 7 below. Amendments 1 and 2 would not have affected the overall efficacy or safety results since they were implemented prior to patient enrollment. See Dr. Feng Li's statistical review for details regarding Amendment 3 on the final statistical analyses.

Table 7. Amendments to Protocol

| Amendment Number | Date Issued | Key Revisions |
|------------------|-------------|---|
| 1 | 4/13/11 | <ul style="list-style-type: none">• Screening period was extended up to 14 days• Conversion ratio from tapentadol to morphine was included in the conversion table |
| 2 | 5/11/11 | <ul style="list-style-type: none">• Conversion ratio from Buprenorphine to morphine was included in the conversion table |
| 3 | 4/5/12 | <ul style="list-style-type: none">• Numerous changes were made to the statistical analyses to address FDA's concerns regarding the use of retrieved dropout data when one of the patterns of missing data was based on discontinuations due to AEs. |

(Table, reviewer)

Reviewer's Comments: Protocol ONU3701 was adequately designed to assess the primary endpoint. The opioid conversion tables and opioid taper regimen were acceptable.

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Other Individual Efficacy Studies

The Applicant's ISE (Integrated Summary of Efficacy) included a total of 10 non-U.S. studies to support efficacy: (1) four Phase 3 active- and/or placebo-controlled studies OXN3001, OXN3006, OXN3503 and OXN3401 which were randomized, double-blind, multicenter clinical trials with 12-week double-blind periods with extension studies for OXN3001, OXN3006 and OXN3401 in nonmalignant pain patients, (2) one 4-week Phase 2 study (OXN2001) and its 24-week open label extension study (OXN2001S) in malignant pain patients, and (3) one 12- week, Phase 4 study (OXN4502) which compared OXN with codeine/paracetamol in nonmalignant pain due to OA of the knee/hip.

The Applicant concluded the following regarding supportive efficacy:

- Placebo-controlled study OXN3401 showed that OXN was superior to placebo and similar to OxyCR in analgesic efficacy for 12 weeks' duration
- OxyCR comparator studies revealed that OXN was similar to OxyCR in analgesic efficacy for 12 weeks' duration
- Open-label extension studies found that stable pain control was maintained for OXN for an additional 52 weeks
- Malignant pain population studies revealed that OXN was similar to OxyCR in analgesic efficacy through 4 weeks and pain control was maintained for up to an additional 24 weeks
- Chronic knee/hip OA study showed that OXN was similar to codeine/paracetamol in analgesic efficacy through 12 weeks

Findings from the 10 efficacy studies above are not discussed in detail in this review as the Division previously communicated to the Applicant that these studies would provide supportive data only and that the key study for determining efficacy for this submission would be Study ONU3701. The Applicant's supportive efficacy findings were not confirmed or analyzed by the Agency's statistical review team.

The summary table below provides the key parameters including study design, primary pain endpoint and the Applicant's efficacy conclusions for the primary and supportive efficacy studies.

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Table 8. Primary and Supportive Efficacy Studies

| Study ID/ No. Sites/ Location/ Year Completed | Features (Phase, Treatment Period, Control) | Patient Population | Number of Randomized ¹ /Completed Subjects by Treatment Arm | Key Pain Assessment Endpoint | Mean Age [Range] (years) | Sex (%M/%F) | Race | Key Pain Efficacy Conclusion |
|---|---|---|--|---|----------------------------------|--|------|--|
| Pivotal Placebo-Controlled Study | | | | | | | | |
| ONU3701 132 US 2012 | Phase 3, 12-week DB, placebo | Moderate to severe, chronic, nonmalignant, nonneuropathic, low back pain inadequately controlled by a prior opioid analgesic | 298/218 OXN 10/5, 20/10, 30/15 ² , or 40/20 mg q12h 302/181 Placebo q12h | Primary Endpoint: Average pain over last 24 h at wk 12 from an 11-point Numerical Rating Scale | 53 [20 – 85] 43.7%/56.3% | 77.0% White 19.0% Black 4.0% Other | | OXN was superior to placebo in analgesic efficacy through 12 wks. |
| Supportive Placebo- and OXY CR-Controlled Study | | | | | | | | |
| OXN3401 100 Europe 2006 | Phase 3, 12-week DB, placebo and OXY CR | Moderate to severe chronic low back pain that has been adequately controlled by an opioid analgesic | 154/136 OXN 10/5 or 20/10 mg q12h 151/133 OXY CR 10 or 20 mg q12h 158/133 Placebo q12h | Primary Endpoint: Time to multiple (ie, recurring) pain events during DB period | 56.3 [22 – 85] 38.4%/61.6% | 100% White | | OXN was superior to placebo and similar to OXY CR in analgesic efficacy through 12 wks. |
| Supportive OXY CR-Controlled Studies | | | | | | | | |
| OXN3001 93 Europe 2007 | Phase 3, 12-week DB, OXY CR | Moderate to severe chronic nonmalignant pain | 162/144 OXN 10/5 or 20/10 mg q12h 160/133 OXY CR 10 and 20 mg q12h | Secondary Endpoint ³ : Average pain over the last 24 h from PIS at each visit | 58.8 [25 – 87] 39.1%/60.9% | 99.4% White 0.3% Black 0.3% Other | | OXN was similar to OXY CR in analgesic efficacy through 12 wks. |
| OXN3006 86 Europe 2007 | Phase 3, 12-week DB, OXY CR | Moderate to severe chronic nonmalignant pain | 130/108 OXN 10/5, 20/10, or 40/20 mg q12h 135/114 OXY CR 10, 20, or 40 mg q12h | Secondary Endpoint ³ : Average pain over the last 24 h from PIS at each visit | 56.8 [32 – 84] 31.7%/68.3% | 100% White 0 Black 0 Other | | OXN was similar to OXY CR in analgesic efficacy through 12 wks. |
| OXN3503 81 Europe, Israel 2010 | Phase 3, 12-week DB, OXY CR | Moderate to severe pain due to osteoarthritis of the knee/hip | 101/88 OXN 5/2.5, 10/5, 20/10, or 40/20 mg q12h 108/87 OXY CR 5, 10, 20, or 40 mg q12h | Primary Endpoint ³ : WOMAC VA3.1 scale score during DB period | 63.2 [29 – 84] 28.2%/71.8% | 99.5% White 0 Black 0.5% Other | | OXN was similar to OXY CR in analgesic efficacy through 12 wks. |
| Uncontrolled Open-Label Extension Studies | | | | | | | | |
| OXN3401S 100 Europe 2007 | Phase 3, 52-week OL, uncontrolled | Moderate to severe chronic low back pain that has been adequately controlled by an opioid analgesic | 380/296 OXN 10/5, 20/10, or 40/20 mg q12h | Average pain over last 24 h from BPI-SF at each visit | 56.2 [22 – 85] 39%/61% | 100% White 0 Black 0 Other | | Stable pain control was maintained with OXN for up to an additional 52 wks. |
| OXN3001S 93 Europe 2008 | Phase 3, 52-week OL, uncontrolled | Moderate to severe chronic nonmalignant pain | 258/227 OXN 10/5, 20/10, or 40/20 mg q12h | Average pain over the last 24 h from PIS at each visit | 58.4 [26 – 88] 39.5%/60.5% | 99.6% White 0 Black 0.4% Other | | Stable pain control was maintained with OXN for up to an additional 52 wks. |
| OXN3006S 57 Europe 2008 | Phase 3, 52-week OL, uncontrolled | Moderate to severe chronic nonmalignant pain | 216/172 OXN 10/5, 20/10, or 40/20 mg q12h | Average pain over the last 24 h from PIS at each visit | 55.9 [34 – 84] 33.8%/66.2% | 100% White 0 Black 0 Other | | Stable pain control was maintained with OXN for up to an additional 52 wks. |
| Other Studies | | | | | | | | |
| OXN2001 64 Europe, Australia, Israel 2010 | Phase 2, 4-week DB, OXY CR | Moderate to severe cancer pain | 92/66 OXN 5/2.5, 10/5, 20/10, or 40/20 mg q12h 92/67 OXY CR 5, 10, 20, and 40 mg q12h | Primary Endpoint ³ : Average pain score over last 24 h from BPI-SF at wk 4 | 63.1 [36 – 84] 51.1%/48.9% | 99.5% White 0.5% Black 0 Other | | OXN was similar to OXY CR in analgesic efficacy through 4 wks. |

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| | | | | | | | |
|--|---|---|--|--|----------------------------------|---|---|
| OXN2001S 31 Europe, Israel 2010 | Phase 2, 24-week OL, uncontrolled | Moderate to severe cancer pain | 128/68 OXN 5/2.5, 10/5, 20/10, or 40/20 mg q12h | Average pain over last 24 h from BPI-SF at wk 24 | 62.5 [36 – 84] 53.1%/46.9% | 99.2% White 0.8% Black 0 Other | Stable pain control was maintained with OXN for up to an additional 24 wks. |
| OXN4502 36 UK 2010 | Phase 4, 12-week DB, C/P | Moderate to severe chronic, nonmalignant pain due to osteoarthritis of the knee/hip or lower back pain | 124/61 OXN 5/2.5, 10/5, or 20/10 q12h 123/74 C/P 15/500 or 30/500 mg 2 tablets q6h | Primary Endpoint: Average pain over the last 24 h from BS-11 at wk 12 | 64.1 [27 – 89] 36.0%/64.0% | 97.6% White 1.2% Black 1.2% Other | OXN was similar to C/P in analgesic efficacy through 12 wks. |

BPI-SF = Brief Pain Inventory-Short Form; BS-11 = 11-point Box Scale; C/P = codeine/paracetamol; DB = double-blind; h = hours; F = females; M = males; OL = open-label; OXN = oxycodone/naloxone controlled release tablets; OXY CR = oxycodone controlled-release tablets; PIS = Pain Intensity Scale; q6h = every 6 hours; q12h = every 12 hours; UK = United Kingdom; US = United States; VA = visual analogue; wk = week; WOMAC VA3.1 = Western Ontario and McMaster Universities Osteoarthritis Composite Index visual analog scale

¹ Randomized subjects who received at least 1 dose of double-blind study drug in the controlled studies or at least 1 dose of open-label study drug in the extension studies.

² The 30/15 mg dose was composed of a 20/10 mg tablet and a 10/5 mg tablet.

³ Bowel Function Index was a primary or co-primary endpoint.

(ISE, p. 24-26)

Other Studies Included in Submission

In addition to key efficacy study ONU3701 and the 10 supportive efficacy studies (which also contribute to the safety database) already discussed, the other studies in the integrated summary of safety include 15 Phase 1 clinical pharmacology studies, four abuse potential and three special groups studies. The abuse potential and special groups studies are not covered in this section but are described in Section 7 (Review of Safety) as needed when discussing the safety findings for those studies.

Table 9 summarizes the 15 clinical pharmacology studies in healthy subjects are summarized below. Eight of the Phase 1 studies used naltrexone block.

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Table 9. Phase 1 Studies Key Characteristics

| Protocol | N | Design | Single (SD)/ Multiple (MD) Dose/population | Treatment Groups ¹ | Duration of Treatment |
|----------|------|------------------------|--|---|---|
| ONU1001 | N=55 | Randomized, DB, 2xC | SDX, Healthy Sub. | OXN 10/5 mg (North Carolina facility) OXN 10/5 mg (UK facility) | 1 day, 7 days WO 1 day |
| ONU1002 | N=55 | Randomized, DB, 2xC | SDX, Healthy Sub. | OXN 40/20 mg (North Carolina facility) OXN 40/20 mg (UK facility) | 1 day, 7 days WO 1 day |
| ONU1009 | N=24 | Randomized, OL, 4xC | SDX, Healthy Sub. | OXN 20/10 mg tab. fasted OXY CR 20 mg tab. fasted Buprenorphine 2 mg + Naloxone 0.4 mg sublingual, fasted Naloxone 0.4 mg i.v., fasted | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1003 | N=28 | Randomized, OL, 4xC | SDX, Healthy Sub. | OXN 10/5 mg tab. fasted OXN 10/5 mg tab. fed OXN 40/20 mg tab. fasted OXN 40/20 mg tab. fed | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1004 | N=40 | Randomized, OL, 4xC | SDX, Healthy Sub. | 4x OXN 10/5 mg large batch tab. 1x OXN 40/20 mg large batch tab. 4x OXN 10/5 mg small batch tab. 1x OXN 40/20 mg small batch tab. | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1005 | N=15 | Randomized, OL, 5xC | SDX, Healthy Sub. | OXN 10/5 mg tab. OXN 20/10 mg tab. OXY CR 10 mg tab. OXY CR 20 mg tab. Placebo tab. | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1008 | N=29 | Randomized, OL, 3xC | SDX, Healthy Sub. | 1x OXN 40/20 mg tab. fasted 1x OXN 40/20 mg tab. fed OxyIR 20 mg + Naloxone 10 mg liquid | 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1009 | N=20 | Randomized, OL, 3xC | SDX, Healthy Sub. | OXN 10/5 mg tab. fasted OXN 10/5 mg tab. fed OxyIR 10 mg + Naloxone 5 mg, liquid | 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1011 | N=34 | Randomized, OL, 3xC | MD, Healthy Sub. | OXN 40/20 mg tab. OXY CR 40 mg tab. 2x Naloxone CR 10 mg tab. q12h | 4 days, 7 days WO 4 days, 7 days WO 4 days |
| OXN1013 | N=18 | Randomized, OL, 4xC | SDX, Healthy Sub. | OXN 20/10 mg tab. slow dissolution OXN 20/10 mg tab. medium dissolution OXN 20/10 mg tab. fast dissolution OxyIR 10 mg + Naloxone 5-mg liquid | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1016 | N=30 | Randomized, OL, 5xC | SDX, Healthy Sub. | OXN 10/5 mg prod-scale tab. OXN 40/20 mg prod.-scale tab. +NX OXN 10/5 mg prod.-scale tab. + NX OXN 10/5 mg lab.-scale tab. OXN 40/20 mg lab.-scale tab. + NX | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1018 | N=24 | Randomized, OL, 4xC | SDX, Healthy Sub. | OXN 5/2.5 mg tab. fasted OXN 5/2.5 mg tab. fed OxyIR 5 mg + Naloxone 2.5 mg solution fasted OXY CR 10 mg tab. fasted | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| ONU1403 | N=28 | Randomized, 4xC | SDX, Healthy Sub. | 4x OXN 10/5 mg tab. 2x OXN 20/10 mg tab. 1x OXN 40/20 mg tab. 2x OXY CR 20 mg + 2x Naloxone CR 10 mg tab. | 1 day, 7 days WO 1 day, 7 days WO 1 day, 7 days WO 1 day |
| OXN1505 | N=28 | Randomized, 3xC | SDX, Healthy Sub | 1x OXN 80/40-mg tab. fasted +NX 1x OXN 80/40-mg tab. fed +NX 1x OxyIR 20 mg + Naloxone 10 mg, liquid, fasted +NX | 1 day, 7 days WO 1 day, 7 days WO 1 day |

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| | | | | | |
|---------|------|--------------------|------------------|---|---|
| OXN1506 | N=48 | Randomized, 5xC | SDX, Healthy Sub | 1 x OXN 2.5/1.25 mg tab. + NX 1 x OXN 15/7.5 mg tab. + NX 1 x OXN 30/15 mg tab. + NX 1 x OXN 60/30 mg tab. + NX 1 x OXN 80/40 mg tab. + NX 1 x OXN 10/5 mg tab. + NX 1 x OXN 40/20 mg tab. + NX | 1 day, 7 days WO 1 day |
|---------|------|--------------------|------------------|---|---|

¹ Naltrexone blockade was used in ONU1001, ONU1002, ONU1009, OXN1008, OXN1011, OXN1016, OXN1505 and OXN1506. SDX = single dose; MD=multiple dose; OL=Open-label titration; DB=double-blind; WO = wash-out; n x C=n-way crossover study; NX = Naltrexone; tab. = tablet

(ISS, SAP, p. 382-383)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

6.1.1 Methods

The Applicant has conducted one Phase 3 study, ONU3701, to be used as the key study to assess the safety and efficacy of oxycodone/naloxone to support the proposed indication as noted above.

This section of the review will report the findings of key study ONU3701 in detail. The Applicant's other supportive efficacy studies have been briefly summarized and discussed in Section 5.

See Section 5 for the detailed study design of Study ONU3701. In summary, Study ONU3701 was a phase 3, enriched-design, multicenter, randomized, 12-week, double-blind, placebo-controlled, parallel-group study conducted in the U.S. to assess the safety and efficacy of OXN compared with placebo in opioid-experienced subjects with moderate to severe, nonneuropathic, nonmalignant chronic low back pain who required around-the-clock opioid therapy.

Prior to randomization, each subject must have demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label, flexible-dose titration period. Qualified subjects were then randomized to receive either OXN (1 of 4 regimens: 10/5 mg, 20/10 mg, 30/15 mg, or 40/20 mg, given every 12 hours [q12h]) or matching placebo, based on their OXN dose at the end of the open-label titration period.

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6.1.2 Demographics

The demographics and baseline characteristics were generally well balanced between the placebo and OXN groups for the randomized safety population, as shown in Table 10. Most subjects were white (77% in both OXN and Placebo groups), female (58% placebo vs 54% OXN) with a mean age of 53 years for both groups.

Table 10. Study ONU3701 Summary of Demographic and Baseline Characteristics: Randomized Safety Population

| Variable | Placebo (N=302) | OXN (N=298) | Total (N=600) |
|--------------------------------------|--------------------|----------------|------------------|
| Age (years) | | | |
| N | 302 | 298 | 600 |
| Mean (SD) | 53.0 (10.97) | 53.5 (11.69) | 53.2 (11.33) |
| Median | 53.5 | 54.0 | 54.0 |
| Min, Max | 20, 85 | 20, 85 | 20, 85 |
| Sex, n (%) | | | |
| Male | 126 (41.7) | 136 (45.6) | 262 (43.7) |
| Female | 176 (58.3) | 162 (54.4) | 338 (56.3) |
| Race, n (%) | | | |
| White | 233 (77.2) | 229 (76.8) | 462 (77.0) |
| Black or African American | 61 (20.2) | 53 (17.8) | 114 (19.0) |
| Asian | 3 (1.0) | 8 (2.7) | 11 (1.8) |
| American Indian or Alaska Native | 3 (1.0) | 1 (0.3) | 4 (0.7) |
| Other | 2 (0.7) | 7 (2.3) | 9 (1.5) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 29 (9.6) | 43 (14.4) | 72 (12.0) |
| Not Hispanic or Latino | 273 (90.4) | 255 (85.6) | 528 (88.0) |
| Body Mass Index (kg/m ²) | | | |
| N | 300 | 294 | 594 |
| Mean (SD) | 31.29 (7.484) | 31.22 (7.698) | 31.26 (7.584) |
| Median | 30.30 | 30.20 | 30.25 |
| Min, Max | 17.1, 72.2 | 15.2, 62.0 | 15.2, 72.2 |

Cross Reference: [Table 14.1.2.2; Appendix 16.2.4.1](#)

Note: N = Number of subjects in the population; n = Number of subjects with data. SD = Standard deviation.

(CSR 3701, p. 102)

Medical Histories

In general, there were no major differences in the medical histories between randomized placebo and OXN arms. There was a difference of ≥5% between treatment groups in medical diagnoses in placebo vs OXN, respectively in the following: hypertension (45% vs 50%), hyperlipidemia (14% vs 20%) and intervertebral disc degeneration (26% vs 18%).

Prior and Concomitant Therapies

The types of prior medications were expansive with 100% of subjects randomized to placebo or OXN reported having received at least one type of prior medication. The medications were categorized by Anatomic Class, Pharmacological Class and Pharmacological Sub-class. The anatomic class with the highest incidence of prior use reported was the Nervous System due to the sub-classes of *Opioids* (100% placebo vs

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99% OXN) and *Other Analgesic and Antipyretics* (83% placebo vs 78% OXN) primarily because entry criteria required subjects to be on opioids. The *Cardiovascular System* was the Anatomic Class with the next highest incidence (61% placebo vs 66% OXN) driven by a large variety of cardiovascular pharmacological classes and sub-classes of medications. The prior medications for low back pain treatment were similar between the randomized placebo and OXN-treated subjects in both incidence and pharmacological classes.

The overall incidence of concomitant medication use was similar between the two groups with 73% placebo having used a concomitant medication during the double-blind period vs 71% OXN. The pharmacologic classes of the medications varied but there were no major patterns noted between the groups with regard to concomitant medication use which should have affected efficacy.

Rescue Medication Usage

The incoming morphine equivalent doses of subjects in the two treatment groups of the double-blind period were similar.

The average pain score before randomization was three for both groups. The percentage of subjects who took an average of >1 and ≤2 supplemental (rescue) pills was greater for the placebo group (35%) than the OXN group (28%) and considerably greater in placebo (4%) vs OXN (2%) for those using >2 average daily rescue pills as shown in Table 11 below.

Table 11. Summary of Supplemental (Rescue) Pain Medication for LBP – Double-blind Period Full Analysis Population

| Variable | Placebo (N=302) | OXN (N=298) |
|--|--------------------|----------------|
| Average Daily Number of OxyIR Pills, n (%) | | |
| None | 47 (15.6) | 57 (19.1) |
| > 0 to <= 0.5 | 76 (25.2) | 94 (31.5) |
| > 0.5 to <= 1.0 | 60 (19.9) | 59 (19.8) |
| > 1.0 to <= 2.0 | 107 (35.4) | 83 (27.9) |
| > 2.0 | 12 (4.0) | 5 (1.7) |
| Average Daily Number of OxyIR Pills | | |
| n | 302 | 298 |
| Mean (SD) | 0.86 (0.758) | 0.69 (0.687) |
| Median | 0.75 | 0.50 |
| Min, Max | 0, 5 | 0, 4 |

(CSR, pp. 395)

Protocol Deviations and Violations

There were no major protocol deviations (defined as authorized deviations that were requested proactively and approved by either the sponsor or the CRO before the event took place) in the double-blind period for the randomized safety population.

There were a number of protocol violations (defined as unauthorized deviations from the protocol discovered after the event took place). One hundred eight-three subjects had a total of 288 major protocol violations (141 violations among subjects receiving placebo

vs 147 receiving OXN). The most frequently observed major violations (171 of 288) were in the categories of study drug and prohibited concomitant medication.

Table 12, below, provides a summary of major protocol violations by treatment group.

Table 12. Summary of Major Protocol Violations by Treatment Group – Double-Blind Period, Randomized Safety Population

| Protocol Violations | Placebo (N=302) | | OXN (N=298) | | Total (N=600) | |
|--|--------------------|--------|----------------|--------|------------------|--------|
| | n (%) | Events | n (%) | Events | n (%) | Events |
| Number of subjects with at least one major protocol violation and total number of events | 88 (29.1) | 141 | 95 (31.9) | 147 | 183 (30.5) | 288 |
| 01-Inclusion Criteria | 8 (2.6) | 8 | 9 (3.0) | 9 | 17 (2.8) | 17 |
| 02-Exclusion Criteria | 2 (0.7) | 2 | 0 | 0 | 2 (0.3) | 2 |
| 03-Study Drug | 41 (13.6) | 53 | 42 (14.1) | 59 | 83 (13.8) | 112 |
| 04-Assessment Safety | 8 (2.6) | 9 | 18 (6.0) | 22 | 26 (4.3) | 31 |
| 05-Assessment Efficacy | 8 (2.6) | 9 | 4 (1.3) | 4 | 12 (2.0) | 13 |
| 06-Visit Window | 5 (1.7) | 6 | 6 (2.0) | 6 | 11 (1.8) | 12 |
| 07-Informed Consent | 2 (0.7) | 2 | 2 (0.7) | 2 | 4 (0.7) | 4 |
| 08-Prohibited Concomitant Medication | 27 (8.9) | 33 | 28 (8.7) | 38 | 53 (8.8) | 59 |
| 09-Overdose/Misuse | 5 (1.7) | 5 | 3 (1.0) | 3 | 8 (1.3) | 8 |
| 10-Other | 12 (4.0) | 14 | 15 (5.0) | 16 | 27 (4.5) | 30 |

(CSR 3701, p. 201)

The Applicant determined that of the subjects with major protocol violations, 60 (10% placebo vs 10% OXN) had major protocol violations that could have affected efficacy analyses. Of these 60, a total of 57 subjects (81 violations) were identified through the clinical trials management system and another three through listings of prohibited medications. The 81 violations were distributed into the following categories: 7 inclusion criteria, 2 exclusion criteria, 20 study drug, 7 safety assessment, 4 efficacy assessment, 6 visit window, 19 prohibited/concomitant medication, 9 overdose/misuse and 7 “other” violations.

These 60 subjects (10% of the FAP) came from various sites and were excluded from the per-protocol population (PP). No analyses were performed on the PP because less than 20% of the FAP were excluded (as per the SAP).

Specific site violations:

- (b) (4) was placed on hold due to study inconsistencies and the site was subsequently removed from the study following allegations that the investigator was involved in writing prescriptions to illegally provide drug for abuse and no data from this site appeared in the final report. There were (b) (4) (b) (4) who were excluded as a result of this site violation.

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- Site 2085A-4552 was closed as a result of the investigator's decision to discontinue his research program. This site was subsequently audited by the Agency and all findings were addressed. Data from this site were included in the analyses.

The types and frequency of protocol violations were generally similar between the placebo and OXN groups. Appropriate subjects were identified and excluded from the analysis population. This approach appears acceptable and should not have affected the efficacy results.

6.1.3 Subject Disposition

There were 1924 subjects enrolled in Study ONU3701, 1109 of whom qualified for entry into the open-label titration period. Of these, 14 discontinued before entering the open-label titration period. Therefore, there were 1095 subjects who received open-label titration treatment.

In Study ONU3701, to ensure that possible contributions of AEs to discontinuation were fully captured, a blinded Discontinuation Reason Adjudication Committee (DRAC) reviewed key safety and dosing data prior to database lock.

Open-label titration period reasons for discontinuation: Four hundred ninety-four (45% of the safety population) discontinued treatment without completing the open-label titration period or qualifying for randomization. The primary reasons for discontinuation ($\geq 5\%$) during open label titration were: did not qualify for double-blind treatment (16%), lack of therapeutic effect (10%), AEs (9%) and subject's choice (6%).

Double-blind Phase reasons for discontinuation: In the randomized safety population of 600, the reasons for discontinuing study drug were lack of therapeutic effect (17%) and adverse events (8%).

The reasons for discontinuation and subject disposition are summarized in Figure 3, below.

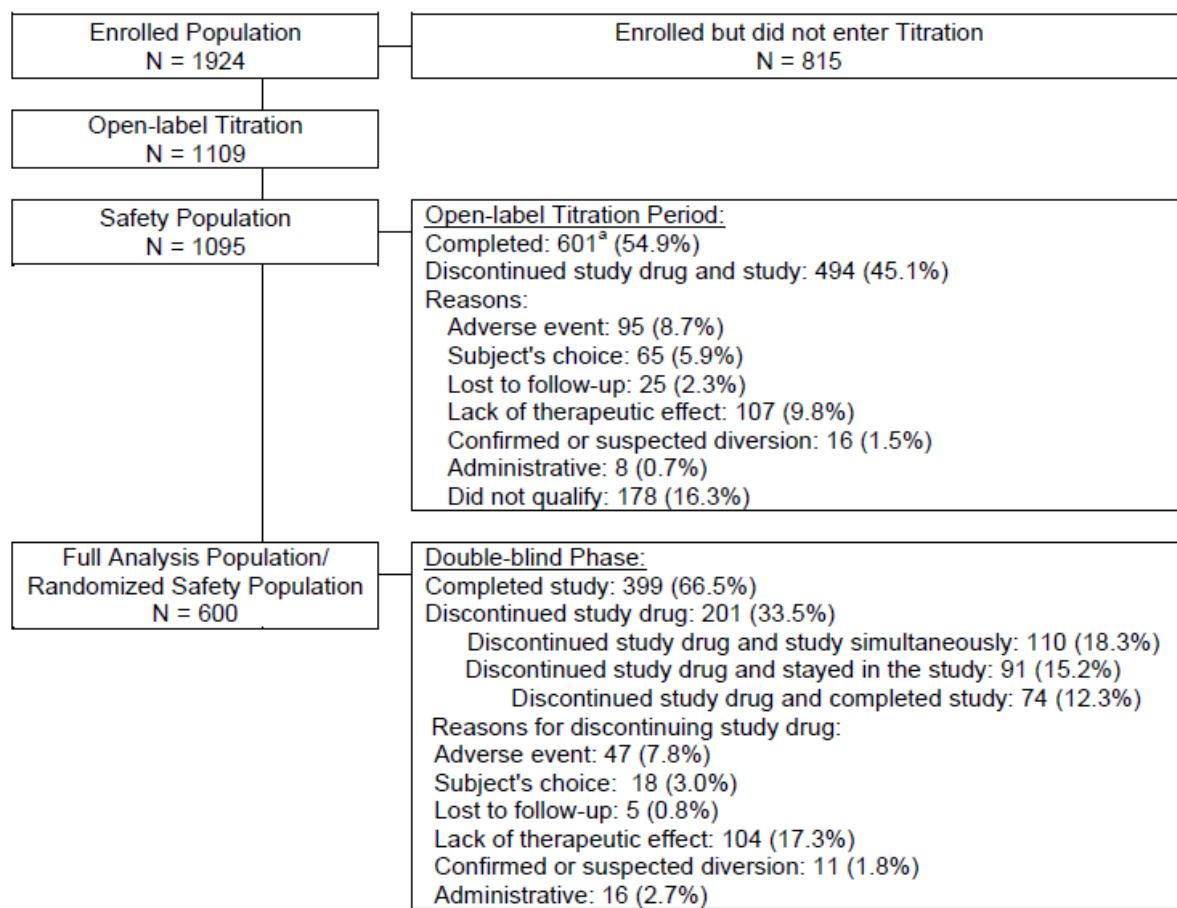
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Figure 3. Disposition of Subjects, Study ONU3701



^a Subject ONU3701-2111A-0081044 was randomized but never received double-blind treatment
(CSR ONU3701, p. 97)

As would be expected, in the double-blind period, a higher proportion of subjects (all cases) discontinued in the placebo treatment group (40%) than in the OXN treatment group (27%), with more subjects in the placebo group (24%) discontinuing due to lack of therapeutic effect compared to OXN (10%) and almost equal incidence of subjects in OXN (8%) compared to placebo (8%) discontinuing due to AEs.

Note that patients could discontinue study drug and stay in the study. Patients were encouraged to stay in the study to complete the assessments through Week 12.

Among the 121 subjects who discontinued the double-blind study treatment in the placebo group, there were 59 (49%) subjects who stayed in the study and 49 (40%) subjects who further completed the study. Among the 80 subjects who discontinued the study drug in the OXN group, there were 32 (40%) subjects who stayed in the study and 25 (31%) subjects who subsequently completed the study. The method for handling the

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pain scores for these patients is discussed in the Reviewer's conclusion section later in this review.

Disposition by treatment arm for those subjects who discontinued study drug and study simultaneously vs those who discontinued study drug and stayed in the study is shown in Table 13.

Table 13. Subject Disposition and Reason for Discontinuation: Safety and Randomized Safety Population

| Category | Open-label Titration Period (N=1095) n (%) ^a | Double-blind Period | | |
|---|---|-----------------------------|-------------------------|---------------------------|
| | | Placebo (N=302) n (%) | OXN (N=298) n (%) | Total (N=600) n (%) |
| Completed Period on Study Drug | 601 (54.9) ^a | 181 (59.9) | 218 (73.2) | 399 (66.5) |
| Discontinued Study Drug - All Cases | - | 121 (40.1) | 80 (26.8) | 201 (33.5) |
| Adverse Event | - | 23 (7.6) | 24 (8.1) | 47 (7.8) |
| Subject's Choice | - | 8 (2.6) | 10 (3.4) | 18 (3.0) |
| Lost to Follow-up | - | 1 (0.3) | 4 (1.3) | 5 (0.8) |
| Lack of Therapeutic Effect | - | 73 (24.2) | 31 (10.4) | 104 (17.3) |
| Confirmed or Suspected Diversion | - | 6 (2.0) | 5 (1.7) | 11 (1.8) |
| Administrative | - | 10 (3.3) | 6 (2.0) | 16 (2.7) |
| Discontinued Study Drug and Study Simultaneously | 494 (45.1) | 62 (20.5) | 48 (16.1) | 110 (18.3) |
| Adverse Event | 95 (8.7) | 14 (4.6) | 15 (5.0) | 29 (4.8) |
| Subject's Choice | 65 (5.9) | 8 (2.6) | 8 (2.7) | 16 (2.7) |
| Lost to Follow-up | 25 (2.3) | 1 (0.3) | 4 (1.3) | 5 (0.8) |
| Lack of Therapeutic Effect | 107 (9.8) | 23 (7.6) | 10 (3.4) | 33 (5.5) |
| Confirmed or Suspected Diversion | 16 (1.5) | 6 (2.0) | 5 (1.7) | 11 (1.8) |
| Administrative | 8 (0.7) | 10 (3.3) | 6 (2.0) | 16 (2.7) |
| Did not Qualify | 178 (16.3) | - | - | - |
| Discontinued Study Drug and Stayed in Study | | 59 (19.5) | 32 (10.7) | 91 (15.2) |
| Adverse Event | - | 9 (3.0) | 9 (3.0) | 18 (3.0) |
| Subject's Choice | - | 0 | 2 (0.7) | 2 (0.3) |
| Lack of Therapeutic Effect | - | 50 (16.6) | 21 (7.0) | 71 (11.8) |
| Completed Week 12 | - | 49 (16.2) | 25 (8.4) | 74 (12.3) |
| Discontinued Study prior to Week 12 | - | 10 (3.3) | 7 (2.3) | 17 (2.8) |
| Adverse Event ^b | - | 0 | 7 (2.3) | 7 (1.2) |
| Subject's Choice ^b | - | 8 (2.6) | 0 | 8 (1.3) |
| Lost to Follow-up ^b | - | 2 (0.7) | 0 | 2 (0.3) |

Cross-references: Table 14.1.1.3 and Table 14.1.1.4; Appendices 16.2.1.1 and 16.2.1.2.

a One subject completed titration and qualified for double-blind treatment but did not receive double-blind treatment.

b Subjects were no longer on study drug at time of discontinuation.

(CSR 3701, p. 99)

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint Analysis

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The Applicant found that the analysis of the primary endpoint, “difference in mean average pain in the last 24 hours score between placebo and OXN at week 12” showed a statistically significant difference with the least-square mean difference (placebo minus OXN) for week 12 average pain over the last 24 hours’ scores being 0.45 (95% CI: 0.13 to 0.77; p=.0055). The least-square mean “average pain over the last 24 hours” scores at week 12 were 4.32 for subjects receiving placebo vs 3.86 for subjects receiving OXN.

Dr. Feng Li, statistical reviewer, agreed with the Applicant’s findings, which are summarized in Table 14.

Table 14. Primary Efficacy Analysis Results

| Visit | Statistics | Placebo (N=302) | OXN (N=298) | 95% CI | P- value |
|----------------------------|-------------------|----------------------------|------------------------|---------------|---------------------|
| Screening | Mean (SE) | 7.1 (0.06) | 7.0 (0.06) | | |
| Pre-randomization | Mean (SE) | 3.1 (0.06) | 3.1 (0.06) | | |
| Week 12 | Mean (SE) | 4.2 (0.1) | 3.7 (0.1) | | |
| Overall Week 12 Difference | Difference | 0.5 (0.2) | | (0.1,0.8) | 0.006 |

(Dr. Feng Li’s Statistical Review); [Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval]

Sensitivity analyses

Results of the five sensitivity analyses, seen in Table x below, were consistent with the primary analysis. All were statistically significant ($P <.05$) favoring subjects receiving OXN, and the least-square mean differences from placebo were similar to the primary analysis (results ranged from 0.37 to 0.50 in the 5 sensitivity analyses). Per Agency advice, the fourth sensitivity analysis was added (NMAR – differential handling of opioid withdrawal in the two treatment groups). The fifth sensitivity analysis was added by the statistical reviewer to account for observed data on study drug, excluding potential repeat subjects.

Dr. Li’s sensitivity analyses findings are summarized in the table below.

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Table 15. Sensitivity Analysis Results

| Type of Analysis | Difference from Placebo (SE) | 95% CI | P-value |
|--|---------------------------------|--------------|---------|
| Analyses reported by the applicant | | | |
| 1. NMAR - all observed data | 0.46 (0.16) | (0.14, 0.77) | 0.004 |
| 2. MAR – observed data on study drug | 0.50 (0.18) | (0.14, 0.86) | 0.006 |
| 3. NMAR – partial AE penalty | 0.45 (0.16) | (0.14, 0.77) | 0.005 |
| 4. NMAR – differential handling of opioid withdrawal in the two treatment groups | 0.37 (0.17) | (0.05, 0.7) | 0.02 |
| 5. NMAR – observed data on study drug, excluding potential repeat subjects | 0.44 (0.16) | (0.12, 0.76) | 0.008 |
| Additional analysis by reviewer | | | |
| MAR: all observed data | 0.50 (0.17) | (0.17, 0.84) | 0.003 |

Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval

(Dr. Feng Li's statistics Review, modified) –[Source: Clinical Study Report, Table 14.2.1; SE: standard error; CI: confidence interval]

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints' results generally supported the primary endpoint, as shown below in Table 16.

Table 16. Secondary Endpoints Variable and Results

| Variable | Result |
|-----------------|--|
| MOS Sleep Scale | At week 12, the mean MOS Sleep Disturbance Subscale score least-square mean difference (placebo minus OXN) indicated an improvement in sleep disturbance with OXN as compared with placebo (5.3 [95% CI: 0.9 to 9.8; p=.0191]) |
| PGIC | The proportion of subjects choosing "very much improved" or "much improved" at week 12 was greater for subjects receiving OXN compared to placebo (OXN-treated =55.6%) vs Placebo (39.9%); p=.0002 |

(Reviewer); MOS=Medical Outcomes Survey; PGIC=Patient Global Impression of Change

6.1.6 Other Endpoints

The other endpoints' results generally supported the primary and secondary endpoints, as shown in Table 17.

Table 17. Other Endpoints Variable and Results

| Variable | Result |
|----------|--------|
|----------|--------|

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| Responder analysis | <p>A higher proportion of patients treated with OXN (55%) had at least a 30% reduction in pain score from baseline to week 12 compared to placebo patients (41%), $p=0.0006$. Also, a higher proportion of patients treated with OXN (37%) had at least a 50% reduction in pain score from baseline to week 12 compared to placebo patients (25%), $p=0.0018$</p> <p style="text-align: center;">Responder Analysis Curve</p> <p>The graph plots the cumulative percentage of subjects achieving a specific level of pain reduction against the percentage improvement in NRS from screening mean at Week 12. The Y-axis ranges from 0 to 100 in increments of 10. The X-axis shows percentage improvement levels: > 0%, >= 10%, >= 20%, >= 30%, >= 40%, >= 50%, >= 60%, >= 70%, >= 80%, >= 90%, >= 100%. Two curves are shown: OXN (dashed line with solid circles) and Placebo (dashed line with open diamonds). The OXN curve is consistently above the Placebo curve, indicating better response rates across all levels of improvement.</p> <table border="1"> <thead> <tr> <th>Percent Improvement in NRS from Screening Mean at Week 12</th> <th>Cumulative Percentage of Subjects with Response - OXN</th> <th>Cumulative Percentage of Subjects with Response - Placebo</th> </tr> </thead> <tbody> <tr><td>> 0%</td><td>70</td><td>55</td></tr> <tr><td>>= 10%</td><td>68</td><td>52</td></tr> <tr><td>>= 20%</td><td>62</td><td>48</td></tr> <tr><td>>= 30%</td><td>55</td><td>42</td></tr> <tr><td>>= 40%</td><td>48</td><td>35</td></tr> <tr><td>>= 50%</td><td>38</td><td>25</td></tr> <tr><td>>= 60%</td><td>25</td><td>15</td></tr> <tr><td>>= 70%</td><td>15</td><td>8</td></tr> <tr><td>>= 80%</td><td>8</td><td>4</td></tr> <tr><td>>= 90%</td><td>3</td><td>1</td></tr> <tr><td>>= 100%</td><td>0</td><td>0</td></tr> </tbody> </table> <p>(Source: ONU3701 CSR p. 113)</p> | Percent Improvement in NRS from Screening Mean at Week 12 | Cumulative Percentage of Subjects with Response - OXN | Cumulative Percentage of Subjects with Response - Placebo | > 0% | 70 | 55 | >= 10% | 68 | 52 | >= 20% | 62 | 48 | >= 30% | 55 | 42 | >= 40% | 48 | 35 | >= 50% | 38 | 25 | >= 60% | 25 | 15 | >= 70% | 15 | 8 | >= 80% | 8 | 4 | >= 90% | 3 | 1 | >= 100% | 0 | 0 |
|---|--|---|---|---|------|----|----|--------|----|----|--------|----|----|--------|----|----|--------|----|----|--------|----|----|--------|----|----|--------|----|---|--------|---|---|--------|---|---|---------|---|---|
| Percent Improvement in NRS from Screening Mean at Week 12 | Cumulative Percentage of Subjects with Response - OXN | Cumulative Percentage of Subjects with Response - Placebo | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| > 0% | 70 | 55 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 10% | 68 | 52 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 20% | 62 | 48 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 30% | 55 | 42 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 40% | 48 | 35 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 50% | 38 | 25 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 60% | 25 | 15 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 70% | 15 | 8 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 80% | 8 | 4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 90% | 3 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >= 100% | 0 | 0 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Supplemental Pain Medication for LBP | Percentage of subjects who took an average of >1 supplemental medication capsule daily was greater for placebo than OXN | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oswestry Disability Index (ODI) | At Week 12, the mean % disability in the OXN group was 30 vs 32 in placebo. The Applicant considers that the mean ODI disability scores were similar between treatments at screening, prerandomization and Week 12. Generally, I agree with this. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pain Right Now Score before Taking Supplemental Pain Medication | Pain right now scores prior to taking supplemental pain medication in the DB period were similar between treatment groups (range by subject: 5.09-5.56 for subjects receiving OXN compared with 5.19-5.81 for subjects receiving placebo) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BPI-SF (Brief Pain Inventory) – Short Form | <ul style="list-style-type: none"> Prerandomization BPI-SF severity of pain subscale scores were similar. After randomization, scores were 0.36 to 0.64 (raw difference between means) higher for subjects receiving placebo than OXN, with mean Week 12 scores =4.2 for placebo group vs 3.6 for OXN. Prerandomization BPI-SF interference of pain subscale score were similar. After randomization, scores were 0.09 to 0.65 (raw difference between means) higher for subjects receiving placebo than for subjects receiving OXN, with mean Week 12 scores being 3.34 vs 3.25 for placebo and | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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| | OXN, respectively |
| Weekly Average of the “Average Pain over the Last 24 Hours” Score during the DB Period (Reviewer) | Prerandomization scores were similar between the treatment groups. For every week during the DB period, the score was higher in placebo compared to OXN. |

6.1.7 Subpopulations

The Applicant conducted a subgroup analysis in 33 subjects receiving placebo vs 34 subjects receiving OXN at pre-randomization using allowed antidepressants and antiepileptics. The mean difference favored OXN at all time points during the double-blind period with a difference of 1.23 between the two groups. The Applicant concluded that there was no confounding effect from the use of antidepressants and antiepileptics. Dr. Feng Li confirmed the Applicant’s findings for this subgroup analysis.

The applicant also investigated the subgroup effects on the primary endpoint for age, gender, and race by adding an indicator for a subgroup in the MMRM model and presented the results in the Integrated Summary of Efficacy. Dr. Li confirmed the Applicant’s findings. None of the subgroups investigated was found to have significant factors affecting the primary efficacy endpoint.

Dr. Li conducted subgroup summaries by age, gender, and race. Findings from the subgroup summaries of the primary efficacy endpoints were generally consistent with those observed in the overall population and are shown below in Table 18, from Dr. Li’s review. Dr. Li did, however, determine that the percentage of subjects who achieved 30% or 50% improvement from baseline was higher in the non-white subjects treated with placebo than that of non-white treated with OXN. Dr. Li’s impression was that this difference was not significant and likely due to differences in baseline pain and dropout rates. The clinical significance or importance of this is not clear, especially since the percentage of nonwhites (23%) in placebo and OXN groups was small compared to whites (77%) in placebo and OXN.

Table 18. Subgroup Summaries

| Subgroups | Statistics | Placebo (N=302) | OXN (N=298) |
|------------------|-------------------|------------------------|--------------------|
| Sex | | | |
| Female | n (%) | 176 (58%) | 162 (54%) |
| | Mean (SD) | 4.2 (2.1) | 3.7 (1.8) |
| Male | n (%) | 126 (42%) | 136 (46%) |
| | Mean (SD) | 4.0 (2.0) | 3.5 (1.6) |
| Race | | | |
| White | n (%) | 233 (77%) | 229 (77%) |
| | Mean (SD) | 4.3 (2.1) | 3.6 (1.7) |

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| | | | |
|-----------|-----------|-----------|-----------|
| Non-white | n (%) | 69 (23%) | 69 (23%) |
| | Mean (SD) | 3.6 (1.9) | 3.5 (1.7) |
| Age | | | |
| <65 | n (%) | 258 (85%) | 249 (84%) |
| | Mean (SD) | 4.2 (2.1) | 3.6 (1.7) |
| ≥65 | n (%) | 44 (15%) | 49 (16%) |
| | Mean (SD) | 3.7 (1.6) | 3.5 (1.8) |

(Source: Dr. Feng Li, Agency statistical reviewer) SD: Standard deviation

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study drug (OXN) was studied in dose strengths of 10/5 mg, 20/10 mg, 30/15 mg, or 40/20 mg, given every 12 hours [q12h]. The recommended maximum daily dosage of Targiniq ER is 40/20mg q 12 hours (80/40 mg/day).

The Applicant determined that OXN provided pain relief at all doses tested (up to 80/40 mg/day) based upon the following findings:

- The “average pain over the last 24 hours” scores at week 12 were similar for subjects receiving OXN at all dose levels (range: 3.02 – 4.33).
- At all dose levels, the week 12 scores for subjects receiving OXN were lower (indicating less pain) than those for the corresponding subjects receiving placebo (range: 3.30 – 4.89).
- Consistency of effectiveness was observed across dose groups for the PGIC and responder analyses:
 - For the PGIC analysis, the proportions of subjects responding “very much improved” or “much improved” at week 12 were similar for subjects at all dose levels of OXN (range: 48.2% – 60.8%). At all dose levels, these proportions were greater than those for the corresponding subjects receiving placebo (range: 27.0% – 50.9%).
 - For the responder analysis, the proportion responding was greater for subjects receiving OXN compared with placebo at all 4 dose levels, at any response level and at 30% and 50% response levels.

Additional information regarding the Applicant’s proposed dosing recommendations is discussed in Safety Section 7.2.2, Explorations for Dose Response.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The pivotal efficacy study was a 12-week duration, which is standard for the evaluation of drugs intended for chronic use. Patients appeared to maintain efficacy throughout

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the 12 week period. There was no evidence that the addition of naloxone impacted the persistence of efficacy and/or tolerance effects. Dr. Li concurred that the drug effect was roughly maintained from Week 2 to Week 12.

The Applicant determined that there was persistence of efficacy based upon the following findings:

- OXN provided pain relief that was sustained over time for the duration of the 12-week double-blind period.
- During the double-blind period in the OXN treatment group, “average pain over the last 24 hours” scores were stable and consistently better than scores in the placebo group.
- Durability of effect was also observed with the MOS Sleep Disturbance Subscale, and scores were also consistently better for the OXN treatment group compared with the placebo group.

Applicant's Key Efficacy Conclusions (Study ONU3701):

1. The study met its primary endpoint in demonstrating the superiority of OXN compared with placebo.
2. The secondary endpoints supported the primary endpoint results.
3. Results of the other (exploratory) efficacy endpoints supported the primary and secondary findings.
4. Discontinuation rates due to lack of therapeutic effect were more than twice as high in the placebo group than the OXN treatment group (24% vs 10%, respectively).

Reviewer's Efficacy Conclusions (Study ONU3701)

In general, I agree with the Applicant's efficacy findings.

Dr. Li determined that there were some minor issues with the statistical analyses that did not affect the overall statistical conclusions from the study. See Dr. Li's review for a full discussion of these issues, briefly summarized below:

1. Six randomized subjects appeared to have actually represented three unique subjects. Sensitivity analyses excluding the six subject numbers produced similar results to the primary analysis.
2. Dose entries at the end of the open-label titration period were found to have been incorrectly entered by 57 subjects in the electronic diaries which subsequently led to the mismatch between the randomized dose level and the actual dose level administered. In response to an IR, the Applicant provided additional information and clarification regarding these subjects. Because this

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randomization issue occurred only at the dose level, this did not affect the overall comparison between OXN and placebo.

3. There was some ambiguity in the proposed estimand, which might lead to different interpretations and judgments of the primary analysis approach. The proposed estimand was the treatment difference at Week 12 of all randomized subjects regardless of study drug compliance. It did not mention explicitly how the pain scores collected after subjects discontinued the study drug should be handled. Dr. Li opines that the pain scores collected after the discontinuation of the study drug should be included in the primary analysis. In contrast, the Applicant seemed to believe that the estimand only entails including all randomized subjects and excluding pain scores collected off study drug in the primary analysis. Dr. Li conducted a sensitivity analysis including all collected pain scores which yielded similar results and, therefore, his concern regarding the ambiguity of the estimand was alleviated.

6.1.10 Additional Efficacy Issues/Analyses

See Section 5 for efficacy findings from the supportive efficacy studies.

7 Review of Safety

Safety Summary

During the review cycle, we had multiple communications with the Sponsor via email for Information Requests and clarifications.

In general, the safety profile of OXN appears similar to that of OxyContin. In key Study ONU3701, the most common individual TEAEs ($\geq 2\%$) seen during the open-label titration (OLT) and double-blind treatment periods were GI-related (nausea, headache, diarrhea, constipation, vomiting) with most events mild or moderate.

There were no OXN-treated subjects who died in Study ONU3701, with most deaths occurring in studies which enrolled cancer patients.

Special AEs of interest include opioid withdrawal and cardiovascular. No definite evidence of MACE (major adverse cardiac events) was seen in the studies per Cardiovascular and Renal Consultant, Dr. Preston Dunmon. Opioid withdrawal occurred with slightly greater incidence in OXN-treated than placebo in Study ONU3701. This will be reflected in the label.

There were no unexpected safety issues identified.

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7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 46 studies were used in the safety analysis. Refer to Section 5 (Sources of Clinical Data) and Section 7.1.3 (Pooling of Data) for a listing and brief description of the studies included in this submission.

The integrated safety database includes 3,073 subjects who were exposed to study drug OXN.

The primary sources for the safety review were pertinent sections of the submission including the ISS, relevant final clinical study reports and study synopses, pertinent narratives, line listings, approved labels of listed drugs OxyContin and naloxone, Applicant's proposed label, Applicant's responses to clinical information requests, literature, and the 120-day Safety Update.

Although all key integrated safety data was reviewed, in general this report focuses on the safety findings conducted in pain patients from the placebo-controlled efficacy study ONU3701, placebo-controlled study OXN3401 and pooled safety findings from these two studies (Group A1A) since these are most clinically relevant for the intended population and the Applicant's proposed label claims. Safety findings from the Group A1B (OxyCR comparator) are also discussed in more detail in some sections of the review to determine if OXN presents a different safety profile from OxyCR (OxyContin).

7.1.2 Categorization of Adverse Events

Adverse Events were coded to MedDRA version 14.0 terms. The Applicant's definitions of AEs, SAEs, and significant AEs were appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Forty-seven clinical studies are included in this NDA (see Section 5). The Integrated Summary of Safety (ISS) contained safety information from a pool of 33 studies (referred to as Group A, Group B, Group C and Additional Studies Group C) as follows:

- Group A: A total of 11 studies which include seven controlled, double-blind, multiple-dose, studies in subjects with chronic pain (ONU3701, OXN3001, OXN3006, OXN3401, OXN3503, OXN4502 and OXN2001) plus four of these studies which had open-label extension phases (OXN3001S, OXN3006S, OXN3401S and OXN2001S).
 - Group A1 (subset of group A), was created pooling nine Group A studies conducted in chronic, nonmalignant pain to provide a separate analysis of studies that used an enriched design based on open-label titration prior to the double-blind period. Group A1 excludes the two Group A studies conducted in malignant pain (OXN2001 and OXN2001S)

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- Group A1A (placebo-controlled studies in nonmalignant pain)
- Group A1B (OXY CR-controlled studies in nonmalignant pain)
- Group B: 15 controlled and uncontrolled single- and multiple dose phase 1 pharmacokinetic studies in healthy subjects (ONU1001, ONU1002, ONU1009, OXN1003, OXN1004, OXN1005, OXN1008, OXN1009, OXN1011, OXN1013, OXN1016, OXN1018, OXN1403, OXN1505 and OXN1506)
- Group C: Group A + Group B + Additional Studies Group C Pool
 - Additional Studies Group C Pool: 4 cross-over abuse liability studies in subjects that are either recreational users or opioid dependent (ONU1003, ONU1004, ONU1007, and ONU1008)
 - Additional Studies Group C Pool: 3 single-dose pharmacokinetic studies in subjects from special populations: (OXN1006 – hepatic impairment, OXN1007 – renal impairment and OXN1017 – younger and elderly healthy subjects).

The pooled clinical study groups are summarized in Table 19, below.

Table 19. Clinical Study Groups in the SAP for the ISS

| Pool Study Periods Analyzed | Purpose of Pool | Studies Included in Pool |
|--|---|---|
| Group A DB Ext Overall (OLT + DB + Ext) | <ul style="list-style-type: none">• To summarize deaths, SAEs, & AEDCs across all phase 2/3/4 studies with OXN• To estimate total exposure to OXN for ≥ 3, ≥ 6, & ≥ 12 months• To identify rare or uncommon AEs• To evaluate long-term safety data from Exts | Controlled & open-label Ext studies involving subjects with chronic nonmalignant or malignant pain (11 studies): ONU3701 , OXN2001¹ , OXN3001 , OXN3006 , OXN3401 , OXN3503 , OXN4502 Exts OXN2001S¹ , OXN3001S , OXN3006S , OXN3401S |
| Group A1 OLT DB Ext Overall (OLT + DB + Ext) | <ul style="list-style-type: none">• To provide a data pool for phase 3/4 studies with an enriched design (OLT) prior to DB• To summarize all safety data collected during each study period (OLT, DB, & Ext)• To provide comparative safety information during DB• To evaluate long-term safety data from Exts | Controlled & open-label Ext studies involving subjects with chronic nonmalignant pain; core studies used enriched design with OLT prior to DB (9 studies): ONU3701 , OXN3001 , OXN3006 , OXN3401 , OXN3503 , OXN4502² , Exts OXN3001S² , OXN3006S² , OXN3401S² |
| Group A1A DB | <ul style="list-style-type: none">• To evaluate differences in the safety profile of OXN & placebo• To explore dose relationship of safety data | Double-blind placebo-controlled studies involving subjects with chronic nonmalignant pain (2 studies): ONU3701 , OXN3401³ |
| Group A1B DB | <ul style="list-style-type: none">• To evaluate differences in the safety profile of OXN & OXY CR | Double-blind OXY CR-controlled studies involving subjects with chronic nonmalignant pain (4 studies): OXN3001 , OXN3006 , OXN3401³ , OXN3503 |
| Group B Treatment periods | <ul style="list-style-type: none">• To evaluate safety of OXN in healthy populations | Clinical pharmacology studies involving healthy subjects (15 studies): ONU1001 , ONU1002 , ONU1009 , OXN1003 , OXN1004 , OXN1005 , OXN1008 , OXN1009 , OXN1011 , OXN1013 , OXN1016 , OXN1018 , OXN1403 , OXN1505 , OXN1506 |
| Group C Overall (OLT + DB + Ext) | <ul style="list-style-type: none">• To evaluate the number of subjects exposed to OXN in the clinical development program• To evaluate incidence of deaths, SAEs, AEDCs, AEs, treatment-related AEs, and AE severity for all subjects who received at least 1 dose of OXN | All pooled studies (33 studies): <ul style="list-style-type: none">• All studies defined for groups A & B above (26 studies)• Four abuse potential studies (ONU1003, ONU1004, ONU1007, ONU1008)• Three studies involving special groups & situations (OXN1006, OXN1007, OXN1017) |

(SCS, p. 25)

The Applicant's rationale for the pooling strategy was acceptable, with the most informative pool being the Group A1A (nonmalignant, placebo-controlled studies ONU3701 and OXN3401). Findings from the totality of these pooled safety databases provide the basis to estimate and compare disposition, demographic and baseline characteristics, extent of exposure and treatment-emergent adverse events (TEAEs) across groups to allow for the determination of safety of OXN at the proposed dosing.

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7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Key Study ONU3701 Exposure

The median cumulative exposure to study drug during the double-blind period was 74 days vs 79 days for placebo vs OXN, respectively. Cumulative exposure to study drug of at least 8 weeks was 63% in the placebo group and 74% in the OXN treatment group. Compliance was between 80% and 100% for 92% in the placebo group and 93.0% in the OXN treatment group, respectively. The Applicant surmises that the large apparent decrease in exposure at ≥ 12 weeks likely reflects the window of time in which subjects could complete their visits (i.e., a window of ± 3 days for visits 3–8); subjects could have had less than 12 weeks (84 days) of treatment with OXN and still have completed the study per protocol. Table 20 shows the cumulative number of days on study drug.

Table 20. Study ONU3701 Cumulative Number of Days on Study Drug (Overall and Double-blind Period): Randomized Safety Population

| Category | Overall OXN (N=1095) | Double-blind Period | |
|---|----------------------------|---------------------|----------------|
| | | Placebo (N=302) | OXN (N=298) |
| Subjects by Cumulative Number of Days on Study Drug, n (%) | | | |
| Any Exposure | 1095 (100.0) | 302 (100.0) | 298 (100.0) |
| ≥ 1 Weeks | 1002 (91.5) | 284 (94.0) | 282 (94.6) |
| ≥ 2 Weeks | 830 (75.8) | 250 (82.8) | 275 (92.3) |
| ≥ 4 Weeks | 358 (32.7) | 213 (70.5) | 255 (85.6) |
| ≥ 8 Weeks | 247 (22.6) | 190 (62.9) | 222 (74.5) |
| ≥ 12 Weeks | 209 (19.1) | 59 (19.5) | 70 (23.5) |
| Cumulative Number of Days Exposed | | | |
| n | 1095 | 302 | 298 |
| Mean (SD) | 35.9 (33.96) | 56.8 (31.17) | 65.7 (25.99) |
| Median | 23.0 | 74.0 | 79.0 |
| Min, Max | 1, 124 | 1, 92 | 1, 93 |
| Compliance | | | |
| < 80% | | 25 (8.3) | 21 (7.0) |
| $\geq 80\%$ to $\leq 100\%$ | | 277 (91.7) | 277 (93.0) |

Cross Reference: [Table 14.1.6.1](#) and [Table 14.1.6.3](#); [Appendix 16.2.5.1](#)

Note: For overall OXN, cumulative number of days on OXN is the total number of days on OXN during the open-label titration and the double-blind periods. Only days of actual dosing were counted in this calculation.

For the double-blind period, cumulative number of days exposed is the total number of days on placebo or OXN. The dosing intervals cover exposure to placebo or OXN during the double-blind period. Only days of actual dosing were counted in this calculation. Each subject is counted under their double-blind randomized treatment group.

Compliance is based on diary data.

(Applicant's table, CSR, p. 135)

Overall, there appears to have been adequate exposure of the study drug for an acceptable duration to determine safety.

Integrated (Pooled) Exposure: A total of 3,073 subjects (Table 21 below) were exposed to total daily doses of OXN ranging from 10/5 mg to >100/50 mg (all pooled studies, Group C).

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Table 21. Cumulative Exposure to OXN in All Pooled Studies (Group C Safety Population)

| Exposure Variable | OXN (N=3073) |
|---|-----------------|
| Cumulative Exposure Categories, n (%) | |
| Any Exposure | 3073 (100.0) |
| >= 1 month | 1473 (47.9) |
| >= 2 months | 1330 (43.3) |
| >= 3 months | 1084 (35.3) |
| >= 4 months | 862 (28.1) |
| >= 5 months | 839 (27.3) |
| >= 6 months | 794 (25.8) |
| >= 9 months | 725 (23.6) |
| >= 12 months | 621 (20.2) |
| Cumulative Days of Exposure | |
| N | 3073 |
| Mean (SD) | 123.5 (180.44) |
| Median | 28.0 |
| Min, Max | 1, 492 |
| Average Total Daily Oxycodone Dose (mg) | |
| N | 2672 |
| Mean (SD) | 41.4 (23.06) |
| Median | 40.0 |
| Min, Max | 5, 120 |

max = maximum; mg = milligram; min = minimum; OXN = oxycodone /naloxone controlled-release tablets; SD = standard deviation.

Note: Cumulative exposure is defined as the total number of days the subject is exposed to OXN during all study periods. OXN dose is presented as total daily oxycodone dose in mg from the OXN regimen.

Subject-years of exposure was 1039.8 (n=3073 x [mean exposure of 123.5 days/365]).

(Applicant's table, ISS, p. 113)

Of the 2,396 patients with chronic, nonmalignant or malignant pain (Group A), 1,084 subjects (45%) were exposed to OXN for ≥ 3 months, 794 (33%) were exposed to OXN for ≥ 6 months, and 621 (26%) were exposed to OXN for ≥ 12 months across all study periods.

Of patients with chronic, nonmalignant pain (Group A1A), the extent of exposure during the double-blind period was similar between OXN and placebo groups, with the exception of a longer mean cumulative duration of exposure in the OXN treatment group (approximately 70 days) compared with the placebo group (approximately 63 days) and was comparable between the OXY (oxycodone) and OXY CR (oxycodone controlled-release) treatment groups in OXY CR controlled studies.

The mean and median average total daily dose of OXN (oxycodone component) was 41.4 mg and the maximum average total daily dose was 120 mg during the double-blind periods.

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During the open-label extension period of the group A studies, 523 subjects (54%) were exposed to OXN for ≥ 12 months. The mean average total daily dose of OXN (OXY component) was 56.7 mg; the maximum average total daily dose was 120 mg.

Disposition

Study ONU3701: See Section 6 discussion

Integrated (Pooled) Disposition: In all studies, the subjects' primary reason for discontinuing study drug was recorded in the case report form (CRF). To ensure that possible contributions of AEs to discontinuation were fully captured, a blinded Discontinuation Reason Adjudication Committee (DRAC) reviewed key safety and dosing data in the pivotal study ONU3701 prior to database lock and retrospectively for the other studies. As such, in the ISS, subjects were assigned both a primary (coded by the investigator on the CRF and included in the final clinical study reports) and a secondary (coded by the Adjudication Committee and included in the ISS) reason for discontinuation. Secondary reasons for discontinuation were imported into the integrated database and reported as a separate category for discontinuation in the ISS and, thus, were not presented in the individual CSRs.

Primary Reason for Discontinuation: This was the reason for discontinuation recorded by the investigator on the CRF.

Secondary Reason for Discontinuation: If panel members agreed as to the reason for a subject's discontinuation, the adjudication for that subject was considered complete. If panel members disagreed or agreed the information was inadequate to reach a conclusion, they further discussed the subject and/or requested additional information from the sponsor until consensus was reached. For each discontinued subject, the final consensus decision of the panel was recorded along with all other relevant information. An explanation was provided for all cases that required additional discussion due to initial disagreement among the panel members, all cases for which additional information was requested to help the panel members determine reason for discontinuation, and all cases in which the final consensus decision of the panel was discrepant with the case report form and included in the final adjudication report.

Subjects listed as discontinued due to the primary reason of 'investigator decision', 'sponsor request', 'withdrew consent', 'lack of efficacy', 'other', etc., where the adverse events occurring within 7 days of study drug discontinuation and where the verbatim reason for discontinuation indicated that the subject may have been discontinued due to adverse events were assessed by the Adjudication Committee and given a secondary reason for discontinuation.

Results: Of the 3073 subjects in the Group C pool, the majority exposed to OXN (67%) completed treatment. Of the subjects in the Group A1A (chronic, nonmalignant pain), the incidence of discontinuation during the double-blind period was lower in OXN treatment group (21%) compared with placebo (32%) and was slightly lower in the OXN treatment group (13%) compared with OxyCR treatment group (Group A1B) being 13%

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in OXN and 17% in OxyCR. In the Group B (healthy clinical pharmacology studies), 84% completed treated with OXN.

Table 22, below, summarizes the reasons for discontinuation using the primary reason (stated in the CRF) and secondary reason (as determined by the Adjudication Committee). As shown, the Adjudication Committee identified 61 subjects who discontinued with a secondary reason of adverse event.

Table 22. Subject Disposition and Reasons for Discontinuation for OXN for Subjects Exposed to OXN in All Pooled Studies (Group C Safety Population)

| Category | OXN (N=3073) | n (%) |
|--|-----------------|--------------|
| Completed OXN Medication | | 2049 (66.7) |
| Discontinued OXN Medication | | 1024 (33.3) |
| Reason for Discontinuation | | |
| Adverse Event | | 294 (9.6) |
| Subject's Choice | | 154 (5.0) |
| Lost to Follow-up | | 34 (1.1) |
| Administrative | | 112 (3.6) |
| Lack of Therapeutic Effect | | 170 (5.5) |
| Suspected Diversion | | 21 (0.7) |
| Did not Qualify | | 178 (5.8) |
| Subjects With a Secondary Reason Being Discontinuation for Adverse Event | | |
| Subject's Choice and Adverse Event | | 39 (1.3) |
| Lost to Follow-up and Adverse Event | | 4 (0.1) |
| Administrative and Adverse Event | | 8 (0.3) |
| Lack of Therapeutic Effect and Adverse Event | | 10 (0.3) |

OXN = oxycodone/naloxone controlled-release tablets

Studies in group C: Studies in groups A and B and studies [ONU1003](#), [ONU1004](#), [ONU1007](#), [ONU1008](#), [OXN1006](#), [OXN1007](#), and [OXN1017](#).

(SCS, p 53)

Integrated Demographics

Demographics for Study ONU3701 have been discussed in Section 6. Most of the pooled studies were conducted in non-U.S. countries. For the pooled (integrated) demographics, there were differences in demographic and baseline characteristics across the different study pools which included the types of chronic pain studied, the geographic locations and the study designs.

The Group C pool included healthy subjects (group B) and subjects with chronic nonmalignant or malignant pain (group A). The pooled studies enrolled a higher proportion of female subjects (ranging from approximately 54% to 76% across the

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studies and treatment groups) compared with males (ranging from approximately 24% to 46% across the studies and treatment groups). The mean age across the studies and treatment groups was from approximately 53 to 63 years (range 18 to 88 years) of age. There were 576 subjects ≥ 65 years of age and 133 subjects ≥ 75 years of age.

The U.S. study, ONU3701, enrolled 23% nonwhite subjects (19% black) while almost all the subjects enrolled in the supportive studies, conducted in Europe, were white. In the pooled studies, the majority of subjects with pain had chronic low back pain.

Despite these differences in demographic and baseline characteristics between treatment groups and study periods as the result of combining studies with different designs, there were no major imbalances among treatment groups or study periods within individual studies and, overall, the demographics between the Integrated (pooled) subjects and randomized subjects in StudyONU3701 were comparable (seen in Table 23) and informative for the safety population as it reflects the types of patients most likely to be using the intended drug.

Table 23. Key Demographics of Subjects in ONU3701 vs Integrated Studies

| | ONU 3701 N=600 (randomized) | Integrated N=3073 |
|-------------|--------------------------------|----------------------|
| Sex | | |
| Male | 44% | 41% |
| Female | 56% | 59% |
| Age (years) | | |
| Mean | 53 | 56 |
| Race | | |
| White | 77% | 88% |

(Table, Reviewer)

7.2.2 Explorations for Dose Response

There were no specific studies designed to explore dose response. The issue of the determination of the maximum daily dose was the subject of extensive communication between the Division and the Applicant with the key communication points summarized below:

We determined that the Applicant had not adequately explored dose response:

- In a 1/14/14 email IR (information request), we raised our concern regarding the Applicant's determination of the maximum daily dose of oxycodone/naloxone. Because some patients treated with extended-release oxycodone require more than 80 mg per day, the Division was concerned that a limitation on the dose of Targiniq ER could be problematic since extended-release oxycodone is prescribed at doses higher than 80 mg/day for some patients. The Division acknowledged the concern that total daily doses higher than 80mg/40mg per day could result in an increased risk of opioid withdrawal or a decrease in efficacy

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due to the increase in naloxone exposure, and advised the Applicant to 1) provide the rationale and cite supporting documents for limiting the dose of Oxycodone/Naloxone to 80/40 mg daily, and 2) identify studies in the NDA in which subjects received dosing greater than 80/40 mg/day.

On 1/29/14 the Applicant responded that the primary rationale for determining the MDD (maximum daily dosing) was because the original intent of OXN clinical development was to produce a fixed combination product that preserved the analgesic benefit of oxycodone [REDACTED] (b) (4).

[REDACTED]. Dose finding study OXN2401 identified the fixed 2:1 ratio and given that this study evaluated doses only up to 80/40 mg of oxycodone/naloxone daily, the pivotal trials for approval in Europe evaluated subjects randomized to total daily doses up to OXN 80/40 mg daily. Additionally, OXN is marketed in 29 countries and all except one have a labeled recommendation of 80/40 mg maximum total daily dose. The Applicant also identified studies in the ISS in which a limited number of subjects had been exposed to doses >80/40 mg/ day.

- In a 1/31/14 email communication we informed the Applicant that after review of their response to our initial IR, additional information was needed since we determined that the Applicant had not presented a scientific rationale to limit the total daily dose of OXN to 80/40 mg in the proposed population for this application. Additional information for any studies conducted in which the dose of naloxone in the combination that may interfere with the efficacy of the combination in terms of analgesia or trigger withdrawal symptoms was requested and the Applicant was advised to submit to the NDA any data (PK or clinical) relative to this issue.

On 2/25/14, we received the Applicant's response as follows:

- They had not conducted clinical trials to specifically identify the total daily dose of naloxone administered as OXN that may interfere with the efficacy of the oxycodone component or that may trigger withdrawal.
- They cited the following as support of limited safety data on higher doses:
 - Clinical trial data from studies 038-002 and 038/002s in 59 subjects with chronic, non-cancer pain in a 4-week, double-blind, placebo-controlled crossover study with 34 subjects who entered an open-label extension period up to 6 months where total daily OXN dose was up to 160/80 mg. The safety results were that OXN was well tolerated and reported AEs, apart from bowel-related symptoms were low and comparable to CR oxycodone.
 - NDA 205777: Includes safety data for 111 patients who received total daily doses of OXN over 80/40 mg for at least 7 days. Specifically, Study OXN3006 included 19 patients treated with OxyCR and 26 patients treated with OXN. The conclusions were that (1) analgesia was similar in the higher dose subgroup compared with the overall treatment group, and (2) there were no

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new or unexpected adverse reactions attributable to the administration of OXN at higher doses. This CSR was included in the submission and was reviewed. The total number of subjects is so small that no meaningful conclusions can be drawn regarding safety at the higher doses.

- Case Reports in Literature: The Applicant identified two case reports in the literature, included in the NDA submission, describing cases in which OXN was associated with loss of analgesia or opioid withdrawal. One case was of a 72 year old male patient with lung cancer titrated to OXN 240/120 mg over four days who experienced lack of efficacy. No signs or symptoms of opioid withdrawal were observed. Analgesia was achieved after a switch to OxyCR at the same dose. The authors speculated that lack of efficacy with OXN was due to the high dose of naloxone resulting in increased naloxone exposure and central antagonism of analgesia. The second case included was in the 120-day safety update of a 50 year-old female with gastric cancer and portal vein thrombosis who experienced opioid withdrawal following OXN 20/10 mg per day. The authors noted that portosystemic collateral circulation secondary to portal vein thrombosis in this patient may have led to higher than anticipated systemic naloxone concentrations from reduced hepatic first-pass metabolism.
- In a 3/5/14 IR email, we advised the Applicant of the following:
 - Based on the information provided to date, you have concluded that there are insufficient data to support dosing above 80 mg oxycodone/40 mg of naloxone per day via your drug product. However, you have not provided any data to support that Targiniq ER should not be used at higher daily doses. We note that all currently approved single-entity oxycodone drug products have no maximum daily dose listed in the drug product labeling. Therefore in the absence of data to support the proposed dosing limit, we will use the maximum theoretical daily dose of 1.5 grams of oxycodone (750 mg of naloxone) per day that is applied to extended-release oxycodone products. Therefore, you must address the following concerns as soon as possible:
 - 1) *Revise your drug product degradant specifications to NMT ^{(b)(4)} % or ^{(b)(4)}, whichever is lower, based on the MTDD of 1.5 grams of oxycodone per day. If you cannot meet these specifications, provide adequate safety data to qualify these degradants at the proposed specifications of NMT ^{(b)(4)} %. Adequate safety qualification data must include a minimal genetic toxicology screen (one *in vitro* bacterial mutation assay and one *in vitro* assay for genetic damage) and a 90-day repeat-dose toxicology study in a single species, unless otherwise justified.*
 - 2) *Submit safety justification for all excipients when the drug product is consumed up to the MTDD of 1.5 grams of oxycodone.*

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Your toxicological risk assessment should include copies of all cited publications and specifically address any novel excipients as per the FDA guidance for industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>.

- 3) Submit a reasonably aggressive time-line and plan for reducing the specification of [REDACTED] ^{(b) (4)} to NMT [REDACTED] ^{(b) (4)}/day based on the MTDD of this drug product. Alternatively, you may propose to conduct additional weight-of-evidence genetic toxicology studies for this drug substance impurity to qualify this as nongenotoxic.
- On 3/25/14 a t-con was held between the Applicant and the Division to discuss the above IR. Purdue agreed that if they could provide data to support a lower upper dose limit for Targiniq ER (e.g., via PK/PD modeling) that is less than the MTDD for oxycodone (1.5 g/day), toxicology assessments and CMC and toxicological specifications would be based on this lower upper dose limit.
- On 6/5/14 we received written communication from Purdue as follows: We have reviewed the data that we have on hand and have concluded that we currently have insufficient data to identify and justify an upper dose limit for Targiniq ER that is less than the MTDD for oxycodone. We have also made initial attempts at PK/PD modeling, but the results to date are inconclusive. Accordingly, we believe that in order to definitively determine an upper dose limit for Targiniq ER, additional modeling and/or data will be needed, and we will not be able to amend our application with these data prior to the PDUFA date. We understand that because of this deficiency in the application, the Agency will likely issue a Complete Response letter by the PDUFA date for this application, and we are prepared to accept this while we consider our options.

At the time of this review, the issue of the MDD has not been resolved. Refer to the CDTL memo for updated information.

7.2.3 Special Animal and/or In Vitro Testing

Animal Studies: No special animal studies were conducted.

In Vitro Testing: As part of the Applicant's Evaluation of Drug Abuse Liability, laboratory-based studies were conducted to evaluate the ease with which the abuse-deterrent properties of OXN could be defeated or compromised. See Dr. Tolliver's CSS review for the Agency's discussion and interpretation of the in-vitro testing. The Applicant's interpretation of the in vitro manipulation and extractability studies revealed the following:

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- OXN tablets were resistant to many forms of chemical manipulation intended to differentially extract OXY (oxycodone) or NAL (naloxone), or to specifically “inactivate” NAL such that OXY could be isolated from the OXN formulation for purposes of abuse.
- [REDACTED] (b) (4)
Ethanol did not increase release rates of either OXY or NAL, indicating no vulnerability to “dose-dumping” from all strengths of intact OXN tablets.
- A wide range of exposures to [REDACTED] (b) (4) resulted in high recovery or significant decomposition of both OXY and NAL.
- [REDACTED] (b) (4) extraction of crushed OXN tablets was the most effective means of separating OXY from NAL

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of OXN appears adequate for the proposed label dosing not to exceed 80/40 mg of oxycodone/naloxone per day.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 and the Clinical Pharmacology review of Dr. Srikanth Nallani for information regarding the metabolic, clearance and interaction workup.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 2.4 regarding important safety issues with consideration to related drugs.

The Applicant monitored for the expected AEs of the opioid drug class and naloxone by objective observation during examinations and subjective spontaneous reporting by the subjects. In addition, the Applicant conducted a safety analysis of AEs of special interest based on the known safety profile of the listed drugs naloxone and oxycodone CR (OxyContin). Monitoring and analyses of opioid withdrawal, abuse potential and overdose were conducted. The data collected and analyzed allows for adequate evaluation of the potential adverse events noted for similar drug classes.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant's ISS stated that across the studies of chronic nonmalignant or malignant pain (Group A study pool), a total of 57 deaths occurred in 2,396 subjects exposed to OXN through the cutoff date of December 31, 2012.

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However, in response to an information request sent by DAAAP, the Applicant clarified that there were actually a total of 60 deaths in the clinical trials. The three additional deaths were identified using a supplemental version of the final CSR for studies OXN2001 and OXN2001S which contained additional and/or corrected information not included in the original CSR. Two of these deaths (subjects OXN2001-204A-0020403 and OXN2001-8803A-0080316) occurred during the screening period before exposure to study drug. The third death (subject OXN2001-0807A-008076) occurred approximately seven months after completion of study OXN2001S.

There were no deaths in the Phase 1 studies or abuse-liability studies. No deaths were reported in the double-blind periods of studies OXN3001, OXN3006, OXN4502 and dose-finding study, OXN2401.

As shown in Table 24 below, there were a total of 60 deaths across all studies: 44 subjects died during or after treatment with OXN, 14 deaths occurred in subjects in treatment arms other than OXN (i.e., OXY CR [12 deaths], OXY IR [one death], placebo [one death]) and two deaths occurred in subjects during prerandomization (screening) before any study drugs were received. As seen in the table, 54 of the total 60 deaths (90%) occurred in Studies OXN2001/2001S in cancer patients. The other deaths occurred in studies with non-malignant pain patients. There were no OXN-treated patients who died in placebo controlled Study ONU3701.

Table 24. Deaths By Study and Treatment Group

| Study | Treatment Group | | | | | |
|---------------|-----------------|-------|-------|---------|---------|-------|
| | OXN | OxyCR | OxyIR | Placebo | No Drug | Total |
| ONU3701 | | | | 1 | | 1 |
| OXN2001/2001S | 41 | 11 | | | 2 | 54 |
| OXN3001S | 1 | | | | | 1 |
| OXN3006S | 1 | | | | | 1 |
| OXN3401 | 1 | | 1 | | | 2 |
| OXN3503 | | 1 | | | | 1 |

(Reviewer) OXN=oxycodone naloxone; OxyCR=oxycodone controlled release; OxyIR=oxycodone immediate release

Causality: All death narratives in the clinical trials were reviewed. None of the deaths was considered by the investigator to be related to OXN treatment. I found no cases where death was definite, probable or likely causally related to study drug. I did, however, identify two patients in whom death was possibly causally related to study drug (i.e., the role of study drug could not be excluded).

Of the total 60 deaths in the integrated safety database, 54 occurred in the cancer population (41 OXN-treated and 13 OxyCR-treated). Of these 41 deaths, two were determined by me to be possibly related to study drug , 20 cases were identified where causality was unlikely due to the timing of onset or other factors and 19 cases in which

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there was insufficient information or confounders. The remaining six deaths occurred in non-cancer studies with three of these deaths in the OXN-treated subjects. Of the three deaths in OXN-treated subjects in noncancer studies, causality of study drug was determined to be unlikely in all three cases. In key placebo-controlled Study ONU3701, there was only one death which was in a placebo-treated subject.

Preferred terms: The most common preferred term was malignant neoplasm (also coded as neoplasm malignant, malignant neoplasm progression and cancer disease progression) which was coded in 22 patients who died, followed by dyspnea (five patients), respiratory failure/circulatory collapse (three patients) and cardiac terms [excluding pericarditis] (two patients) . All other terms occurred in only one patient each. Aside from the malignant neoplasm term, there were no other major trends noted.

Key Findings (Malignant Population):

Of the 41 patients who died in Studies OXN2001/2001S, the following conclusions are drawn:

- 16 of the deaths were in OXN-treated cancer patients who received OXN for a duration \leq 30 days. Of these, three deaths occurred while on study drug, one did not have sufficient information in the narrative to determine when death occurred, and the others occurred after study drug was discontinued.
- 25 of the deaths were in OXN-treated cancer patients who received OXN for a duration \geq 30 days. Of these, six deaths occurred while on study drug and the remainder occurred after study drug was discontinued.
- Of the total 41 deaths, 13 of the deaths were in OXN-treated cancer patients that occurred during the double-blind phase of the study and the remainder were in the OLE phase. This is relevant because although there were more patients who died while on OXN compared to OxyCR in Studies OXN2001/2001S (41 OXN vs 11 OxyCR), the number of patients who died during the double-blind phase of the study was similar (i.e., 13 OXN vs 11 OxyCR). The remainder of deaths in OXN occurred during the OLE phase where all subjects were treated with OXN and there was no OxyCR comparator arm. Therefore, although the total number of deaths in OXN-treated patients was greater than OxyCR, the majority of the OXN deaths were in the OLE, OXN-only phase of the study. The types and timing of deaths in the OxyCR treatment arm were similar to those in the OXN treatment arm.
- There was no pattern noted regarding the MDD (maximum daily dose) of OXN received and death outcome.

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- For those patients in whom death occurred after study drug was discontinued, the time from the discontinuation of study drug to death varied considerably and no trends were identified.
- There was a higher incidence of deaths in males (29/41=71%) compared to females in the cancer studies. Otherwise, there were no trends noted in demographics.

A summary table of all of the deaths in cancer patients with subject ID, pertinent demographics, preferred terms, duration of exposure, maximum daily dose (MDD) and causality assignment (as determined by this reviewer) is shown in Appendix C.

Death Narratives

The narratives for the two patients with possible causality to study drug are included below in Table 25. The narratives for deaths with preferred terms of interest (i.e., respiratory failure, cardiac terms or unexpected terms) were not included because in each case there was either insufficient information to assign causality or the cases were confounded (i.e., patients with underlying cancer and multiple comorbidities and concomitant medications).

In the following table, the subject ID is listed first, followed by the subject's demographics, MedDRA preferred term coded to the death, onset of event, maximum daily dose achieved during the study, and causality assignment as determined by this reviewer in bold font.

Table 25. Death Narratives Studies OXN2001/2001S – Possible Causality

| |
|---|
| 0040902 - 61 year old male; Cardiac failure/circulatory collapse (onset after [b] days of exposure); MDD OXN=90 mg; Possible causality 61 year old male with underlying cancer with history of metastases to multiple sites. Presstudy opioid was morphine. The subject was randomized to OXN and began taking a total daily dose of 30/15 mg OXN on [b]. Oxy IR was available as rescue medication for breakthrough pain. The subject's total daily dose of study drug was increased to 45/22.5 mg OXN on [b], to 60/30 mg OXN on [b], and to 75/37.5 mg OXN on [b]. On [b], the subject's total daily dose of study drug was increased to 90/45 mg OXN . On the same day, the subject experienced the events of headache and dizziness, while waiting for the computerized tomography scan for tumor evaluation. The subject was found to be unconscious and gasping. Resuscitation was unsuccessful, and on the same day, the subject died due to the serious adverse event of heart and circulation failure . An autopsy was not performed. The patient apparently was diagnosed with pulmonary embolism and intracerebral bleeding (although the narrative was not clear about when or how those diagnoses were made). There was no cardiac past medical history reported. <i>Reviewer's comment:</i> Causality to study drug cannot be excluded and, therefore, is possible given that the onset was [b] days after starting study drug and on the same |
|---|

day as an increase in dose (from 75 mg to 90 mg). However, this patient had extensive metastases and was on multiple concomitant medications making causality to study drug alone possible but confounded. The diagnoses of PE and intracerebral bleed (though not confirmed) make an association to study drug alone less likely.

0080601 - 55 year old male; Neoplasm Malignant (onset after (b)(6) days of exposure); MDD=80 mg; Possible causality

Prestudy opioid was transdermal fentanyl. This subject entered the double-blind phase and began OXN on [REDACTED] at a total daily dose of **30/15 mg OXN**. Oxy IR was available as rescue medication for break through pain. The subject's total daily dose of study drug was increased to **60/30 mg OXN** on [REDACTED], to **70/35 mg OXN** on [REDACTED], and to **80/40 mg OXN** on [REDACTED]. On [REDACTED] the subject experienced "an SAE of progression of lung cancer associated with symptoms of dyspnea, weakness and consciousness disturbance". On [REDACTED], the subject died [REDACTED]. No other relevant details were provided in the narrative.

Reviewer's comments: The role of OXN in the patient's death cannot be excluded, and therefore, there is possible causality given the timing of death to OXN exposure. Although limited information was provided in the narrative, the SAE symptoms described are consistent with opioid-related AEs and, therefore, I determined that they could be possibly causally related to study drug. The dosage of OXN was doubled by Day [REDACTED] and increased by 10 mg daily thereafter for the next [REDACTED] days. However, death did not occur until [REDACTED] days after the last increase in study medication dosage.

(Table, Reviewer)

Non-cancer Deaths

In addition to the deaths which occurred in the cancer population in Studies OXN2001/2001S, there were three deaths in OXN-treated patients which occurred in non-cancer patients in other studies. All three of these deaths occurred in the extension phases of the studies after a long duration of exposure to OXN and were determined to be unlikely causally related to study drug. The narratives are summarized below in Table 26:

Table 26. Narratives for Non-malignant OXN-Treated Patient Deaths

Study OXN3001S: Subject 0093803; Necrotizing Fasciitis; Unlikely causality

This 71 year old male completed the OXN double-blind period on 7-06-06 with a maximum dose of 40 mg OXN. He began the open-label extension phase and was treated with a maximum daily dose of 40 mg OXN. On [REDACTED] (approximately [REDACTED] months of exposure to OXN) he experienced an SAE of necrotizing fasciitis accompanied by flu-like symptoms, swollen legs and abdominal pain and was hospitalized. On [REDACTED] the subject discontinued study drug due to the SAE of necrotizing fasciitis and died. An autopsy confirmed the diagnosis.

Reviewer's comments: Causality to study drug alone is unlikely. The patient had been taking OXN from April to October with no significant events. The patient had an underlying medical history of diabetes, which is a known risk factor for necrotizing fasciitis. The patient did not discontinue study drug until the time of death, so is considered to have been on study drug at the time of death.

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Study OXN3401S: Subject 0067009; Chest crushing/Road traffic Accident; Asphyxia; Unlikely causality

This 62 year old male had been on OxyPR in the double-blind phase of the study with a maximum total daily dose of 20 mg OxyPR. He entered the extension phase of the study in December, 2005 and on [REDACTED] (b) (6), the subject took a total daily dose of 20 mg OXN, and was discontinued from study drug (reason for discontinuation was not identified). On [REDACTED] (b) (6), (onset Day [REDACTED] (b) (6) of the study) the subject experienced the serious adverse event of quadricycle accident, when driving his quadricycle in a mountain forest, which resulted in the serious adverse events of chest crushing and suffocation. The subject was located by family members and found dead. On [REDACTED] (b) (6), an autopsy was performed. The cause of death was suffocation due to thoracic compression by the quadricycle.

Reviewer's comments: Causality of death to study drug is unlikely. Study drug was discontinued [REDACTED] (b) (6) prior to the onset the accident but the subject had been on study drug for approximately [REDACTED] (b) (6) months prior to the onset of the fatal event.

Study OXN3006S: Subject 0019706; Sepsis; Unlikely causality

This 66 year old female was in the OxyPR double-blind treatment arm from 2-09-07 to 5-29- 07. She entered the open-label extension phase on 5-30- 07 at 80 mg OXN increased to a maximum of 100 mg on 11-13- 07. On [REDACTED] (b) (6) (approximately Day [REDACTED] (b) (6) of the study) she experienced gangrene of the left leg; seven days later she was diagnosed with sepsis and on [REDACTED] (b) (6), she died due to sepsis.

Reviewer's comments: Causality of death to study drug is unlikely given the long duration of exposure to OXN without other significant AEs. This patient also had a risk factor of history of prior amputation of the right leg for gangrene.

(Table, reviewer)

Based upon Dr. Preston Dunmon's Cardiovascular and Renal Products consultant review, six deaths were adjudicated for possible CV deaths, four of which occurred on OXN, two of which occurred on comparators, all in Study OXN2001-2001S in cancer patients. The preferred terms of the four OXN deaths are as follows: Subject 0080201 (pericarditis), 0040902 (pulmonary embolism and intracerebral bleeding), 0080707 (cardiac arrest) and 0050401 (pulmonary embolism). Dr. Dunmon could not assign causality in three of the subjects' death due to confounders or insufficient information and determined that the pericarditis case was possibly related to underlying esophageal cancer.

Postmarketing Deaths

Oxycodone/naloxone has been marketed outside if the U.S. since 2006. As of 31-December-2012, the Applicant identified a total of 86 cases associated with a fatal outcome based upon a world-wide drug safety database query.

The majority of the cases associated with a fatal outcome involved malignant neoplasms (n = 43 [2.3%]). All of these reports involved patients with underlying malignancies, treated with OXN for pain, and were reported as not related to OXN therapy by the reporting health care provider.

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120-day Safety Update

The safety information compiled from January 1, 2013 through April 30, 2013 revealed no new safety data regarding deaths which would alter the overall safety profile or labeling of the drug.

Death Summary: Of the total 60 deaths in the integrated safety database, 54 occurred in the cancer population (41 OXN-treated and 13 OxyCR-treated). Of these 41 OXN-treated deaths, two were determined by me to be possibly related to study drug (i.e., the role of study drug could not be excluded). The remaining six deaths occurred in non-cancer studies with three of these deaths in the OXN-treated subjects. Targiniq ER did not appear to be causally related to these three deaths. In key placebo-controlled Study ONU3701, there was only one death which was in a placebo-treated subject.

7.3.2 Nonfatal Serious Adverse Events

I) Study ONU3701 (Key Phase 3, placebo-controlled efficacy study): The overall incidence of SAEs in the open-label titration period and double-blind period is shown below in table 27, in which there were 6% OXN-treated and 4% placebo who experienced an SAE during the double-blind period.

Table 27. Incidence of SAEs in Open-label Titration Period and Double-blind Period, Study ONU3701

| Category | Open-label Titration Period | | | Double-blind Period | |
|---------------|-----------------------------|-----------------------|-------------------|-----------------------|----------------|
| | Non- | | Total (N=1095) | Placebo (N=302) | OXN (N=298) |
| | Randomized (N=494) | Randomized (N=601) | | | |
| Serious TEAEs | 10 (2.0) | 1 (0.2) | 11 (1.0) | 12 (4.0) ^a | 19 (6.4) |

(Applicant's table, modified by reviewer, CSR 3701, p. 142); Note: the placebo number includes the subject who died so the actual non-fatal SAEs for placebo n=11

Open-label titration (OLT): There were 11 subjects (1%) who experienced 16 SAEs. Eight of the 11 subjects in the OL titration period had 9 SAEs of either drug screen positive or drug abuse and one of the eight subjects had an SAE of drug overdose. Three subjects (0.3%) of the OLT experienced a total of six non-abuse-related SAEs. All six of these cases, preferred terms (esophageal stenosis, dehydration/vomiting/ impaired gastric emptying/ nausea, and arthritis) were considered by the investigator to be not related to study drug. Upon my review of the narratives, I determined that the terms dehydration/vomiting/impaired gastric emptying/nausea (Subject 0065002) and esophageal stenosis (Subject 0027031) were possibly related. The narratives are below in Table 28. The SAE of arthritis was not causally related to study drug.

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Table 28. Study ONU3701 SAEs Possibly Related to Study Drug – Open Label Titration Period

| Subject | Mini-narrative |
|---------|--|
| 0065002 | <p>60 year old female, began OLT period on OXN 40/20 mg TDD on 9-13-11. On [REDACTED] ^{(b) (6)} the subject was admitted to the hospital with acute dehydration, vomiting, worsening of gastroparesis (impaired gastric emptying) and worsening of nausea. The symptoms required treatment. The subject previously experienced mild vomiting before beginning treatment with OXN. Past medical history was significant for esophageal reflux and gastroparesis. The subject was not randomized. Study drug was stopped permanently and the last dose was on [REDACTED] ^{(b) (6)}. The subject was discontinued from the study. Reviewer's comments: Causality of the SAE to study drug is possible although the patient did have a prior GI medical history. Proposed labeling includes a warning against use in patients with GI obstruction or ileus.</p> |
| 0027031 | <p>67 year female entered the OLT period with OXN 40/20 mg TDD on 5-12-12, increased to 60/30 mg on 5-16-12 and to 80/40 mg on 5-23-12. On [REDACTED] ^{(b) (6)}, she presented to the ED with complaints of abdominal pain, nausea and severe vomiting. The patient had a past medical history of bowel decompression secondary to small bowel obstructions, small bowel obstructions and peptic stomach ulcer. EGD revealed an esophageal ring, which was dilated. The SAE worsening of esophageal stricture was reported. The subject was not randomized, study treatment was stopped permanently and the final dose of study drug was taken on [REDACTED] ^{(b) (6)}. The event resolved and the subject was discharged from the hospital. Reviewer's comments: Although it is possible that study drug was causally related to the AEs of abdominal pain, nausea and vomiting, the esophageal stricture did not likely develop within a [REDACTED] day period. Additionally, there is a past GI history of small bowel obstructions. Proposed labeling for OXN includes a warning against use in patients with GI obstruction. No additional labeling is needed based on this one report.</p> |

(Table, reviewer)

Double-blind period: There were 30 subjects (5%) who experienced a total of 35 nonfatal SAEs. Eleven subjects (4%) receiving placebo experienced 13 non-fatal SAEs and 19 subjects (6%) who received OXN experienced 22 non-fatal SAEs.

In the 19 OXN-treated subjects who experienced an SAE, when the preferred term Drug screen positive was excluded, 10 patients were identified with the terms: cellulitis, rectal perforation, cholecystitis, non-cardiac chest pain/hypokalemia/abdominal pain, angina pectoris, pneumonia, Ludwig's angina, atrial fibrillation, syncope, and bladder

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cancer. All SAEs were determined to be not causally related to study drug by the investigators.

The following case (although determined by the investigator to be not related to study drug) was determined by the Applicant to be possibly causally related to study drug:

Narrative (Subject 0034003: SAE preferred term Rectal Perforation): This was a 62 year old female with multiple co-morbidities and concomitant medications. (b)(6) days after starting OXN 20/10 mg total daily dose and one day after OXN was increased to OXN 40/20 mg total daily dose, the patient experienced moderate rectal bleeding. According to the investigator, the subject had a long history of constipation due to opioid use. The subject refused constipation medications. The event resolved 14 days after onset. Approximately one month later, the patient had severe abdominal pain and two days after the onset of the abdominal pain, she experienced the SAE of rectal perforation (day (b)(6) of the double-blind treatment). Surgical procedure (exploratory laparotomy) was required. Study drug was stopped and the patient discontinued from the study. The investigator determined that the SAE was not related to study drug but rather to the subject's long past history of constipation. The Sponsor determined that a causal association between the SAE of rectal perforation and the treatment could not be excluded and thus, there was possible causality to study drug. I concur that study drug was possibly causally related to the SAE.

II) Group A1A (Double-blind, placebo-controlled studies): In the placebo-controlled, Group A1A studies with nonmalignant pain patients, the overall incidence of SAEs was 26 (6%) in OXN and 14 (3%) in placebo-treated during the double-blind period. Drug screen positive and abdominal pain were the only SAE terms which occurred in more than two subjects in either treatment group. Although the incidence of SAEs was higher in OXN group compared to placebo, this increased incidence was due primarily to the term, drug screen positive, which occurred in 9 subjects [2%] OXN compared to 1 subject [0.2%] placebo. Abdominal pain was experienced by 3 subjects [0.7%] OXN compared to 1 subject [0.2%] Placebo. The incidence of nonfatal SAEs during the double-blind period of the placebo-controlled studies (group A1A) is summarized for events that occurred in \geq 2 subjects in Table 29 below.

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Table 29. Incidence of Nonfatal Serious Adverse Events (≥2 Subjects in Any Treatment Group) During the Double-blind Period of Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A Safety Population)

| MedDRA System Organ Class Preferred Term | Placebo (N=460) n (%) | OXN (N=451) n (%) |
|--|-----------------------------|-------------------------|
| Subjects With Any Nonfatal Serious Adverse Events | 14 (3.0) | 26 (5.8) |
| Cardiac Disorders | 2 (0.4) | 3 (0.7) |
| Atrial fibrillation | 0 (0.0) | 2 (0.4) |
| Acute myocardial infarction | 2 (0.4) | 0 (0.0) |
| Gastrointestinal Disorders | 1 (0.2) | 5 (1.1) |
| Abdominal pain | 1 (0.2) | 3 (0.7) |
| Nausea | 0 (0.0) | 2 (0.4) |
| Vomiting | 0 (0.0) | 2 (0.4) |
| Investigations | 2 (0.4) | 11 (2.4) |
| Drug screen positive | 1 (0.2) | 9 (2.0) |
| Social Circumstances | 2 (0.4) | 0 (0.0) |
| Substance use | 2 (0.4) | 0 (0.0) |

MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets.

Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Adverse events are sorted alphabetically by system organ class and by descending frequencies in the OXN column. Multiple occurrences of the same adverse event in one individual are counted only once.

(ISS, p. 176)

II) Group C: Overall, 203 out of 3,073 (7%) subjects exposed to OXN experienced at least one non-fatal SAE. The SOCs with the highest incidence (1%) in this pooled group were Neoplasms benign, malignant and unspecified (including cysts and polyps), GI and Musculoskeletal and connective tissue disorders. No overall trends were identified.

The Applicant also analyzed the SAEs by incidence rate (e.g., incidence per 100 subject-years of exposure) to account for the different exposure rates of OXN compared to other treatment arms. The incidence rate for the 203 subjects who were exposed to OXN who experienced SAEs was 18.3 per 100 subject-years of exposure. Normalization for subject exposure did not change the profile of the most common types of SAEs.

IV) Group B (Phase 1 clinical pharmacology studies in healthy subjects): There were five subjects who experienced seven SAEs in the Group B pool. Of those, four subjects were in the OXN treatment group and one was OXY (oxycodone). The SAE preferred terms in the OXN-treated group were one each for pericarditis, pharyngitis/ dyspnea (two SAEs in one subject), atrial fibrillation/vomiting (two SAEs in one subject), and upper limb fracture. All of the events occurred during Period 1 except for upper limb fracture which occurred after treatment. The narratives for these cases were reviewed. There was one possible case identified by this reviewer that may be related to study drug, narrative below:

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- Narrative: (Subject OXN1003-0471A-0001024); Preferred term Pharyngitis: 36 year old male received OXN 10/5 mg and the next day he experienced acute laryngopharyngitis and dyspnea which was severe and required hospitalization for two days where he received IV antibiotics and IV prednisolone. The subject was discontinued from the study as a result of the SAEs. The subject recovered. The SAEs were considered by the investigator to be not related to study drug. In my opinion, this may represent a possible case of hypersensitivity to the study drug. The narrative did not provide sufficient details to determine this (i.e., no rechallenge).

SAEs SMQ (Standardized MedDRA query) and CMQ (Custom MedDRA query)

The Applicant reported that safety in specific organ systems was investigated by examining CMQs based on the known safety profile of oxycodone, as reported in the OxyContin label. The SMQs were defined by the CIOMS Working Group and were groupings of terms from one or more MedDRA SOCs that related to a defined medical condition or area of interest.

CMQs

- Diarrhea-related AEs (included MedDRA preferred terms diarrhea, frequent bowel movements, antidiarrheal supportive care, defecation urgency): There were two reports of diarrhea-related SAEs in the double-blind period of OXN treated subjects in the Group A pool (compared to none in other treatment arms).
- Opioid Bowel Dysfunction (included MedDRA preferred terms nausea, vomiting, constipation, abdominal pain, abdominal distension, decreased appetite, flatulence): There were a total of 30 subjects in the Group A pool with reports of SAE terms in this CMQ with all in the OXN except one each in placebo and OxyIR and three in OxyCR. There were 11 subjects in the cancer population of the OXN-treated. GI events are known and expected AEs for the opioid class of drugs.

SMQs

- Possible drug related hepatic disorders – comprehensive search SMQ: Possible drug-related hepatic disorder SAEs occurred in two OXN subjects in Group A, both occurred during the OLE period in cancer patients and included a subject with hepatic function abnormal and one with INR (internal normalized ratio) increased. The SAE events which occurred in this SMQ would not result in the need for additional labeling as both of these events occurred in cancer patients who were on multiple medications and had other confounders making the determination of causality to study drug alone unlikely.

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- Acute central respiratory depression (SMQ): This SMQ was identified in 14 subjects who experienced SAEs across all treatment periods. Most of the cases were in the extension phases and have already been discussed under the deaths section of this review. Respiratory depression is included as a boxed warning in the proposed TARGINIQ ER label and in the approved OxyContin label.
- Gallbladder related disorders (SMQ): During the double-blind period (Group A1), three OXN subjects experienced gallbladder related SAEs: two subjects with acute cholecystitis and one subject with cholelithiasis compared to one subject each in the placebo and OxyCR groups who experienced an SAE of cholelithiasis and one placebo with an SAE of acute cholecystitis. The proposed label contains the following statement in the MedGuide: "*Before taking TARGINIQ ER, tell your healthcare provider if you have a history of pancreas or gallbladder problems*", otherwise there is no labeling regarding gallbladder related AEs. However, due to the small number of subjects who experienced SAEs in this SMQ additional labeling is not required.
- Drug abuse (sub-SMQ): Most of the abuse-related events occurred in study ONU3701, which required periodic urine drug testing. There were eight subjects who experienced an SAE of any abuse-related event during the open-label titration period. During the double-blind period, 11 (4%) OXN-treated and 5 (2%) placebo experienced SAEs in abuse-related SMQ. Both the approved OxyContin label and proposed TARGINIQ ER ER label include a boxed warning regarding abuse potential.
- Drug withdrawal (sub-SMQ): Two SAEs of opioid withdrawal were reported in subjects exposed to OXN. Details regarding drug withdrawal are discussed in Section 7.3.5 of this review (Submission Specific Safety Issues). Of note, both of these subjects were transitioned from OxyPR 20 mg to OXN 20 mg/10 mg, and within 48 hours of the transition, they each experienced drug withdrawal syndrome and subsequently were discontinued from study drug. These cases lend support to the idea that the naloxone contributed to the withdrawal symptoms, as the subjects' dose of oxycodone was not changed.
 - Subject OXN3001-00096217: 76 year old female, prestudy opioid was Oxycodone 30 mg; was randomized to OxyPR; titrated to a dose of OxyPR 20 mg then entered the DB phase randomized to OXN 20 mg. While on a total daily dose of OXN 40 mg (day 2 of DB), she experienced sweating, hot flushes, chills, trembling, muscle pain, nausea, diarrhea, weakness and social avoidant behavior withdrawal syndrome and was discontinued from study drug due to the SAE of drug withdrawal

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syndrome. Two days later, the subject experienced an SAE of ECG deviation (disturbance of repolarization) with negative cardiac enzymes. The events resolved.

- Subject OXN3503-0170401: 84 year old female, pre-study opioid was Oxycodone 20 mg, was randomized to OxyPR; titrated to a dose of OxyPR 20 mg then entered the DB phase randomized to OXN 20 mg and on the same day (day 2 of DB), the subject experienced the SAE of opioid withdrawal and hypertension crisis (BP 200/100 mm Hg). On day 3 of DB, the subject discontinued from the study and study drug due to the SAEs of hypertension crisis and opioid withdrawal and due to the events of abdominal pain, anxiety, sweating and lymphocytes absolute decreased. The events resolved (except for lymphocytes absolute decreased which was ongoing at the time of the last available report). The investigator considered the event of hypertensive crisis to be due to a secondary effect of opioid withdrawal syndrome. The subject continued taking pre-study anti-hypertensive as treatment for the event of hypertension crisis and no treatment was reported for any of the events.
- Accidents and injuries: There were 12 OXN-treated patients who experienced SAEs in this SMQ. Preferred terms included retinal detachment, chest crushing, falls, femoral neck fracture, laceration, ligament sprain, limb traumatic amputation, muscle strain, road traffic accident. These narratives did not suggest causality to study drug alone.
- Adverse pregnancy outcome/reproductive toxicity (including neonatal disorders): Two pregnancies were reported in completed clinical trials up to the data cutoff of 31-December-2012. Both reports were in study ONU3701 with narratives as follow:
 - Subject ONU3701-2063A-0037005 was a 25-year-old female subject who began open-label titration in study ONU3701 on 10-Oct-2011 and began taking OXN 20/10 mg daily. The urine pregnancy test was negative at screening on 26-Sep-2011. Subsequently her urine pregnancy test was positive on 14-Oct-2011 (day 5 of open-label titration) and OXN was discontinued the same day. Follow-up information indicated that the subject delivered a healthy newborn male by cesarean section at [redacted] weeks on [redacted].
 - Subject ONU3701-2014A-0126011 was a 34-year-old female who began open-label titration in study ONU3701 on 07-Jan-2012 and began taking

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OXN 20/10 mg daily. The urine pregnancy test was negative at screening on 14-Dec-2011. The event of pregnancy was reported on day 14 of the open-label titration period. The subject was lost to follow-up and no additional information is available concerning the course of the pregnancy or the outcome. Per the subject diary, the last dose of study drug was taken 25-Jan-2012.

SMQ-based CV SAE. Out of 3 subjects in OXN group, one subject each experienced atrial fibrillation (ONU3701-0513A-0076013), angina pectoris (ONU3701-2335A-0142013) and syncope (ONU3701-2208A-0090018). Dr. Dunmon, Division of Cardiovascular and Renal Products' consultant, determined that, "*SAEs for OXN-treated patients do not seem to have a common theme (manifestation/etiology/pathophysiology).*"

120 day safety Update: This resulted in no additional findings regarding nonfatal SAEs which would change the overall findings discussed above.

Nonfatal SAE Summary: The pattern of serious adverse events observed during the Phase 1 and Phase 3 studies of OXN appears consistent with the expected adverse event profile of opioids in general. There were two subjects who experienced SAEs possibly causally related to study drug in the OL titration period of Study ONU3701. Overall, during the double-blind period of studies of nonmalignant pain, nonfatal SAEs were experienced by similar percentages in the OXN (5%), placebo (3%) and OxyCR (4%) treatment groups. Most SAEs were experienced by no more than one subject in any treatment group. No trends were identified which would result in labeling actions.

7.3.3 Dropouts and/or Discontinuations

Study ONU3701: In the OLT (open-label titration) period, the incidence of discontinuation adverse events was higher in the non-randomized (18%) compared to randomized (<1%). Per protocol, the study was designed that those subjects who could not tolerate study drug were not randomized. For those subjects who discontinued during the open-label titration period and were not randomized, the highest incidence of AEs occurred in the GI SOC (7%) with the preferred terms, nausea (5%), vomiting (2%), abdominal pain upper (2%) and diarrhea (1%) being the terms listed.

In the double-blind period, discontinuation adverse events occurred with nearly equal incidence for placebo and OXN, being approximately 7% for both. Drug screen positive accounted for the highest incidence in OXN (4%). When drug screen positive is not included, the highest incidence of discontinuation AEs occurred in the GI SOC with an overall low incidence (1%) in both placebo and OXN groups.

Table 30 below displays the incidences and types of discontinuation AEs in the open-label titration and double-blind periods of Study ONU3701.

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Table 30. Study ONU3701: Incidence of TEAEs Leading to Study Drug Discontinuation ≥1% Safety Population (Open-label Titration Period) and Randomized Safety Population (DB-Period)

| MedDRA System Organ Class Preferred Term | Open-label Titration Period | | | Double-blind Period | |
|---|------------------------------------|--------------------------------|----------------------------|-----------------------------|-------------------------|
| | Non-Randomized (N=494) n (%) | Randomized (N=601) n (%) | Total (N=1095) n (%) | Placebo (N=302) n (%) | OXN (N=298) n (%) |
| Any Adverse Events | 89 (18.0) | 5 (0.8) | 94 (8.6) | 20 (6.6) | 21 (7.0) |
| Gastrointestinal disorders | 33 (6.7) | 2 (0.3) | 35 (3.2) | 3 (1.0) | 4 (1.3) |
| Nausea | 22 (4.5) | 1 (0.2) | 23 (2.1) | 2 (0.7) | 1 (0.3) |
| Vomiting | 9 (1.8) | 0 | 9 (0.8) | 1 (0.3) | 2 (0.7) |
| Abdominal pain upper | 6 (1.2) | 0 | 6 (0.5) | 0 | 1 (0.3) |
| Diarrhea | 5 (1.0) | 0 | 5 (0.5) | 0 | 0 |
| General disorders and administration site conditions | 15 (3.0) | 1 (0.2) | 16 (1.5) | 3 (1.0) | 1 (0.3) |
| Drug withdrawal syndrome | 4 (0.8) | 1 (0.2) | 5 (0.5) | 3 (1.0) | 1 (0.3) |
| Investigations | 10 (2.0) | 2 (0.3) | 12 (1.1) | 4 (1.3) | 12 (4.0) |
| Drug screen positive | 8 (1.6) | 2 (0.3) | 10 (0.9) | 4 (1.3) | 11 (3.7) |
| Nervous system disorders | 22 (4.5) | 0 | 22 (2.0) | 1 (0.3) | 1 (0.3) |
| Headache | 5 (1.0) | 0 | 5 (0.5) | 0 | 0 |
| Psychiatric disorders | 17 (3.4) | 0 | 17 (1.6) | 2 (0.7) | 2 (0.7) |
| Drug abuse | 6 (1.2) | 0 | 6 (0.5) | 2 (0.7) | 1 (0.3) |

Cross Reference: [Tables 14.3.1.17](#) and [Table 14.3.1.18](#); [Appendix 16.2.7.1](#). Narratives are contained in section 14.3.3.

Percentages are based on N. Multiple occurrences of the same adverse event in 1 individual are counted only once. MedDRA Version 15.0 was used to code adverse events.

(CSR ONU3701, p. 149)

In response to an IR, the Applicant provided incidence tables for the incidence of TEAS leading to study drug discontinuation for subjects who remained in the study but discontinued study drug and those who discontinued both study drug and the study. Based upon terms and a sample of narratives, it appears that those patients who discontinued the study drug and discontinued study experienced the more serious or severe AEs. These findings are shown in Tables 31 and 32 below.

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Table 31. Study ONU3701: Incidence of TEAS Leading to Study Drug Discontinuation for Subjects Who Remained in the Study in the double-blind period.

| MedDRA System Organ Class Preferred Term | Placebo (N=302) n (%) | OXN (N=298) n (%) | Total (N=600) n (%) |
|--|-----------------------------|-------------------------|---------------------------|
| Any Adverse Events | 9 (3.0) | 7 (2.3) | 16 (2.7) |
| Eye disorders | 0 | 2 (0.7) | 2 (0.3) |
| Lacrimation increased | 0 | 1 (0.3) | 1 (0.2) |
| Ocular hyperaemia | 0 | 1 (0.3) | 1 (0.2) |
| Gastrointestinal disorders | 2 (0.7) | 3 (1.0) | 5 (0.8) |
| Nausea | 2 (0.7) | 1 (0.3) | 3 (0.5) |
| Vomiting | 0 | 2 (0.7) | 2 (0.3) |
| Abdominal pain upper | 0 | 1 (0.3) | 1 (0.2) |
| General disorders and administration site conditions | 3 (1.0) | 1 (0.3) | 4 (0.7) |
| Drug withdrawal syndrome | 3 (1.0) | 1 (0.3) | 4 (0.7) |
| Investigations | 0 | 1 (0.3) | 1 (0.2) |
| Drug screen positive | 0 | 1 (0.3) | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 0 | 1 (0.3) | 1 (0.2) |
| Intervertebral disc disorder | 0 | 1 (0.3) | 1 (0.2) |
| Nervous system disorders | 1 (0.3) | 0 | 1 (0.2) |
| Cognitive disorder | 1 (0.3) | 0 | 1 (0.2) |
| Psychiatric disorders | 0 | 1 (0.3) | 1 (0.2) |

(Applicant's response to IR, 5/22/14, DARRTS entry)

Table 32. Study ONU3701: Incidence of TEAS Leading to Study Drug Discontinuation and Study Discontinuation

| MedDRA System Organ Class Preferred Term | Placebo (N=302) n (%) | OXN (N=298) n (%) | Total (N=600) n (%) |
|---|-----------------------------|-------------------------|---------------------------|
| Any Adverse Events | 11 (3.6) | 14 (4.7) | 25 (4.2) |
| Cardiac disorders | 1 (0.3) | 0 | 1 (0.2) |
| Acute myocardial infarction | 1 (0.3) | 0 | 1 (0.2) |
| Gastrointestinal disorders | 1 (0.3) | 1 (0.3) | 2 (0.3) |
| Rectal perforation | 0 | 1 (0.3) | 1 (0.2) |
| Vomiting | 1 (0.3) | 0 | 1 (0.2) |
| Hepatobiliary disorders | 0 | 1 (0.3) | 1 (0.2) |
| Cholecystitis | 0 | 1 (0.3) | 1 (0.2) |
| Infections and infestations | 1 (0.3) | 0 | 1 (0.2) |
| Gangrene | 1 (0.3) | 0 | 1 (0.2) |
| Investigations | 4 (1.3) | 11 (3.7) | 15 (2.5) |
| Drug screen positive | 4 (1.3) | 10 (3.4) | 14 (2.3) |
| Weight decreased | 0 | 1 (0.3) | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 2 (0.7) | 0 | 2 (0.3) |
| Arthralgia | 1 (0.3) | 0 | 1 (0.2) |
| Systemic lupus erythematosus | 1 (0.3) | 0 | 1 (0.2) |
| Nervous system disorders | 0 | 1 (0.3) | 1 (0.2) |

(Applicant's response to IR, 5/22/14, DARRTS entry)

Discontinuation AE Terms of Interest Study ONU3701

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One case was identified with a discontinuation AE term of interest (determined by this reviewer as unexpected or unusual terms) and possible causality to study drug, narrative below:

- Study ONU3701 - Subject 0036017; 57 year old female, developed **angioedema** on day ^(b) ₍₆₎ of open-label treatment while on OXN 40/20 mg. The subject was treated with diphenhydramine and ranitidine. The subject was not randomized, study drug was stopped the same day, and the subject discontinued from study the following day. The event was listed as ongoing in the narrative. This proposed label contains information regarding allergic reactions.

Integrated (Pooled) Discontinuation AEs

- Group C (Chronic Pain, Healthy, Abuse Liability and Special Populations and Situations): Overall, 280 subjects who were exposed to OXN discontinued study drug because of AEs with an incidence rate (incidence per 100 subject-years of exposure) of 25%. Normalization for subject exposure did not change the profile of the most common types of AEs resulting in discontinuation, which were SOCs for GI (100 cases, rate 9.0 per 100 subject years), Nervous system disorders (58 cases, rate 5.2 per 100 subject years) and general disorders and administration site conditions (47 cases, rate of 4.2 per hundred subject years).
- Group B (Phase 1 Single and Multiple Dose Studies in Healthy Subjects): The incidence of discontinuations in the treatment arms of interest was 0% in placebo, 3% in OxyCR, 2% in Naloxone and 1% in OXN.
- Group A1B (Oxycodone-controlled studies): The overall incidence of AE discontinuations across all treatment periods was similar in the OxyCR treatment group (7%) compared to OXN treatment group (6%) with similar types of discontinuation AEs with the incidence of gastrointestinal AEs leading to discontinuation (3.2% and 2.9%, respectively).
- Group A1A (nonmalignant pain): Overall, the incidence of AEs leading to discontinuation was similar in the OXN treatment arm (6%) and placebo (7%) during the double-blind period of these studies. The types of discontinuation AE terms were generally similar between the two groups. Although the SOC, Investigations, had the overall highest percentage of patients with AE discontinuations (3%), this was due to the preferred term, "drug screen positive." GI disorders was the SOC with the second highest incidence occurring in placebo 2% and OXN 1%. Interestingly, the incidence of GI discontinuation due to nausea was higher in placebo (1%) compared to OXN (<1%) with vomiting occurring equally in placebo and OXN (<1%).

Table 33 displays the types of AEs leading to discontinuation in ≥2 subjects in the placebo-controlled studies in nonmalignant pain (Group A1A).

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Table 33. Incidence of AEs leading to Discontinuation (≥ 2 Subjects in Any Treatment Group) During the Double-blind Period of Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A Safety Population)

| MedDRA System Organ Class Preferred Term | Placebo (N=460) n (%) | OXN (N=451) n (%) |
|---|-----------------------------|-------------------------|
| Subjects With Any AEs Leading to Discontinuation | 34 (7.4) | 27 (6.0) |
| Ear and Labyrinth Disorders | 3 (0.7) | 0 (0.0) |
| Vertigo | 3 (0.7) | 0 (0.0) |
| Gastrointestinal Disorders | 9 (2.0) | 6 (1.3) |
| Nausea | 8 (1.3) | 3 (0.7) |
| Vomiting | 3 (0.7) | 3 (0.7) |
| General Disorders and Administration Site Conditions | 8 (1.7) | 2 (0.4) |
| Drug withdrawal syndrome | 3 (0.7) | 1 (0.2) |
| Malaise | 2 (0.4) | 0 (0.0) |
| Investigations | 4 (0.9) | 13 (2.9) |
| Drug screen positive | 4 (0.9) | 11 (2.4) |
| Musculoskeletal and Connective Tissue Disorders | 4 (0.9) | 1 (0.2) |
| Myalgia | 2 (0.4) | 0 (0.0) |
| Nervous System Disorders | 4 (0.9) | 2 (0.4) |
| Dizziness | 3 (0.7) | 0 (0.0) |
| Headache | 2 (0.4) | 0 (0.0) |
| Psychiatric Disorders | 5 (1.1) | 4 (0.9) |
| Anxiety | 0 (0.0) | 2 (0.4) |
| Drug abuse | 2 (0.4) | 1 (0.2) |
| Apathy | 2 (0.4) | 0 (0.0) |
| Vascular Disorders | 3 (0.7) | 1 (0.2) |
| Hypertension | 2 (0.4) | 1 (0.2) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets.

Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Adverse events are sorted alphabetically by system organ class and by descending frequencies in the OXN column. Multiple occurrences of the same adverse event in one individual are counted only once.

(ISS, p. 185)

Discontinuation AEs Summary: In general, the discontinuation AEs for study drug OXN were consistent with the known profile of opioid analgesics.

7.3.4 Significant Adverse Events

In the ISS, the Applicant identified Opioid Bowel Dysfunction (MedDRA preferred terms nausea, vomiting, constipation, abdominal pain, abdominal distension, decreased appetite, flatulence) and Diarrhea-Related AEs (MedDRA preferred terms diarrhea, frequent bowel movements, antidiarrheal supportive care, defecation urgency) as CMQ (Custom MedDRA Query) based on the known safety profile of oxycodone and interest in gaining a better understanding of the safety profile of OXN with regard to GI function.

The overall incidence of opioid bowel dysfunction was slightly lower in OXN-treated (11%) compared to OxyCR (15%) in the Group A1 (controlled and open-label extension studies in patients with chronic nonmalignant pain) safety population during the OLT (open-label titration) period. Specifically, nausea and vomiting occurred with less

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frequency in OXN than OxyCr. Interestingly, constipation occurred with a higher incidence in OXN, as shown in Table 34 below.

Table 34. Incidence of Opioid Bowel Dysfunction-related AEs during the Open-Label Titration Period (Group A1 Safety Population)

| Selected AE Grouping Preferred Term | OXY CR (N=1122) n (%) | OXY IR (N=586) n (%) | Previous Prescribed Medication (N=297) n (%) | OXN (N=1095) n (%) |
|--|-----------------------------|----------------------------|--|--------------------------|
| Opioid Bowel Dysfunction | 173 (15.4) | 84 (14.3) | 9 (3.0) | 125 (11.4) |
| Nausea | 110 (9.8) | 23 (3.9) | 2 (0.7) | 80 (7.3) |
| Constipation | 22 (2.0) | 49 (8.4) | 4 (1.3) | 28 (2.6) |
| Vomiting | 58 (5.2) | 22 (3.8) | 1 (0.3) | 25 (2.3) |
| Abdominal pain | 12 (1.1) | 2 (0.3) | 1 (0.3) | 13 (1.2) |
| Decreased appetite | 14 (1.2) | 1 (0.2) | 1 (0.3) | 7 (0.6) |
| Flatulence | 8 (0.7) | 1 (0.2) | 0 (0.0) | 4 (0.4) |
| Abdominal distension | 5 (0.4) | 0 (0.0) | 0 (0.0) | 3 (0.3) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets.

Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Multiple occurrences of the same adverse event in one individual are counted only once.

Studies in group A1: [ONU3701](#), OXN3001, OXN3006, [OXN3401](#), OXN3503, and [OXN4502](#).

Only study ONU3701 used OXN during open-label titration. Group A1B studies required a medical history of constipation as an inclusion criterion.

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However, in the double-blind period of the Group A1 safety population, there was an overall greater incidence of opioid bowel dysfunction (17%) in OXN-treated vs placebo (11%) and OxyCR (16%). The incidence of nausea and vomiting was slightly higher in OXN compared to OxyCR and placebo. The incidence of constipation was slightly lower in OXN (4%) compared to OxyCR (6%) but higher than placebo (3%) as shown in Table 35 below.

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Table 35. Incidence of Opioid Bowel Dysfunction-related AEs during the Double-blind Period (Group A1 Safety Population)

| Selected AE Grouping Preferred Term | Placebo (N=460) n (%) | OXY CR (N=554) n (%) | Codeine/ Paracetamol (N=123) n (%) | OXN (N=968) n (%) |
|--|-----------------------------|----------------------------|---|-------------------------|
| Opioid Bowel Dysfunction | 51 (11.1) | 87 (15.7) | 38 (30.9) | 164 (16.9) |
| Nausea | 26 (5.7) | 40 (7.2) | 19 (15.4) | 83 (8.6) |
| Constipation | 13 (2.8) | 31 (5.6) | 16 (13.0) | 42 (4.3) |
| Vomiting | 11 (2.4) | 18 (3.2) | 6 (4.9) | 38 (3.9) |
| Abdominal pain | 9 (2.0) | 8 (1.4) | 5 (4.1) | 25 (2.6) |
| Decreased appetite | 2 (0.4) | 5 (0.9) | 2 (1.6) | 10 (1.0) |
| Flatulence | 2 (0.4) | 3 (0.5) | 3 (2.4) | 7 (0.7) |
| Abdominal distension | 2 (0.4) | 2 (0.4) | 2 (1.6) | 3 (0.3) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets.

Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Multiple occurrences of the same adverse event in one individual are counted only once.

Studies in group A1: [ONU3701](#), [OXN3001](#), [OXN3006](#), [OXN3401](#), [OXN3503](#), and [OXN4502](#). Studies OXN3001, OXN3006, and OXN3503 required a medical history of constipation as an inclusion criterion.

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The clinical significance of this is unclear, given the variability in study designs and patient population in the Group A1 pool. Similar findings were seen in double-blind period of Group A1A (placebo-controlled nonmalignant pain) with the percentage of subjects with opioid bowel dysfunction-related AEs 16% in OXN vs 11% in placebo. Based upon CMQ findings in the placebo-controlled studies, there was a greater incidence of opioid bowel dysfunction-related AEs in OXN compared to placebo but similar to OxyCR.

7.3.5 Submission Specific Primary Safety Concerns

Opioid Withdrawal:

Due to the differences in study designs of the pooled studies, it is problematic to compare the incidences of opioid withdrawal among studies. Therefore, although the opioid withdrawal findings from pooled Group A studies are included in this review, my primary discussion of opioid withdrawal relies upon the findings from key efficacy study ONU3701 since this study was conducted in the US, included prespecified protocol parameters to actively identify opioid withdrawal (i.e., investigators were required to evaluate any subject with a COWS score ≥ 5 or a modified SOWS score ≥ 10 to determine whether an AE of opioid withdrawal had occurred), and was placebo-controlled.

Study 3701: Methods Used to Identify Findings Consistent with Opioid Withdrawal (OW)
Opioid withdrawal and possible opioid withdrawal were identified by the Applicant in the as follows:

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- Investigator-identified OW AEs captured by either the MedDRA SMQ search using the terms “drug withdrawal” or “withdrawal syndrome”. Investigators were required to evaluate all subjects who reported COWS scores ≥ 5 or SOWS scores ≥ 10 to determine if an AE of opioid withdrawal occurred
- Prospective, blinded Independent Adjudication Committee Review (medical and statistical personnel from an independent third-party contactor). The criteria used by the committee is as follows:
 - 1) COWS score (if available) ≥ 13 ; 2) AE of opioid withdrawal recorded by the investigator in the CRF; 3) 3 or more criteria of opioid withdrawal as defined by the DSM-IV diagnostic criteria occurring within a span of 7 days; and/or 4) committee member clinical judgment. For criterion 3, additional preferred terms of AEs related to the DSM-IV diagnostic criteria were used to identify additional potential opioid withdrawal cases, described as sensitivity 1 and 2 in the adjudication report. The committee could conclude that the symptoms did not represent opioid withdrawal if there was another illness (reported in the AEs or other data) that better accounted for a subject’s symptoms. Subjects could have more than one episode of opioid withdrawal based on any of the four criteria. Episodes of opioid withdrawal occurring in subjects within 7 days after transitioning from OXY CR to OXN in the extension period were attributed to OXN. For episodes identified by the adjudication committee based on 3 or more symptoms of opioid withdrawal, the severity was based on the worst severity identified by the investigator for the AE symptoms related to opioid withdrawal. Episodes of possible opioid withdrawal based on a COWS score ≥ 13 did not have a severity rating. The adjudication committee did not use the SOWS score alone as a criterion for opioid withdrawal given the subjective nature of the scale, but did have access to the SOWS scores of subjects in making their determinations.
- Plasma concentrations of oxycodone, naloxone and naloxone- 3β glucuronide collected per protocol in Study ONU3701 at prerandomization (Visit 3), midtreatment (Visit 6), end of treatment (visit 8), and while in opioid withdrawal.

Limitations of OW Interpretation of Findings:

1. Plasma concentrations of oxycodone and naloxone were not collected on all subjects who experienced OW and specifically not during the event of OW in many cases.

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2. OxyIR was allowed as rescue medication up to 40 mg total daily dose at the time of conversion to OXN in the OLT and could be used during the DB period. Thus, OW might not have occurred if a person took more opioid than the fixed dose.

Study ONU3701 Opioid Withdrawal Results

Key Findings

- There were a total of 41 (4%) subjects [27 investigator-identified + 14 adjudication committee identified] of 1095 subjects in the safety population who experienced a total of 43 TEAEs of opioid withdrawal during open-label titration (23 subjects) and double-blind periods (18 subjects [7 placebo; 11 OXN]
 - Investigator-identified OW: The incidence of investigator-reported opioid withdrawal during the double-blind period was slightly higher in the OXN treatment group (8 of 298 subjects [3%]) compared to the placebo group (6 of 302 subjects [2%]). The incidence of investigator-identified OW in the OL was 13 of 1095 (1%).
 - Adjudication-identified: In addition to the investigator-identified reports of OW, an additional three subjects were identified in OXN-treated and one in placebo-treated, making the total percentage 11/298 (4%) OXN-treated and 7/302 (2%) in the double-blind period. The number of Adjudication Committee-identified OW in the OL was ten subjects for a total of 23/1095 (2%).
- Of the 41 subjects with evidence of opioid withdrawal, 26 were female and 15 were male. Of the 43 total cases, most (95%) were mild or moderate. Two cases were severe (Subject 0036013 and Subject 0042009), discussed below. There were no SAEs of opioid withdrawal reported in these subjects.

Strategy for Conversion from Incoming Opioid to OXN: The Applicant's full strategy (conversion tables) for converting the subject from their incoming (pre study opioid) to OXN for Study ONU3701 is found in Appendix A and B. Investigators were given a recommended starting point for converting from a subject's incoming opioid therapy to OXN but investigator judgment was to be used for selecting the initial starting dose of OXN based on both the recommended starting dose per the conversion chart and the subject's medication information.

- There were 1095 subjects entering the OLT period, of whom 601 (54%) were converted to a dose of OXN and randomized at Visit 3. Of the 494 subjects (45%) who did not qualify for randomization, 107 (10%) discontinued due to lack of therapeutic effect and 95 (9%) discontinued due to an AE.
- Of the 1095 subjects entering the OLT period, 13 subjects (1%) experienced opioid withdrawal or possible opioid withdrawal after conversion from their incoming opioid therapy to OXN. Based on morphine equivalent calculations, in

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8 subjects the OXN daily dose was lower than the dose of the incoming opioids. All of the cases were mild to moderate in intensity of withdrawal except two. Of the two severe cases:

- Subject 0042009 experienced severe OW after converting from morphine 30 mg 2 times daily and Oxycocet 7.5/325 mg prn to OXN 10/5 mg BID. The use of prn Oxycocet may have resulted in the investigator underestimating the dose of OXN as the actual conversion dose of OXN should have been OXN 20/10 mg BID (although the investigator judgment was allowed).
- Subject 0036013 had severe opioid withdrawal after discontinuing OXN in open-label titration and switching to cyclobenzaprine and a lidocaine patch (he did not qualify for the double-blind treatment due to inadequate pain control).
- The Applicant maintains that the conversion strategy was appropriate because the low discontinuation rate (10%) due to lack of therapeutic effect in the OLT period with uncontrolled moderate to severe pain despite receiving their incoming opioids is indicative that excessive pain due to conversion to an inadequately low dose was not a significant issue and that the conversion factor was not too high because there was only one report or overdose (an SAE in a subject 0039071 who took 30 rescue capsules of OxyIR 5mg and five extra doses of OXN 10/5 mg over a 4-day period but did not have any symptoms).

Opioid Withdrawal and Morphine Equivalent Dose Changes

There were five times during the study when changes in morphine equivalents (transitions) could have occurred: 1) OLT when patients were being converted (transitioning) from their incoming pre-study opioid to OXN, (2) OLT when patients were on OXN and being titrated to a higher or lower dose, (3) Randomization/Double-blind when patients were transitioning from OL OXN to DB OXN or to placebo (4) During the double-blind when OXN was being titrated and (5) During DB when OXN was being tapered or subjects were transitioning from their OXN dose to their original opioid treatment at the end of study. In order to determine the association between morphine equivalents and the onset of OW, the morphine equivalent changes were categorized as increased, decreased, unchanged or indeterminate in relation to the onset of OW symptoms. In cases where the subject had been on a stable dose of opioid (or placebo) for 7 or more days, the dose was considered "the same" for the purpose of these tables (for the placebo group, the 7 days were counted from the end of the blinded opioid taper period). The morphine equivalents of the opioid therapies before and after each transition based on the investigator's assessments and the conversion ratio in the protocol were used to determine whether the morphine equivalents had decreased, remained the same or increased.

It is anticipated, based upon the known physiology of opioids, that OW may be experienced when morphine equivalents are decreased (i.e., subject is moving from a higher to lower dose of morphine equivalents). However, in theory, OW should not have occurred during times when the morphine equivalents were unchanged or

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increased. OW events during these times may suggest that naloxone has some causal role.

The total number of cases (events) of OW and the relation to the morphine equivalents are summarized in the Table 36 below, with discussion in Table 37.

Table 36. Study ONU3701 Morphine Equivalent Changes and OW Onset

| Treatment Group | ME Increased | ME Decreased | ME Unchanged | Indeterminate |
|-------------------|--------------|--------------|--------------|---------------|
| OXN [Cases=36] | 5 (14) | 22 (61) | 9 (25) | 0 |
| Placebo [Cases=7] | 0 | 5 (71) | 2 (28) | 0 |

(Table, reviewer); ME=morphine equivalent

Table 37. Study ONU3701 ME Summary by Period

| ME | Reviewer Comments |
|-----------|--|
| Increased | All five cases of OW with ME increased occurred in OLT (two when the subject was being converted from incoming opioid to OXN and the other three cases when subjects were being titrated on OXN). Two cases were at OXN doses of 40 mg, one OXN 60 mg and two OXN 80 mg. It is difficult to explain why OW occurred when the ME dose was higher. One possible explanation is that the conversion ratio was not appropriate. In this small number of subjects, however, no generalizability regarding the adequacy of conversion factors can be made. Additionally, the investigator could determine the dose based on investigator judgment. |
| Decreased | Six cases of OW occurred when subjects were being converted from incoming opioid to OXN and 6 cases (events) when subjects were being tapered from OXN to outgoing opioid in the OLT period. In the DB period, seven cases occurred when subjects were being tapered from OXN to outgoing opioid after the double-blind period. There were five cases of OW in Placebo cases. The majority of cases occurred when ME were being decreased. The occurrence of opioid withdrawal when a ME dose is being decreased is expected and consistent with what is known regarding opioid withdrawal and opioids. Most of these cases had onset of OW within 3 days of the dose adjustment. This would suggest that the role of naloxone is minimal or nonexistent in these cases. |
| Unchanged | There were three cases when OW occurred when subjects were being converted from incoming opioid to OXN and one case when the subject was being titrated while on OXN in the OLT period. In the DB period, there were five cases when subjects were on a "stable" dose of OXN but were transitioning from OLT to DB. There were two cases in placebo. See discussion below regarding those cases where OW occurred in unchanged ME. |

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The OW cases of concern are those that occurred when the conversions of morphine equivalents were the same (unchanged). Eleven cases involved conversions with essentially the same morphine equivalents or occurred while on a stable dose of OXN.

- Four cases occurred during the open-label titration period. In 3 cases, withdrawal occurred within 3 days of conversion from the incoming opioid. In 1 case, withdrawal occurred while on a stable dose of OXN during open-label titration (19 days after uptitration to the 80/40 mg total daily dose).
- In 7 cases, opioid withdrawal occurred during the double-blind period while on a stable dose of study drug (5 cases with subjects receiving OXN and 2 cases with subjects receiving placebo). In the 5 cases receiving OXN, the onset of opioid withdrawal occurred within a range of 9-96 days from the start of the current dose of study drug. The two placebo cases occurred 25 and 56 days after randomization.

Opioid Withdrawal and Dose Response

In the investigator-identified cases of opioid withdrawal, although there was not a dose-response for drug withdrawal syndrome in the OXN arm, the highest incidence of withdrawal (5%) occurred at the highest dose, as shown in Table 38.

Table 38. Incidence of TEAEs reported in ≥2% Of Subjects by Dose Level: Randomized Safety Population (Double-blind Period)

| MedDRA System Organ Class Preferred Term | Placebo (N=302) n (%) | OXN 10/5 mg (N=59) n (%) | OXN 20/10 mg (N=78) n (%) | OXN 30/15 mg (N=69) n (%) | OXN 40/20 mg (N=92) n (%) |
|---|-----------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Drug withdrawal syndrome | 6 (2.0) | 0 | 1 (1.3) | 1 (1.4) | 5 (5.4) |

(Sponsor's table, CSR ONU3701, p. 138)

Opioid Withdrawal and Pre-study Opioid: Overall, no trends could be identified with regard to the occurrence of opioid withdrawal and pre-study (incoming) opioid. In Study ONU3701, most cases of OW in OXN-occurred during the OLT period (24 events) compared to the double-blind period (12 events). The most common pre-study opioid in the OLT was Vicodin alone or in combination (11 subjects), but morphine sulfate, Ultracet, tramadol and methadone were also reported. In response to an IR sent by the Agency for the Applicant to analyze subjects' pre-study opioid and the occurrence of OW or lack of therapeutic effect, no major differences were identified.

Opioid Withdrawal and Preferred Terms: The terms with the highest incidence in the OLT period were Drug Withdrawal Syndrome, nausea, chills, diarrhea, hyperhidrosis, withdrawal syndrome, abdominal pain upper, nervousness, cold sweat and the most frequent terms in the DB period in cases of opioid withdrawal was Drug Withdrawal Syndrome in OXN-treated (64%) and placebo (86%). Other frequently occurring terms in the OXN-treated subjects during the DB period who experienced OW were hot flush, nausea, anxiety, cold sweat, and insomnia.

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Opioid Withdrawal and Temporal Relationship: In general, in those events which occurred due to a change in ME, the onset of OW was typically within three days. Events which occurred during the double-blind were more variable. Overall, no trends were identified.

Opioid Withdrawal and Withdrawal Scales: Opioid Withdrawal Scales (see Appendix C) included the COWS (Clinical Opioid Withdrawal Scale) and modified SOWS (Subjective Opioid Withdrawal Scales). COWS and mSOWS scores were obtained during the Prerandomization Phase at Screening (visit 1) and V2 , during the Double-blind Phase at every visit and in the Follow- up Phase. Mean COWS and SOWS scores had no clinically meaningful differences in terms of actual identified cases of opioid withdrawal symptoms across placebo and OXN treatment groups in the double-blind treatment periods. No subject was identified by the Adjudication Committee in Study ONU3701 as a possible OW case due to COWS score ≥ 13 .

Opioid Withdrawal and Plasma Concentration: Among 41 subjects in Study ONU3701 who experienced possible OW, 14 subjects randomized to OXN treatment had one or more plasma concentrations obtained at steady state before, during and/or after opioid withdrawal events. Of the 11 subjects who experienced OW during the double-blind period when ME dose was unchanged, six had available mean naloxone concentrations. The subject with the highest plasma concentration of naloxone was 1.09 ng/ml (on 30/15 mg OXN) with the highest plasma concentration of naloxone in all subjects being 2.04 ng/mL. The Applicant determined that mean naloxone concentrations were similar between those subjects who experienced OW and those who did not and that there is no clear evidence to indicate a relationship between plasma concentrations and OW in Study ONU3701. Because of the wide range of values and missing data, I am unable to draw any conclusions regarding opioid withdrawal and plasma concentrations. As per Dr. Nallani's clinical pharmacology review, "The average plasma naloxone concentrations observed with the use of Targiniq ER 40/20 mg bid in chronic pain patients were low and highly variable. There were a few individuals who had plasma concentrations up to 2 ng/mL; however, these individuals did not exhibit opioid withdrawal symptoms in study ONU3701".

Discontinuation OW: The Discontinuation Review Adjudication Committee (DRAC) reviewed all reasons for discontinuation, and also reviewed each of the discontinued patient's COWS score ≥ 13 , AE of opioid withdrawal recorded by the investigator in the CRF, and patients with ≥ 3 symptoms of opioid withdrawal defined by DSM-IV Diagnostic criteria following opioid dose reduction or cessation for Study ONU3170. Using these criteria, the DRAC identified 11 subjects who discontinued during the double-blind study treatment as having evidence of opioid withdrawal at the time of discontinuation. Of these eleven, four (0046002, 0037013, 0053005 and 0016003) were placebo-treated. An additional two subjects who discontinued during the double-

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blind treatment period were identified as having evidence of opioid withdrawal at some other point in the study.

Pooled Group A (malignant and nonmalignant chronic pain patients)

The interpretation of the pooled OW results is limited by the following factors:

1) Different study designs and patient populations and, 2) Uncontrolled (open-label extension) studies contribute 20 of the 100 subjects identified with possible OW.

Results:

- A total of 100 subjects of 3286 (3%) experienced 108 possible opioid withdrawal episodes (determined by the investigator and/or the Adjudication Committee) in the pooled Group A studies across all periods and treatments.
- Of the 100 subjects who experienced OW, 2% occurred in OXN during OL titration compared to 2% OxyCR and in the Double-blind period, 3% OXN-treated experienced OW compared to 2% placebo. In the Open-label extension period, all subjects received OXN and the incidence of OW in the open-label extension period was 2%.
- The Adjudication Committee identified a total of 22 subjects with evidence of opioid withdrawal close to time of double-blind study medication discontinuation

The opioid withdrawal results from the Group A pooled studies are shown below in Table 39.

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Table 39. Number of Episodes (All Events of Opioid Withdrawal Regardless of Method of Identification) With Opioid Withdrawal Symptoms (Group A, Safety Population)

| Period Treatment | Number of Subjects (N) | Identification Method | | | Total Number of Episodes n | Total Number of Subjects With Episodes n (%) |
|---|------------------------|-----------------------|--------|-------------------|----------------------------|--|
| | | Adverse Events n | COWS n | Combined Events n | | |
| Total Across All Periods and Treatments | 3286 | 58* | 6 | 51 | 2 | 108 |
| Open-label Titration | | | | | | |
| OXY CR | 1122 | 1 | 2 | 10 | 0 | 13 (1.2) |
| OXY IR | 586 | 0 | 0 | 1 | 0 | 1 (0.2) |
| Previously Prescribed Medication | | | | | | |
| OXN | 297 | 0 | 0 | 0 | 0 | 0 (0.0) |
| | 1095 | 13* | 0 | 10 | 1 | 23 (2.0) |
| Double-Blind | | | | | | |
| Placebo | 460 | 7 | 1 | 3 | 0 | 9 (2.0) |
| OXY CR | 646 | 5 | 0 | 5 | 0 | 10 (1.5) |
| Codeine/Paracetamol | | | | | | |
| OXN | 123 | 0 | 0 | 0 | 0 | 0 (0.0) |
| | 1060 | 18 | 3 | 15 | 1 | 32 (2.8) |
| Open-label Extension | | | | | | |
| OXN | 970 | 14 | 0 | 7 | 0 | 20 (2.1) |

COWS = Clinical Opiate Withdrawal Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; OXN = oxycodone /naloxone controlled-release tablets; OXY CR = oxycodone controlled release tablets; OXY IR = oxycodone immediate- release..

Note: N = Number of subjects in the treatment group and period shown. Percentages are based on N. Some subjects may have had more than 1 episode, so the total number of episodes may be greater than the total number of subjects with episodes. Any single episode could have been identified by multiple methods, so the sum of the numbers across a row may be greater than the total number of episodes.

"Combined Events" includes the DSM-IV adverse events-related method, plus 2 sensitivity methods: "Sensitivity 1" is similar to DSM-IV, but uses adverse events related to events described in COWS; "Sensitivity 2" is similar to DSM-IV, but uses other adverse events related to those in the DSM-IV criteria.

"Committee" denotes committee's clinical judgment.

Studies in group A: [ONU3701](#), [OXN3001](#), [OXN3006](#), [OXN3401](#), [OXN3503](#), [OXN4502](#), and [OXN2001](#). Studies with extensions: OXN3001, OXN3006, OXN3401, and OXN2001.

*See text in [section 7.7.6.3](#) for explanation of differences in these values from Post-text Table 8.2.5

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Narratives: Narratives of subjects identified as having experienced OW or possible OW were reviewed, with particular attention to those in which OW occurred when the OXN doses were stable or increased, when OW occurred when subjects were converted from oxycodone to OXN, discontinuations and severe cases. Most cases of OW resolved without treatment (one case required antihypertensive medication). Because OxyIR was allowed, the total daily oxycodone dose when OW occurred was not based solely on the OXN dose so this confounded the interpretation. In general, there were no trends identified other than those already discussed.

Applicant's OW Conclusions:

- In Group A studies, the incidences of withdrawal episodes were low, with an approximately 1% higher incidence of OW with OXN compared with OxyCR in the OL and double-blind treatment periods (Integrated Studies).
- This difference may be due to the presence of naloxone or due to chance variation.
- Overall, the incidence of OW with OXN was low and the severity typically mild to moderate.

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- Any potential increase in incidence due to the presence of naloxone in OXN appears to be minimal.

Reviewer's OW Conclusions:

The Applicant maintains that most cases of opioid withdrawal in OXN-treated patients occurred during times of transition (i.e., changes in morphine equivalents up or down). Although opioid withdrawal occurred in Study ONU3701 in OXN-treated subjects when: 1) Transitioning from their original, non-study opioid to OXN in the open-label titration (OLT) period, 2) Titrating to a higher or lower dose of OXN in the open label titration period, 3) Titrating OXN during the Double-blind period or transitioning to placebo from OXN, and 4) Transitioning from their OXN dose to their original opioid treatment at the end of the study, opioid withdrawal occurred at other times as well. However, I agree with the Applicant's assessment that most cases of OW occurred during times of transition as summarized below:

- There were a total of 43 OW events which occurred in Study ONU3701 (one subject each experienced more than one event in OLT and DB periods)
 - OLT: Most (24/43 [56%]) of OW events occurred during the OLT period. There was no dose effect noted and most (15/24 [62%] events occurred when morphine equivalents were being decreased during a transition. Of the 24 events of withdrawal in the OLT, the dose of OXN was as follows:
 - OXN 20 mg: 8/24 events (33%); 6/8 [75%] events of withdrawal occurred at OXN 20 mg (total daily dose) when subjects were being transitioned from incoming opioid to OXN with a decrease in morphine equivalents. Two occurred when ME were unchanged.
 - OXN 80 mg: 8/24 events (33%); 5/8 [62%] occurred when patients were transitioning from OXN to outgoing opioid with a decrease in morphine equivalents; 2 when ME increased and one ME unchanged.
 - The remainder (8 events) of withdrawal in the OL titration period occurred at OXN 40 mg (4 events with one decreased in ME and OXN 60 mg (4 events with 3 decrease in ME)
 - DB: In the double-blind period, a total of 19/43 (44%) events of OW occurred. There were 12 events which occurred in OXN-treated and 7 events in placebo. Of the OXN-treated, 7/12 [58%] occurred when ME were being decreased and 5/12 [42%] when ME were unchanged. There was not a consistent dose response, but most 7/12 [58%] occurred on OXN 80 mg total daily dose. The 12 OXN-treated events occurred at the following doses:
 - OXN 80 mg: 7 events (58%); 4 decreased in ME and 3 unchanged
 - OXN 40 mg: 3 events (25%) with all 3 decreased ME
 - OXN 20 mg and OXN 60 mg: one event each
- I agree with the Applicant's assertion that potential causes of opioid withdrawal in Study ONU3701 include: 1) conversion to an inadequate (i.e., too low) dose of

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OXN at visit 2, (2) conversion to an inadequate dose of ongoing opioid therapy after discontinuation of study drug, (3) randomization to the placebo group (despite the blinded opioid taper); (4) systemic exposure to naloxone, and (5) subject noncompliance. Other considerations in interpreting OW results in Study ONU3701 and the pooled studies include: (1) calculation of incoming morphine equivalent dose complicated by the use of prn opioid analgesics for breakthrough and by reliance on subject recalls and (2) misdiagnosis of opioid withdrawal which can be mimicked by other conditions such as viral infections, panic attacks, and other medical conditions.

- I agree with Applicant's assessment that most cases of OW occurred during time of transition, but several occurred when morphine equivalent doses were either increased or unchanged, a setting where opioid withdrawal would not be expected. It may be that the presence of naloxone played a role in these cases, however no definitive conclusions can be drawn regarding the role of naloxone in contributing to OW given the limitations noted.

II) Cardiovascular (CV) Safety

The Applicant conducted several analyses using data from the OXN clinical database, the postmarketing safety database and an epidemiologic study which served as the basis for their *Evaluation of Cardiovascular Events* document. The Division of Anesthesia, Analgesia and Addiction consulted the Division of Cardiovascular and Renal (DCRP) and the Division of Biometrics to provide input regarding whether 1) there appears to be a signal for cardiac adverse events associated with the use of OXN (including the type and extent of the signal if present), and 2) whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

Applicant's Cardiovascular Conclusions: The Applicant found that MACE (Major Adverse Cardiovascular Event) events were more frequent in the comparator arms as compared to the OXN treatment arms of both pooled GroupA1A (placebo controlled trials) and Group A1C (OXY CR-controlled trials). Exposure-corrected non-MACE cardiovascular adverse event rates were similar between OXN and comparator-treated patients. These observations were limited by the very high percentages of antecedent dropouts in the run-in periods, high censoring rate of premature withdrawals, sub-optimal CV event ascertainment in all trials, and the brief duration of follow-up in these short studies.

Agency Cardiovascular Conclusions

A) Dr. Preston Dunmon, DCRP, (consult DARRTS entry 3/20/14) addressed the following issues from DAAAP:

- 1) Assessment of whether there appears to be a signal for cardiac AEs associated with the use of OXN (including the type and extent of the signal if present). Dr. Dunmon determined that no signals for excess MACE, non-MACE CV AEs, or repolarization/conduction system toxicity with OXN are identified from these studies based on the following:
 - a. MACE events were more frequent in the comparator arms as compared to the OXN treatment arms of both pooled GroupA1A (placebo controlled

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- trials) and Group A1C (OXY CR-controlled trials) as per the limitations acknowledged by the Applicant.
- b. While no TQT (thorough QT) study was performed with the OXN combination, ECG interval analysis from pivotal trial 3701 does not demonstrate a clinically meaningful prolongation of the QT, QTcB, or QTcF.
 - c. While there were numerically more occurrences of atrial fibrillation in OXN-treated patients (by one or two cases, depending on the analysis), the numbers are too small to draw any conclusions.
 - d. Additional comments: It is unclear what if any relevance that the side effect profile of IV naloxone has to the clinical safety to oral oxycodone naloxone. However, given the lack of clinical experience with OXN in post-operative patients, it would be reasonable to at least reference the warning about these patients from the IV naloxone label.
- 2) An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal. The following conclusions were drawn:
- a. OXN appears to be associated with elevations of both SBP and DBP in patients previously treated (presumably for hypertension) and hypertensive AEs occurred. Of the nine patients experiencing an SMQ-based CV AE and opioid withdrawal symptoms in the overall population (Group C) during any study period, three of the nine experienced blood pressure elevations in close proximity to OXN dosing, one of which was a hypertensive crisis. There were no concomitant AEs involving BP elevation with withdrawal symptoms in any comparator group.
 - b. Though the numbers of subjects in which a CV AE/SAE occurred within 28 days of withdrawal symptoms was small, the hazard ratio for the time to first CV SAE was 14 times higher in patients with opioid withdrawal symptoms within 28 days ($p=0.0006$), and 5 times higher for the time to first nonserious CV AE in patients with opioid withdrawal symptoms within 28 days ($p=0.0014$), regardless of treatment.
 - c. From a mechanistic point of view, the above observations should be interpreted in the context of an understanding of the determinants of myocardial oxygen demand. Opioid withdrawal induces physiologic stress in some patients. This physiologic stress will increase myocardial work and myocardial oxygen demand. Any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease (these are not “confounders”). These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important. In the overall target populations of all of these therapies, however, this risk is small.
- B) Dr. Janelle Charles, Division of Biometrics (consult DARRTS entry dated 3/25/14) was asked by DAAAP to comment on the statistical analysis methods that were used in the CV assessments, and discuss the statistical evidence in support of the Applicant's

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CV conclusions. Dr. Charles' statistical review was based on pooled analyses and results from the clinical trial database and an epidemiologic study of the United Kingdom (UK) The Health Improvement Network (THIN) database. Dr. Charles determined that although the Applicant concluded that consistent findings across all methods of evaluation support the conclusion that there is no apparent increased CV risk with OXN treatment, a definitive conclusion that there is no CV safety concern with OXN use cannot be made from the data sources evaluated in her statistical review. Therefore, *should OXN be approved, the recommendation is that further assessment of CV safety be conducted through a postmarketing controlled study, if there is a need to further characterize the CV risk of OXN.* Some important characteristics to be considered for such a study are specific CV outcome definition, requirement for prospective blinded independent adjudication, and sufficient follow-up time to observe CV outcome in a population at risk for CV related events. Additionally, if OXN is approved, the recommendation is that findings from these CV assessments not be included in the product label.

Reviewer's Comments: I agree with the recommendations from Dr.'s Dunmon and Charles. Although no definite cardiovascular risks were seen in this program, there were limitations in study designs which interfered with the ability to interpret the findings. The final determination regarding whether additional CV studies will be required will depend, in part, upon recommendations from an Advisory Committee meeting to be held June 11 and 12, 2014 at which time cardiovascular risks associated with Peripherally Acting Mu-Opioid Receptors (PAMORA) [REDACTED] (b) (6)

[REDACTED] At the present time, there does not appear to be compelling evidence to require additional premarketing CV testing for this product and the CV safety profile included in the submission does not appear unremarkable or unexpected given the patient population.

III) Hepatic Safety: SMQ-based Hepatic Safety

Study ONU3701: There were no Hy's Law cases identified. Five subjects (0.5%) in the safety population had ALT or AST $\geq 3 \times$ ULN at any time during the study. Only one of these was OXN-treated, the others were placebo. The narratives for these patients were reviewed. The OXN-treated subject (ID 0090014) was a 36-year old male with an AST of 359 U/L (9 \times ULN [reference range 0-40 U/L]) at the end of double-blind (study day 101, day 86 after randomization) and an ALT of 90 U/L (<2xULN [reference range 0-55 U/L] which resolved 15 days later. The OXN dose was 80 mg. The subject was treated with moxifloxacin for an upper respiratory infection on day 2 of double-blind which could have affected transaminases. The subject's bilirubin was within normal limits throughout the study. No subjects had bilirubin $\geq 1.5 \times$ ULN at any time during the study.

Integrated Hepatic Safety: The effect of OXN on hepatic safety was examined by the Applicant using the SMQ "possibly drug-related hepatic disorders". In the Group A1 study pool, no subject experienced an event that was classified as severe or

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categorized as an SAE or resulted in discontinuation during the titration period. In the double-blind, there were no notable differences in the incidences of hepatic AEs between groups. No subject in the OXN treatment group experienced a possibly drug-related hepatic SAE and one subject discontinued because of GGT increased. The incidence of possibly drug-related hepatic adverse events during the DB period is shown below in Table 40.

Table 40. Incidence of Possibly Drug-Related Hepatic Adverse Events During the Double-blind Period (Group A1, Safety Population)

| SMQ/ Sub-SMQ/ MedDRA Preferred Term | Narrow/ Broad Search Terms | Placebo (N=460) n (%) | OXY CR (N=554) n (%) | Codeine/ Paracetamol (N=123) n (%) | OXN (N=968) n (%) |
|---|-------------------------------------|-----------------------------|----------------------------|---|-------------------------|
| Subjects with at least one preferred term | Narrow Broad | 7 (1.5) 7 (1.5) | 12 (2.2) 12 (2.2) | 5 (4.1) 5 (4.1) | 13 (1.3) 13 (1.3) |
| Drug-related hepatic disorders - comprehensive search (SMQ) | Narrow Broad | 7 (1.5) 7 (1.5) | 12 (2.2) 12 (2.2) | 5 (4.1) 5 (4.1) | 13 (1.3) 13 (1.3) |
| Cholestasis and jaundice of hepatic origin (SMQ) | Narrow Broad | 0 (0.0) 0 (0.0) | 1 (0.2) 1 (0.2) | 0 (0.0) 0 (0.0) | 0 (0.0) 0 (0.0) |
| Jaundice cholestatic | Narrow | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Liver related investigations, signs and symptoms (SMQ) | Narrow Broad | 7 (1.5) 7 (1.5) | 11 (2.0) 11 (2.0) | 5 (4.1) 5 (4.1) | 13 (1.3) 13 (1.3) |
| Gamma-glutamyltransferase increased | Narrow | 0 (0.0) | 7 (1.3) | 4 (3.3) | 5 (0.5) |
| Alanine aminotransferase increased | Narrow | 6 (1.3) | 4 (0.7) | 1 (0.8) | 3 (0.3) |
| Aspartate aminotransferase increased | Narrow | 6 (1.3) | 4 (0.7) | 1 (0.8) | 2 (0.2) |
| Blood bilirubin increased | Narrow | 0 (0.0) | 2 (0.4) | 0 (0.0) | 2 (0.2) |
| Hepatic enzyme increased | Narrow | 1 (0.2) | 1 (0.2) | 0 (0.0) | 1 (0.1) |
| Liver function test abnormal | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |

MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets; SMQ = standardized MedDRA query.

Note: Percentages are based on N. Adverse events are sorted alphabetically by main/sub-SMQs, narrow/broad search category, and by descending frequencies in OXN column within narrow/broad search terms. Frequencies for broad search terms for main/sub-SMQs include broad and narrow defined preferred terms. Multiple occurrences of the same adverse event in one subject are counted only once. MedDRA Version 15.0 was used to code adverse events.

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7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 3701

The most common AEs in placebo-controlled study 3701 (incidence $\geq 2\%$ of subjects) in any group during the open-label titration and double-blind periods are GI-related as shown below in Table 41, which identifies TEAS $\geq 2\%$ of subjects taking Targiniq ER in

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the open-label titration periods and double-blind period. Note that the Drug withdrawal syndrome preferred term includes only those seven subjects who were investigator-identified (not Adjudication-identified subjects). Additionally, there was one subject (0037001) coded as Physical withdrawal symptoms who was not included in the table in the Targiniq ER double-blind period. If the physical withdrawal symptom subject is included, the total number of subjects that should be represented in the table for Drug withdrawal syndrome is eight (not seven) and the percentage of subjects who experienced Drug withdrawal syndrome in the Targiniq ER treated group is 8/298 (3%). This subject will be included in the incidence table in the label accordingly. Language will also be added to reflect the Adjudicated Cases of Drug withdrawal syndrome identified as follows:

Percentages in the table are based on adverse event reports of Drug Withdrawal in Study ONU3701. In addition to the adverse event reports, an independent Adjudication Committee identified additional possible opioid withdrawal in 10 subjects in the Open-label Period; 1 placebo and 3 Targiniq ER in the double-blind period, resulting in a total of 23/1095 (2%) in the open-label period, and in the double-blind period 7/302 (2%) in subjects treated with placebo and 11/298 (4%) in subjects treated with Targiniq ER.

Table 41. Incidence of Treatment-Emergent Adverse Reactions Reported in ≥2% of Subjects Taking Targiniq ER: Safety Population (Open-label Titration Period) and Randomized Safety Population (Double-bind Period)

| MedDRA System Organ Class Preferred Term | Open-Label Period | | Double-blind Period | |
|---|-----------------------------|---------------------------|----------------------------|--|
| | TARGINIQ (N=1095) (%) | Placebo (N=302) (%) | TARGINIQ (N=298) (%) | |
| Nausea | 7 | 5 | 8 | |
| Headache | 4 | 3 | 3 | |
| Constipation | 3 | 1 | 3 | |
| Diarrhea | 3 | 5 | 2 | |
| Abdominal pain upper | 2 | 1 | 1 | |
| Dizziness | 2 | 1 | 1 | |
| Fatigue | 2 | 1 | 1 | |
| Pruritus | 2 | 1 | 2 | |
| Vomiting | 2 | 2 | 5 | |
| Abdominal pain | 1 | 2 | 2 | |
| Anxiety | 1 | 0 | 3 | |
| Drug withdrawal syndrome | 1 | 2 | 2 | |
| Insomnia | 1 | 1 | 2 | |
| Nasopharyngitis | 1 | 2 | 2 | |
| Upper respiratory tract infection | 1 | 4 | 3 | |
| Back pain | 0 | 1 | 3 | |
| Urinary tract infection | 0 | 3 | 2 | |

(Proposed Targiniq ER label)

Integrated Findings

Group A1B pool were those studies designed to compare OXN and OXY CR. During the double-blind period, 329 subjects (60%) OXN-treated compared to 313 (56%) OxyCR-treated experienced a TEAE. The most common TEAEs during the double-blind period of the group A1B studies revealed that the types of AEs were similar between the two groups, although the incidence of any AE was higher in OXN group vs placebo except for the AEs of constipation and fatigue which occurred with a higher incidence in OXY CR (6%) and (3%) respectively compared to OXN (3%) and (2%), respectively in OXN.

7.4.2 Laboratory Findings

Study ONU3701: Overall, no clinically important differences in the incidence of blood chemistry and hematologic AEs were seen between the placebo and OXN treatment groups.

Integrated Findings: As would be expected with a population which included cancer patients, there were a number of subjects with abnormal laboratory findings. However, when analyzing Group A1A (nonmalignant) pain, the laboratory findings were not determined to be clinically important or to have patterns or trends.

7.4.3 Vital Signs

Study ONU3701: There was no evidence of a clinically significant shift in mean or median values from screening to end of open-label titration or during the double-blind period in any vital sign value for any group. Vital sign abnormalities reported as AEs during open-label titration were weight increased (3 subjects, 0.3%) and blood pressure increased (1 subject, 0.1%). Vital sign abnormalities reported as AEs during double-blind treatment were hypertension (4 subjects [1.3%] in the placebo group vs 4 subjects [1.3%] in the OXN treatment group), weight decreased (0 subjects in the placebo group vs 2 subjects [0.7%] in the OXN treatment group), and blood pressure increased and HR increased (each reported by 1 subject [0.3%] in the OXN treatment group).

Integrated Findings: The interpretation of the pooled data is somewhat limited due to the different study designs. In general, in subjects with chronic nonmalignant pain, mean changes in vital signs from baseline to the end of treatment with OXN were similar to Oxy CR and placebo. Overall, the changes from baseline were small, not dose dependent and followed no particular patterns in the Group A1A pool. Table 42 summarizes the AEs related to vital sign abnormalities in Group A1 pool.

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Table 42. Summary of AEs Related to Vital Sign Abnormalities in ≥2 Subjects with Chronic Nonmalignant Pain Treated in Any Double-blind Treatment Group (Group A1, Randomized Safety Population)

| Preferred Term | Placebo (N=460) n (%) | OXY CR (N=554) n (%) | Codeine/ Paracetamol (N=123) n (%) | OXN (N=968) n (%) |
|--------------------------|-----------------------------|----------------------------|--|-------------------------|
| Hot flush | 4 (0.9) | 6 (1.1) | 0 (0.0) | 13 (1.3) |
| Hypertension | 7 (1.5) | 9 (1.6) | 2 (1.6) | 9 (0.9) |
| Feeling cold | 1 (0.2) | 0 (0.0) | 1 (0.8) | 7 (0.7) |
| Chills | 2 (0.4) | 3 (0.5) | 0 (0.0) | 6 (0.6) |
| Weight decreased | 1 (0.2) | 3 (0.5) | 0 (0.0) | 5 (0.5) |
| Pyrexia | 2 (0.4) | 0 (0.0) | 0 (0.0) | 5 (0.5) |
| Hypertensive crisis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) |
| Blood pressure decreased | 1 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.2) |
| Heart rate increased | 0 (0.0) | 1 (0.2) | 1 (0.8) | 2 (0.2) |
| Tachycardia | 3 (0.7) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Feeling hot | 0 (0.0) | 2 (0.4) | 0 (0.0) | 1 (0.1) |

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets; OXY CR=oxycodone controlled-release tablets.

Note: Adverse events are treatment-emergent events and coded with MedDRA Version 15.0. Adverse events related to vital signs were searched by system organ class and listed by descending frequencies for OXN. Multiple occurrences of the same AE in 1 individual were counted only once.

Studies in group A1: [ONU3701](#), [OXN3001](#), [OXN3006](#), [OXN3401](#), [OXN3503](#), and [OXN4502](#)

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The findings from the OLE phases of the studies and studies in malignant patients showed more variability in vital signs, but no patterns of concern were identified. The Group B vital sign findings in healthy subjects identified no safety trends of concern.

7.4.4 Electrocardiograms (ECGs)

Dr. Dunmon, DCARP, reviewed the Applicant's ECG findings as part of his consultation discussed earlier in Section 7.3.5 of this review. His overall impression was that there were no clinically meaningful findings in Study ONU3701 or the integrated pool regarding ECG findings. I agree with that assessment and found no trends that would result in labeling recommendations.

7.4.5 Special Safety Studies/Clinical Trials

I) *Dose Finding Study (OXN2401):* The formulation for this study was not the final to-be-marketed OXN but separate formulations of Naloxone CR (NAL CR) and Oxycodone CR (OXY CR). The data from this study was included in the integrated database but, understandably, not included in the pooled database. Overall, the frequency of AEs was similar between subjects treated with OXY CR + NALCR and subjects treated with OxyCR + placebo. However, the frequency of diarrhea and treatment-emergent AEs increased with increasing NAL CR dose. As the study did not use the OXN product formulation, the findings from this study may not be generalizable to the to-be-marketed

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formulation. The most common AEs during the double-blind maintenance period in the 40 mg NAL CR group were diarrhea (31%), abdominal pain (16%), hyperhidrosis (16%) and muscle spasm (14%). In the 20mg NAL CR group, the most common AEs were abdominal pain (24%), diarrhea (22%), nausea (18%) and muscle spasm (16%). In the 10 mg NAL CR group, hyperhidrosis was most common (22%) and in the placebo group, hyperhidrosis was the most common AE (26%). The incidence of diarrhea increased with the NAL dose as follows: 6%, 18%, 22% and 31% for placebo, 10 mg, 20 mg and 40 mg NAL CR groups, respectively. The clinical significance of these findings as they relate to the final to-be-marketed OXN product is unclear.

II) Abuse Potential Studies (ONU1003, ONU1004, ONU1007, and ONU1008): The overall designs of these studies are summarized in Section 5.1 (Tables of Studies/Clinical Trials) of this review. Key features of the studies include the following:

- Study ONU1003: Abuse potential assessment of OXN tablets when chewed, crushed and insufflated (i.e., intranasal), or IV in recreational non-dependent opioid users
- Studies ONU1004 and ONU1008: Abuse potential and withdrawal effects assessment of OXN tablets when taken orally intact or chewed in methadone-maintained, opioid-dependent subjects
- ONU1007: Abuse potential assessment of OXN tablets when taken orally intact or chewed in recreational non-depend opioid users (similar to ONU1003) but focused on the abuse potential of OXN when administered orally as both intact and crushed tablets

The safety findings for each of these studies were reviewed. There were no safety trends or signals which would result in labeling actions or change the overall safety profile of study drug OXN.

III) Special Groups and Situations

Renal Impaired: Study OXN1007 showed no notable differences in AE frequency and other safety outcomes in subjects receiving OXN with respect to level of renal impairment. However, because of PK findings indicating greater bioavailability of OXY and NAL with renal impairment, caution should be used when administering OXN to patients with any renal impairment.

Hepatic Impaired: Study OXN1006 involved subjects with hepatic impairment. Based on an evaluation of AEs, clinical laboratory tests, vital signs, and ECGs in this study, no clinically important differences in tolerability were observed between the healthy subjects and subjects with mild, moderate, or severe hepatic impairment. However, based on PK findings of higher plasma concentrations of NAL in subjects with hepatic impairment caution is advised regarding the use of OXN in patients with mild hepatic impairment, and OXN should not be used in patients with moderate or severe hepatic impairment.

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Age Effect: Study OXN1017 was a phase 1, open-label, multiple-dose, parallel-group study conducted in the UK to compare the steady-state PK of OXN 10/5 mg in healthy elderly subjects and younger subjects. Elderly subjects were \geq 65 years of age and younger subjects were 18 to 45 years of age, inclusive. Subjects were administered one OXN 10/5 mg tablet orally every 12 hours on days 1 to 3 and on the morning of day 4 (7 doses in total). Naltrexone block was used. A total of 39 subjects were enrolled in the study and included in the safety population (18 subjects in the elderly group and 21 subjects in the younger group); 36 subjects completed the study. **Key Safety Findings:** Adverse events were reported by 14 subjects (78%) in the elderly group and 10 subjects (48%) in the younger group. Nausea, headache, dizziness, constipation and disturbance in attention were the most frequently reported adverse events across both age groups and are consistent with the expected adverse event profile of opioids. Oxycodone-related adverse reactions predominantly affecting the CNS were observed at a higher frequency in the elderly, and predominantly female, subjects. This must be taken into account when treating elderly patients with oxycodone and the combination of oxycodone with naloxone. Therefore, the dose should be carefully titrated to effect starting from the lowest available dose.

See Dr. Srikanth Nallani's Clinical Pharmacology review for further discussion of the Phase 1 studies listed above.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study 3701: The incidence of TEAE reported in $\geq 2\%$ of subjects in the randomized double-blind safety population showed a dose dependent effect overall. Not all preferred terms followed the trend of a dose effect. The incidence of nausea was highest in the lowest dose of OXN 10 mg (14%), then OXN 40 mg (11%), OXN 20 mg (6%) and OXN 30 mg (3%). Constipation and Abdominal pain had the highest incidence (6%) at 30 mg OXN. The overall incidence of diarrhea was highest in placebo (5%) and at the two highest doses of OXN. Drug withdrawal syndrome showed the highest incidence (5%) at the highest dose of 40 mg.

Clinically important AEs of interest by dose are summarized in Table 43 below.

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Table 43. Study ONU3701 Incidence of TEAEs ≥2% of Subjects by Dose Level, Randomized Safety Population (Double-blind Period)

| MedDRA System Organ Class Preferred Term | Placebo (N=302) n (%) | OXN 10/5 mg (N=59) n (%) | OXN 20/10 mg (N=78) n (%) | OXN 30/15 mg (N=69) n (%) | OXN 40/20 mg (N=92) n (%) |
|--|-----------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Any Adverse Events | 137 (45.4) | 24 (40.7) | 37 (47.4) | 37 (53.6) | 58 (63.0) |
| Gastrointestinal disorders | 36 (11.9) | 9 (15.3) | 12 (15.4) | 12 (17.4) | 17 (18.5) |
| Nausea | 14 (4.6) | 8 (13.6) | 5 (6.4) | 2 (2.9) | 10 (10.9) |
| Diarrhoea | 15 (5.0) | 1 (1.7) | 0 | 2 (2.9) | 2 (2.2) |
| Vomiting | 6 (2.0) | 3 (5.1) | 4 (5.1) | 1 (1.4) | 6 (6.5) |
| Constipation | 3 (1.0) | 0 | 3 (3.8) | 4 (5.8) | 2 (2.2) |
| Abdominal pain | 5 (1.7) | 0 | 1 (1.3) | 4 (5.8) | 1 (1.1) |
| Abdominal pain upper | 2 (0.7) | 1 (1.7) | 1 (1.3) | 0 | 2 (2.2) |
| General disorders and administration site conditions | 20 (6.6) | 2 (3.4) | 6 (7.7) | 7 (10.1) | 12 (13.0) |
| Drug withdrawal syndrome | 6 (2.0) | 0 | 1 (1.3) | 1 (1.4) | 5 (5.4) |

(Study ONU3701, Applicant's table 34, modified by reviewer, p. 138)

Integrated Findings: In general, in the Group A1A (nonmalignant, chronic pain population) the incidence of overall TEAEs appears to be related to dose, i.e., there was an increase in the incidence of TEAEs as the randomized total daily dose of OXN increased with the incidence of AEs for the total daily dose of OXN 20, 40, 60 and 80 mg being 45, 52, 54 and 63%, respectively. However, for the overall GI disorders SOC and the preferred terms within this SOC, although there was not consistent increased incidence associated with an increase in OXN dose, the common AE of nausea occurred with greatest frequency at the highest dose. Findings are summarized in Table 44.

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Table 44. Incidence of TEAEs ($\geq 2\%$ of Subjects in the OXN Treatment Group) by Randomized Total Daily Dose of OXN During the DB Period of Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A, Safety Population)

| MedDRA System Organ Class Preferred Term | Total OXN (N=451) n (%) | OXN 20/10 (N=124) n (%) | OXN 40/20 (N=166) n (%) | OXN 60/30 (N=69) n (%) | OXN 80/40 (N=92) n (%) |
|---|-------------------------------|-------------------------------|-------------------------------|------------------------------|------------------------------|
| Subjects with Any Adverse Events | 238 (52.8) | 56 (45.2) | 87 (52.4) | 37 (53.6) | 58 (63.0) |
| Gastrointestinal Disorders | 84 (18.6) | 22 (17.7) | 33 (19.9) | 12 (17.4) | 17 (18.5) |
| Nausea | 35 (7.8) | 11 (8.9) | 12 (7.2) | 2 (2.9) | 10 (10.9) |
| Constipation | 23 (5.1) | 6 (4.8) | 11 (6.6) | 4 (5.8) | 2 (2.2) |
| Vomiting | 21 (4.7) | 5 (4.0) | 9 (5.4) | 1 (1.4) | 6 (6.5) |
| Diarrhoea | 12 (2.7) | 5 (4.0) | 3 (1.8) | 2 (2.9) | 2 (2.2) |
| Infections and Infestations | 64 (14.2) | 15 (12.1) | 22 (13.3) | 7 (10.1) | 20 (21.7) |
| Upper respiratory tract infection | 10 (2.2) | 4 (3.2) | 2 (1.2) | 0 (0.0) | 4 (4.3) |
| Investigations | 57 (12.6) | 15 (12.1) | 16 (9.6) | 9 (13.0) | 17 (18.5) |
| Drug screen positive | 27 (6.0) | 5 (4.0) | 6 (3.6) | 5 (7.2) | 11 (12.0) |
| Musculoskeletal and Connective Tissue Disorders | 29 (6.4) | 4 (3.2) | 15 (9.0) | 5 (7.2) | 5 (5.4) |
| Back pain | 10 (2.2) | 1 (0.8) | 5 (3.0) | 3 (4.3) | 1 (1.1) |
| Nervous System Disorders | 41 (9.1) | 7 (5.6) | 19 (11.4) | 7 (10.1) | 8 (8.7) |
| Headache | 15 (3.3) | 4 (3.2) | 6 (3.6) | 2 (2.9) | 3 (3.3) |
| Psychiatric Disorders | 26 (5.8) | 2 (1.6) | 12 (7.2) | 3 (4.3) | 9 (9.8) |
| Anxiety | 10 (2.2) | 2 (1.6) | 3 (1.8) | 2 (2.9) | 3 (3.3) |
| Skin and Subcutaneous Tissue Disorders | 28 (6.2) | 6 (4.8) | 14 (8.4) | 3 (4.3) | 5 (5.4) |
| Pruritus | 10 (2.2) | 2 (1.6) | 6 (3.6) | 1 (1.4) | 1 (1.1) |

MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone/naloxone controlled-release tablets.

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In the OxyCR vs OXN Studies, adverse events in $\geq 2\%$ of subjects in the OXY or OXY CR treatment groups revealed that there was a tendency for an increase in the incidence of overall AEs with increasing dose of both OXN and OXY CR. Although the dose relationship was less evident at the 2 highest dose levels of both active treatments (OXN 100/50 mg and > 100/50 mg; OXY CR 100 mg and > 100 mg), the number of subjects at these dose levels was small, thereby limiting interpretation. The tendency for the increase in incidence was seen for overall gastrointestinal disorders SOC for the OXN but not the OXY CR treatment group. The highest incidence of gastrointestinal disorders SOC events was at a dose of 80 mg OXY (for OXN) and 60 mg OXY (for OXY CR). There was a mild increase in the incidence of diarrhea with onset at higher doses of OXN but not at higher doses of OXY CR.

7.5.2 Time Dependency for Adverse Events

Study ONU3701: No specific analyses were conducted.

Integrated Analysis: No specific analyses were conducted for time dependence for AE by the Applicant except for the GI CMQ, in which Kaplan-Meier methodology was used to estimate the proportion of subjects experiencing an AE for the first onset time by day of exposure to study drug. Using this analysis, it was noted that for subjects who

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reported GI adverse events, the onset was early in the treatment period and less common with extended treatment.

7.5.3 Drug-Demographic Interactions

Integrated (Pooled) Findings:

- Gender: A pooled analysis of the 15 Phase 1 studies enrolling healthy subjects showed that the PK properties were not affected by sex. The overall frequency of AEs in subjects receiving OXN during the double-blind period of the Group A studies was lower in male subjects than female subjects (52% vs 64%), respectively. However, the types of AEs showed no clinically meaningful differences when compared to placebo or OxyCR.
- Age: Both the Phase 1 study OXN1017 (in which elderly subjects were enrolled) and the pooled analysis of OXN treatment during the double-blind period of the Group A1 studies showed a lower frequency of AEs in younger (<65 years) than older (≥ 65 years). In the phase 1 study OXN1017, subjects 65 years of age and older had a higher frequency of AEs (primarily CNS-related symptoms) than younger subjects. In the pooled group A1 analysis, the overall AE frequency in younger versus older subjects was 57% vs 66%, respectively. These findings are consistent with the observed increased bioavailability of oxycodone and naloxone in elderly subjects and based upon these findings, labeling should include a statement that caution should be used when prescribing OXN to elderly subjects. Elderly subjects (> 65 years) reported similarly higher incidences of totals AEs than younger subjects in all treatment groups.
- Race: The PK studies showed no effect of race on PK of OXN. Most of the studies were conducted in Europe with a predominantly white enrollment. Study ONU3701 contributed most of the black subjects in the pooled analyses. There were no clinically important differences in tolerability based on race in Study ONU3701.

Reviewer's comments: The proposed label will include language to evaluate elderly patients at frequent intervals and consider TARGINIQ ER dose adjustments until stable drug effects are achieved. No labeling is required regarding race or gender as no clinically important safety differences were found in these groups.

7.5.4 Drug-Disease Interactions

See Dr. Nallani's Clinical Pharmacology review for further discussion. The proposed label will reflect these drug-disease interaction recommendations above for renal and hepatic patients.

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7.5.5 Drug-Drug Interactions

No additional studies were conducted and the Applicant references OxyContin label for Section 7 (Drug Interactions) for CNS Depressants, Muscle Relaxants, Mixed Agonist/Antagonist Opioid Analgesics, Diuretics and Anticholinergics.

See the Clinical Pharmacology review of Dr. Srikanth Nallani regarding Agents Affecting CYP3A4 and CYP2D6.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the Agency's pharmacology toxicology review by Dr. Belinda Hayes.

Carcinogenicity studies have not been conducted with oxycodone or the oxycodone and naloxone combination. Naloxone was tested in two carcinogenicity studies in rats and transgenic mice. Naloxone was not carcinogenic in a 2-year rat bioassay at doses as high as 100 mg/kg/day or in Tg.rasH2 mice orally administered naloxone at doses as high as 200 mg/kg/day for a duration of 6 months.

7.6.2 Human Reproduction and Pregnancy Data

Pediatric and Maternal Health Consult was obtained. The naloxone label includes the following:

(b) (4) should be administered cautiously to persons, (b) (4) who are known or suspected to be physically dependent on (b) (4). In such cases, an abrupt (b) (4) complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

In the ISS, seven OXN cases (six pregnancy exposures and one partner pregnancy exposure), were identified in the worldwide safety database through 31-Dec-2012. No AEs were reported resulting from the exposures. To date, two of the six subjects delivered healthy infants, one experienced an uneventful delivery, one was still pregnant and two did not report safety information. The 120-day safety update revealed one case of pregnancy during the report period (January 1, 2013-April 30, 2013). No follow up data were available.

The proposed Targiniq ER label will include warnings regarding Neonatal Abstinence Syndrome as part of the class-wide extended-release, long-acting opioid labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

The drug was not tested in the pediatric population. Three cases (two nonserious and one serious) involving patients 18 years of age or younger were identified in the

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international safety database through 31-Dec-2012. One SAE of petit mal epilepsy was considered unrelated to OXN.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Drug Abuse Potential

Study ONU3701: The protocol defined an AE as any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study drug(s) or protocol specified drug(s); addiction; overdose or withdrawal. Cases of abuse or addiction (substance dependence) were also required to be evaluated as potential SAEs.

Abuse cases were identified from 1) investigator assessment of abuse, (2) AE listings, and (3) positive urine drug tests. Abuse occurred in 82 subjects (7%) of the safety population. Among the 82 subjects, the majority of abuse involved illicit drug abuse and nonprescribed opioid drug use. Abuse of study drug (either OXN, OxyIR or both) occurred in 1% of the safety population. These findings are summarized in Table 45 below.

Table 45. Overall Incidence of Reported Incidence of Abuse: Safety Population

| Abuse-related AE | Total N = 1095 n (%) | Open-label N=1095 n (%) | Double-blind | |
|---|----------------------------|-------------------------------|---------------------------|-----------------------|
| | | | Placebo N=302 n (%) | OXN N=298 n (%) |
| Any abuse-related AE | 82 (7.5) | 40 (3.7) | 17 (5.6) | 25 (8.4) |
| Abuse with corresponding AE reported | 79 (7.2) | 37 (3.4) | 17 (5.6) | 25 (8.4) |
| Illicit drug abuse | 55 (5.0) | 26 (2.4) | 12 (4.0) | 17 (5.7) |
| Nonprescribed opioid drug abuse | 15 (1.4) | 3 (0.3) | 5 (1.7) | 7 (2.3) |
| Abuse of study drug | 11 (1.0) | 9 (0.8) | 1 (0.3) | 1 (0.3) |
| Abuse of study drug (not otherwise specified) | 8 (0.7) | 7 (0.6) | 0 | 1 (0.3) |
| Abuse of OxyIR alone | 2 (0.2) | 1 (0.1) | 1 (0.3) | 0 |
| Abuse of OxyIR and OXN | 1 (0.1) | 1 (0.1) | 0 | 0 |
| Abuse of OXN alone | 0 | 0 | 0 | 0 |
| Alcohol abuse | 3 (0.3) | 3 (0.3) | 0 | 0 |

Refer to Appendix 16.1.9.2.6 for a description of the determination of cases of abuse.

(ONU3701, p. 152)

Integrated (Pooled) Findings: Most cases of drug abuse in the group A studies occurred in Study ONU3701 and the majority of these cases were identified by urine drug testing. Urine drug testing was not conducted after screening in any of the other group A studies.

Overdose: There was one subject who was reported as an overdose in Study ONU3701. This subject, 0039071 (also discussed under Opioid Withdrawal section of this review) had an SAE of study drug overdose based on the return for an up-titration days after visit 2, having taken all 30 rescue capsules of Oxy IR and 5 extra doses of

(b) (6)

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OXN 10/5 mg within those ^(b) ⁽⁶⁾ days. This was considered by the investigator to be an overdose and suspected abuse of study drug. The subject was not randomized.

Diversion: Diversion was actively monitored during study ONU3701 per predefined criteria. Monitoring was conducted via a Clinical Supply Product Complaint form which included any issues involving quality, quantity, packaging, shipping, and storage of study drugs. Seventy-one subjects were reported for diverting in either the open-label or the double-blind period. Of the 71, there were 69 subjects (6%) of the safety population, with CSPC forms that reported diversion as assessed by the investigator and of those 69, 66 subjects (6%) of the safety population were included in the safety population. Three subjects were suspected of diversion (reported on CSPC forms) but did not qualify for the safety population (i.e., no assessments after drug was dispensed at Visit 2). As shown in Table 46 below, the incidence rates of diversion were similar between treatment periods. Overall, however, OxyIR was diverted by more subjects than OXN during both the open-label titration and double-blind periods. The narratives for these subjects were provided and reviewed. No additional clinically important information was added after review of the narratives. Opioids are known risk for diversion (abuse) and this information is adequately reflected in the approved OxyContin and proposed TARGINIQ ER labels.

Table 46. Study ONU3701 Subjects with CSPC Forms that Indicated Diversion/Suspected Diversion

| Open Label Titration Period | | | |
|----------------------------------|--|----------------|------------------|
| Safety Population ^b | | | |
| N = 1095 | | | |
| Drug Diverted | n (%) of Subjects Suspected of Diversion | | |
| Total | 43 (3.9) | | |
| OXN only | 7 (0.6) | | |
| Oxy IR only | 21 (1.9) | | |
| Both OXN and Oxy IR | 15 (1.4) | | |
| Double-Blind Phase | | | |
| Randomized Safety Population | | | |
| N = 600 | | | |
| n (%) | | | |
| | Placebo N = 302 | OXN N = 298 | Total N = 600 |
| Total | 10 (3.3) | 13 (4.4) | 23 (3.8) |
| OXN only | 0 | 2 (0.7) | 2 (0.3) |
| Oxy IR only | 7 (2.3) | 7 (2.3) | 14 (2.3) |
| Both OXN and Oxy IR ^c | 3 (1.0) | 4 (1.3) | 7 (1.2) |

^a As assessed by the investigator.

^b Additionally, subjects 0053010, 0094006, and 0098005 were suspected of diverting both OXN and Oxy IR but did not qualify for the safety population. These subjects are not included in the body of this table.

^c Subjects in the placebo group diverted placebo OXN and active Oxy IR.

(ONU3701 CSR, p. 155); CSPC= Clinical Supply Product Complaint

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Reviewer's conclusions: Overdose, abuse/misuse, and diversion are known risks associated with opioid use which are labeled for all opioids. The profile of these events appear consistent with other opioids in general.

7.7 Additional Submissions / Safety Issues

See Appendix F for the description of the postmarketing studies and ongoing studies not pooled.

Postmarketing studies: There were four completed post- marketing studies not included in the pooled safety database. The submission included a supporting document, *Supplemental Study Information* for Studies 038-001, 038-001S, OXN2501 and OXN2502 which provided data and narratives for subjects with deaths, SAEs, and discontinuation AEs. A review of the data revealed no new safety information which would change the overall safety profile of OXN.

Ongoing Studies: The CIOMS forms from subjects with deaths and SAEs were provided in supporting document *Supplemental Study Information* for studies 038-002, ONU3704, ONU3705, OXN2503, OXN2504, OXN3504, OXN3505 and OXN3506. In the 120-day safety update, the Applicant reported that Studies OXN3505 and OXN1507 completed during the reporting period. There were seven death reports in Study OXN3505 all in cancer patients and none definitely or probably related to OXN. Overall, the types and frequency of adverse events revealed no new safety information which would change the overall safety profile of OXN.

8 Postmarket Experience

As of April, 2013, OXN has been approved in a total of 36 countries, mostly for the treatment of severe pain. It was launched in 20 EU and 9 non-EU countries prior to Dec-2012, the data cut-off date for this NDA. OXN products are marketed in four different strengths at present depending on the specific country: OXN 5/2.5 mg, OXN 10/5 mg, OXN 20/10 mg and OXN 40/20 mg for twice daily administration.

Since the first approval of the product, no marketing authorizations have been withdrawn or allowed to expire during the report periods covered by the 12 PSURs. One action has been taken for safety reasons regarding interactions of opioids with alcohol. As of 12-Apr-2013, OXN has been approved by regulatory authorities in 36 countries, has been launched in 29 countries, and worldwide OXN usage is estimated at approximately [REDACTED]^{(b) (4)} patient-days (> 700,000 patient-years), shown in Table 47, below.

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Table 47. Exposure to OXN Since the International Birthday of OXN

| PSUR No. | PSUR Report Period | Patient Exposure Estimates | |
|----------|----------------------------|----------------------------|---------------|
| | | Patient Treatment Days | Patient-Years |
| 1 | 31-Mar-2006 – 30-Sep-2006 | (b) (4) | – |
| 2 | 01-Oct-2006 – 30-Mar-2007 | | 8863 |
| 3 | 31-Mar-2007 – 30-Sept-2007 | | 14,082 |
| 4 | 01-Oct-2007 – 30-Mar-2008 | | 18,589 |
| 5 | 31-Mar-2008 – 30-Sep-2008 | | 24,055 |
| 6 | 01-Oct-2008 – 12-Apr-2009 | | 28,104 |
| 7 | 13-Apr-2009 – 12-Oct-2009 | | 29,833 |
| 8 | 13-Oct-2009 – 12-Apr-2010 | | 45,334 |
| 9 | 13-Apr-2010 – 12-Oct-2010 | | 52,896 |
| 10 | 13-Oct-2010 – 12-Apr-2011 | | 62,603 |
| 11 | 13-Apr-2011 – 12-Apr-2012 | | 180,822 |
| 12 | 13-Apr-2012 – 12-Apr-2013 | | 256,090 |
| Total | | | 721,271 |

OXN = oxycodone/naloxone controlled-release tablets; PSUR = Periodic Safety Update Report..
(ISS, p. 347)

Safety (Adverse Events)

A query of the international drug safety database (Argus™ Safety) for postmarketing cases involving OXN including phase IV postmarketing clinical trial cases and compassionate use studies received through the data cut-off date of 31-Dec-2012 revealed a total of 1874 unique cases involving a total of 3956 AEs. The majority of AEs were nonserious (2866, 72.4%) and listed (2286, 57.8%).

Patients described in the majority of reports (36.1%) were taking < 20 mg/day of OXY (OXN + other OXY formulations, if any). Others were taking 20-39 mg/day (24.7%), 40-80 mg/day (7.4%), ≥ 80 mg/day (3.2%), or did not report the dosage (36.8%).

The 120-day safety update during the reporting period of January 1, 2013 – April 30, 2013 revealed that there were 329 cases (305 newly received and 15 with major updated to the previously reported clinical information) of which 226 were non-serious (71%) and 94 (29%) were serious.

- Deaths: There were 86 cases associated with a fatal outcome. The highest incidence (2%) was in the SOC Neoplasms Benign, Malignant and Unspecified (including cysts and polyps). Otherwise, there were no definite trends. As a

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result of the 120-day safety update, nine fatal cases were reported. In all nine cases, there was underlying malignancy.

- Non-fatal SAEs: A total of 1090 postmarketing SAEs (970 nonfatal and 120 fatal) identified within the worldwide safety database for OXN received through 31-Dec-2012. The most frequently reported SAEs were drug withdrawal syndrome (3%), and the common opioid-related GI disorders of diarrhea, nausea and vomiting (all 1%). The 120-day safety update included an additional 85 reports of non-fatal SAEs from post marketing data. With the exception of new cases of postprocedural hemorrhage (3%) there were no new non-fatal SAE primary preferred terms. The Applicant is conducting additional analyses on these cases of postprocedural hemorrhage. An information request was sent to the Applicant regarding the report of 86 fatal outcomes in one section of the submission and 120 fatal outcomes in another section. The response is pending.
- Most frequent AEs: Nausea, drug withdrawal syndrome, constipation, diarrhea and dizziness.

Postmarketing Events of Special Interest

Opioid Withdrawal: A query of the international drug safety database was performed to identify cases involving potential drug withdrawal. A case could be defined by 3 methods: (1) cases with a preferred term from the MedDRA SMQ for drug withdrawal; (2) cases with the drug withdrawal tick box selected in the international drug safety database; or (3) cases with ≥ 3 of the following Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) symptoms in the criteria for opioid withdrawal. Method 2 identified cases with signs and/or symptoms consistent with drug withdrawal following a change in therapy (switch, decrease, discontinuation) that were not specifically reported, and thus not encoded, as drug withdrawal syndrome. DSM-IV-TR criteria include diarrhea, dysphoria, hyperhidrosis, insomnia, lacrimation increased, myalgia, mydriasis, nausea, piloerection, pyrexia, rhinorrhoea, vomiting, and yawning.

A total of 216 cases were identified through 31-Dec-2012. The majority, 197 cases, contained a preferred term from the MedDRA SMQ for drug withdrawal. No unique cases were identified via the drug withdrawal tick box criteria. An additional 19 unique cases were identified solely on the basis of containing ≥ 3 DSM-IV-TR symptoms in the criteria. Three of the 216 cases identified were excluded from further discussion as they did not involve drug withdrawal syndrome in a patient treated with OXN, leaving 213 cases of potential drug withdrawal. Most of the cases originated from spontaneous sources ($n = 196$; 92% of the 213) and were reported to have recovered ($n = 105$; 49%) or involved an unknown outcome ($n = 91$; 43%). Two cases had a fatal outcome. One patient experienced a fatal episode of a pre-existing arrhythmia. Another elderly patient with multiple comorbidities experienced cardiac arrest that was assessed as unrelated to OXN.

The majority of withdrawal cases (121) occurred after the patients were switched to OXN therapy from other opioids, including OXY ($n = 70$), fentanyl ($n = 19$), morphine (n

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= 21), hydromorphone (n = 2), buprenorphine (n = 2), tramadol (n = 2), tilidine/NAL (n = 2), methadone (n = 1), Dipidolor (piritramide) (n = 1), and an unspecified opioid (n = 1). The 70 withdrawal cases involving a switch from OXY to OXN included (1) 42 cases with unspecified doses of OXN; (2) 20 cases with an equivalent daily dosage of the OXY component in the formulations; (3) 6 cases to a smaller daily dosage of OXN; and (4) 2 cases to a greater daily dosage of the OXY component of OXN. In 9 of the 20 cases involving equivalent dosages of OXY, the withdrawal syndrome occurred after the first or second dose of OXN.

Of the remaining 92 cases, 37 events occurred following OXN discontinuation or dose reduction, 32 occurred during ongoing OXN therapy (with no reported change in dosage), 8 occurred following IV injection of OXN, and 15 occurred from an unspecified, unclassified cause. Given the increased bioavailability of NAL when administered intravenously, it was not unexpected that withdrawal could be precipitated by abuse of the product.

The 120-day safety update identified 23 postmarketing cases of opioid withdrawal (7%). Of these, 13 (4%) were considered serious.

Reviewer's comments: These postmarketing findings suggest that opioid withdrawal is to be expected post-approval of this drug. Since this information is available, consideration should be given to adding additional wording in the label regarding the details of these findings.

9 Appendices

9.1 Literature Review/References

Numerous articles on oxycodone and naloxone have been published since their introduction into the marketplace many decades ago and the Applicant's submission included a large number of references. Selected references cited in the submission revealed no new safety information which would affect labeling.

9.2 Labeling Recommendations

The labeling review is ongoing. The following information should be included in the proposed labeling:

I) Post operative use and cardiac disease

Parenteral use of naloxone has been associated with abrupt and complete reversal of opioid effects leading to withdrawal symptoms (e.g., abdominal cramping, muscle aches, sweating, anxiety, nausea, vomiting, diarrhea). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with use postoperatively and naloxone should be used with caution in patients with pre-existing cardiac disease or who have received potentially cardiotoxic drugs.

II) Addition of drug withdrawal syndrome to postmarketing safety Section 6.2

- The most frequently reported SAE in the post-marketing international safety data base was the preferred term, Drug withdrawal syndrome (3%). Drug withdrawal syndrome was also the second most frequently reported AE (10%) with only nausea (12%) occurring more frequently. Drug withdrawal syndrome will be added to the postmarketing section of the label.

III) Inclusion of Adjudication-identified Drug withdrawal syndrome cases

- Percentages in the Adverse Reactions table in the label are based on investigator-identified adverse event reports of Drug withdrawal in Study ONU3701. In addition to the adverse event reports, an independent Adjudication Committee identified additional possible opioid withdrawal in 10 subjects in the Open-label Period; 4 placebo and 3 Targiniq ER in the double-blind period, resulting in a total of 23/1095 (2%) in the open-label period, and in the double-blind period 7/302 (2%) in subjects treated with placebo and 11/298 (4%) in subjects treated with Targiniq ER.

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9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this product.

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Appendix A: Table 48. Multiplication Factors for Converting the Current Total Daily Opioid Usage to the Equivalent Total Daily Dose of Oral Morphine

| Opioid | Trade Names | Conversion Ratio (factor) ^a |
|-------------------------------------|--|--|
| Codeine (oral) ^b | Tylenol® with Codeine # 2 Tylenol® with Codeine # 3 Tylenol® with Codeine # 4 | 0.3 |
| Fentanyl (transdermal) ^b | Duragesic® | See note below |
| Hydrocodone (oral) ^b | Vicodin®, Lortab®, Lorcet®, Norco®, Vicoprofen®, Zydome®, Anexia®, Co-Gesic®, Azdone™, Repxain® | 1.8 |
| Hydromorphone (oral) ^b | Dilaudid® | 8 |
| Levorphanol (oral) ^b | Levo-Dromoran® | 15 |
| Meperidine (oral) ^b | Demerol® | 0.2 |
| Methadone ^b | Methadose®, Westadone®, dolophine hydrochloride | 3 |
| Morphine (oral) ^b | Kadian®, Avinza®, MS Contin®, Oramorph® SR, MSIR® | 1 |
| Oxycodone (oral) ^b | Oxycontin®, Percocet®, Percodan®, Tylox®, Combunox™, Roxicodone®, OxyLR®, Roxilox®, Roxicet®, Oxycet™, Alacet®, Magnacet™, Narvox™ | 2 |
| Oxymorphone (oral) ^c | Opana®, Opana ER® | 4 |
| Tramadol (oral) | Ultram®, Ultram®-ER, Ultracet®, Ryzolt® | See note below |

a mg/day current total daily opioid usage x factor = mg/day oral morphine

b Based on the Oxycontin prescriber's information (ref. 37)

c Based on the Opana ER prescriber's information (ref. 38)

For transdermal fentanyl, each 25 µg/h converts to approximately 40 mg total daily dose of morphine

For tramadol, subjects taking ≥ 100 mg are eligible to start at the lowest OXN dose (OXN 10/5 every 12 hours), equivalent to 20 to < 70 mg morphine daily dose.

(Protocol ONU3701, p. 73)

Appendix B:

Table 49. Recommended Transformation of the Daily Oral Morphine Equivalent Dose to Starting Daily Dose of OXN

| Daily Oral Morphine Equivalent Dose | Equivalent OXN Starting Dose |
|-------------------------------------|--|
| 20 to < 70 mg | OXN 10/5 every 12 hours (i.e., 20 mg oxycodone daily) |
| 70 to < 110 mg | OXN 20/10 every 12 hours (i.e., 40 mg oxycodone daily) |
| 110 to < 150 mg | OXN 30/15 every 12 hours (i.e., 60 mg oxycodone daily) |
| 150 to 160 mg | OXN 40/20 every 12 hours (i.e., 80 mg oxycodone daily) |

(Protocol ONU3701, p. 73)

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Appendix C:

Table 50. Summary Table Deaths in Studies OXN2001/2001S (Cancer Population)

| Subject ID | Age/ Sex | Onset Phase/ MDD | Preferred Term [Causality] | Duration of Exposure In days | Duration off study drug before death (b) (6) |
|------------|-------------|------------------------|--|---------------------------------------|---|
| 0080201 | 60/M | DB 80 mg | Pericarditis [Unlikely] | 2 | |
| 0080301 | 63/M | DB 60mg | Dysphagia [Insufficient information] | 2 | |
| 0080709 | 55/M | DB 70 mg | Neoplasm malignant [Unlikely] | 3 | |
| 0060220 | 57/F | OLE 20 mg | Malignant neoplasm progression/Dyspnea [Unlikely] | 4 | |
| 0060209 | 51/M | DB 40 mg | Intestinal perforation [Unlikely] | 5 | |
| 0040902 | 61/M | DB 90 mg | Cardiac failure/circulatory collapse [Possible] | 9 | |
| 0080601 | 55/M | DB 80 mg | Neoplasm malignant [Possible] | 9 | |
| 0080624 | 59/M | DB 20 mg | Convulsion/Respiratory failure/Intracranial pressure increased [Insufficient information] | 11 | |
| 0041003 | 65/M | DB 80 mg | Fatigue/Dyspnea [Indeterminate] | 15 | |
| 0080628 | 82/M | DB 20 mg | Blood creatinine increased [Unlikely] | 16 | |
| 0020205 | 56/M | DB 30 mg | Neoplasm Malignant [Insufficient Information] | 19 | |
| 0080621 | 68/F | OLE 20 mg | Neoplasm malignant [Insufficient information] | 21 | |
| 0060214 | 75/M | DB 50 mg | Neoplasm malignant/Metabolic acidosis/Dyspnea/Renal Failure [Unlikely] | 25 | |
| 0020508 | 69/M | OLE 60 mg | Neoplasm malignant [Insufficient information] | 27 | |
| 0080312 | 64/M | DB 30 mg | Delusion/Asthenia [Indeterminate] | 28 | |
| 0080203 | 78/F | DB 40 mg | Neoplasm malignant [Insufficient information] | 29 | |
| 0020702 | 53/F | OLE 70mg | Neoplasm malignant [Unlikely] | 32 | |
| 0080629 | 80/M | OLE | Dyspnea | 32 | |

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| | | | | | |
|---------|------|---------------|--|-----|---------|
| | | 40 mg | [Insufficient information] | | (b) (6) |
| 0080627 | 65/F | OLE 80 mg | Neoplasm malignant [Insufficient information] | 38 | |
| 0080703 | 75/M | OLE 120 mg | Neoplasm malignant [Insufficient information] | 40 | |
| 0050401 | 55/M | OLE 120 mg | Pulmonary embolism [Insufficient information] | 41 | |
| 0050403 | 80/F | OLE 90 mg | Respiratory failure/circulatory collapse [Insufficient information] | 55 | |
| 0080632 | 59/F | OLE 100 mg | Neoplasm malignant [Insufficient information] | 57 | |
| 0060218 | 71/M | OLE 50 mg | Neoplasm malignant [Insufficient information] | 59 | |
| 0020407 | 52/M | OLE 120 mg | Neoplasm malignant [Unlikely] | 59 | |
| 0050501 | 72/M | OLE 30 mg | Respiratory failure/Circulatory collapse [Insufficient information] | 62 | |
| 0080613 | 73/M | OLE 20 mg | Respiratory failure/Hydrothorax [Unlikely] | 67 | |
| 0080707 | 78/M | OLE 120 mg | Cardiac arrest [Unlikely] | 77 | |
| 0050406 | 67/M | OLE 80 mg | Neoplasm malignant [Insufficient information] | 93 | |
| 0020511 | 65/F | OLE 50 mg | Cancer pain [Insufficient information] | 117 | |
| 0080701 | 72/M | OLE 80 mg | Neoplasm malignant [Insufficient information] PR | 125 | |
| 0020301 | 57/M | OLE 60 mg | Sepsis [Unlikely] | 132 | |
| 0050204 | 65/F | OLE | Dyspnea [Unlikely] | 132 | |
| 0080315 | 64/F | OLE 20 mg | Neoplasm malignant [Unlikely] | 133 | |
| 0080321 | 66/F | OLE 40 mg | Neoplasm malignant [Unlikely] | 148 | |
| 0040204 | 47/F | OLE 40 mg | Malignant pleural effusion [Unlikely] | 166 | |
| 0020102 | 50/M | OLE 100 mg | Malignant neoplasm [Unlikely] | 177 | |
| 0060222 | 63/M | OLE 40 mg | Neoplasm malignant [Unlikely] | 178 | |
| 0080706 | 62/M | OLE 80 mg | Malignant neoplasm progression [Unlikely] | 180 | |
| 0050411 | 42/M | OLE 60 mg | Dehydration/Mets to CNS [Unlikely] | 187 | |

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| | | | | | |
|---------|------|---------------|---|-----|---------|
| 0020517 | 60/M | OLE 100 mg | Neoplasm Malignant [Unlikely] | 190 | (b) (6) |
|---------|------|---------------|---|-----|---------|

(Reviewer); M=male; F=female; MDD=maximum daily dose OXN; DB=double-blind; OLE=open label extension; N/A=not available; 0=on study drug at time of death

Appendix D: COWS (Clinical Opioid Withdrawal Scale)

The COWS is a rating scale that combines objective and subjective signs and symptoms of opioid withdrawal. The COWS consists of 11 symptoms of opioid withdrawal including pulse rate, gastrointestinal upset, sweating, tremor, restlessness, yawning, pupil size, anxiety or irritability, bone or joint aches, gooseflesh skin, and runny nose or tearing. Each symptom is graded with values corresponding to the severity of the symptom. The minimum COWS score is 0, and the maximum is 48.

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Table 51. Clinical Opioid Withdrawal Scale (COWS)

| Reason for Assessment: | |
|---|--|
| Resting Pulse Rate..... | beats/minute |
| Measured after patient is sitting or lying for one minute | GI Upset: over last ½ hour |
| 0 pulse rate 80 or below | 0 no GI symptoms |
| 1 pulse rate 81–100 | 1 stomach cramps |
| 2 pulse rate 101–120 | 2 nausea or loose stool |
| 4 pulse rate greater than 120 | 3 vomiting or diarrhea |
| Sweating: over past ½ hour not accounted for by room temperature or patient activity | 5 multiple episodes of diarrhea or vomiting |
| 0 no report of chills or flushing | Tremor: observation of outstretched hands |
| 1 subjective report of chills or flushing | 0 no tremor |
| 2 flushed or observable moistness on face | 1 tremor can be felt, but not observed |
| 3 beads of sweat on brow or face | 2 slight tremor observable |
| 4 sweat streaming off face | 4 gross tremor or muscle twitching |
| Restlessness: Observation during assessment | Yawning: Observation during assessment |
| 0 able to sit still | 0 no yawning |
| 1 reports difficulty stilling still, but is able to do so | 1 yawning once or twice during assessment |
| 3 frequent shifting or extraneous movements of legs/arms | 2 yawning three or more times during assessment |
| 5 unable to sit still for more than a few seconds | 4 yawning several times/minute |
| Pupil size | Anxiety or Irritability |
| 0 pupils pinned or normal size for room light | 0 none |
| 1 pupils possibly larger than normal for room light | 1 patients reports increasing irritability or anxiousness |
| 2 pupils moderately dilated | 2 patient obviously irritable or anxious |
| 5 pupils so dilated that only the rim of the iris is visible | 4 patient so irritable and anxious that participation in the assessment is difficult |
| Bone or Joint aches: If patient was having pain previously, only the additional component attributed to opiate withdrawal is scored | Gooseflesh skin |
| 0 not present | 0 skin is smooth |
| 1 mild diffuse discomfort | 3 piloerection of skin can be felt or hairs standing up on arms |
| 2 patient reports severe diffuse aching of joints/muscles | 5 prominent piloerection |
| 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort | |
| Runny nose or tearing: Not accounted for by cold symptoms or allergies | |
| 0 not present | Total score..... |
| 1 nasal stuffiness or unusually moist eyes | The total score is the sum of all 11 items |
| 2 nose running or tearing | Initials of person completing assessment: |
| 4 nose constantly running or tears streaming down cheeks | |

Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

(ONU3701 Protocol Amendment, p. 116-117)

Appendix E: SOWS (Subjective Opioid Withdrawal Scale)

The Subjective Opioid Withdrawal Scale (SOWS) is a rating scale for measuring the subjective signs and symptoms of opioid withdrawal. The modified SOWS consists of 15 items reflecting the common motor, autonomic, gastrointestinal, musculoskeletal, and psychic symptoms of opioid withdrawal. The modified SOWS

excludes item 16 ("I feel like shooting up today") because it is not relevant to this subject population. Subjects responded to each sign or symptom by choosing the number to the appropriate response (i.e., 0="not at all", 1="a little", 2="moderately", 3="quite a bit", or 4="extremely") based on how they had felt over the preceding 24 hours. The minimum modified SOWS score is 0, and the maximum is 60.

Table 52. Modified Subjective Opiate Withdrawal (mSOWS) Scale

| Date Time | | Please score each of the 15 items below according to how you feel NOW (circle one number) | | | | |
|-----------------------|---------------------------|--|----------|------------|-------------|-----------|
| | Symptom | not at all | a little | moderately | quite a bit | extremely |
| 1. | I feel anxious | 0 | 1 | 2 | 3 | 4 |
| 2. | I feel like yawning | 0 | 1 | 2 | 3 | 4 |
| 3. | I am perspiring | 0 | 1 | 2 | 3 | 4 |
| 4. | My eyes are teary | 0 | 1 | 2 | 3 | 4 |
| 5. | My nose is running | 0 | 1 | 2 | 3 | 4 |
| 6. | I have goosebumps | 0 | 1 | 2 | 3 | 4 |
| 7. | I am shaking | 0 | 1 | 2 | 3 | 4 |
| 8. | I have hot flashes | 0 | 1 | 2 | 3 | 4 |
| 9. | I have cold flashes | 0 | 1 | 2 | 3 | 4 |
| 10. | My bones and muscles ache | 0 | 1 | 2 | 3 | 4 |
| 11. | I feel restless | 0 | 1 | 2 | 3 | 4 |
| 12. | I feel nauseous | 0 | 1 | 2 | 3 | 4 |
| 13. | I feel like vomiting | 0 | 1 | 2 | 3 | 4 |
| 14. | My muscles twitch | 0 | 1 | 2 | 3 | 4 |
| 15. | I have stomach cramps | 0 | 1 | 2 | 3 | 4 |

(ONU3701, Protocol Amendment, p. 118)

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Appendix F: Table 53. Clinical Studies in Non-pooled Safety Database

Dose-Finding Study

| Study ID | No. of Sites | Major Safety Endpts ¹ | Treatment Group | Dose | Frequency Route | Duration | Open-label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race |
|-----------------------------|--------------|---|--------------------------------|---|---|--|--|---|--|
| OXN2401 | 28 | AEs, labs, PE, OOWS, SOWS, BFI, lax use | OLT OXY CR OLT OXY CR | 10 &/or 20 mg 10 &/or 20 mg To achieve stable pain relief with 40-80 mg OXY/d, 40, 60, or 80 mg OXY CR + 10 mg NAL CR DB OXY CR + NAL CR DB OXY CR + NAL CR DB OXY CR + NAL CR DB OXY CR + PLAC | q12h, PO q12h PO q12h, PO q12h, PO q12h, PO q12h, PO q12h, PO | 1 wk 2-3 wk 4 wk 4 wk 4 wk 4 wk | OXY CR 10 mg, lax Safety: 202 PLAC: 50 10 mg: 51 20 mg: 51 40 mg: 50 | 230/202/166 Safety: 202 PLAC: 50 10 mg: 51 20 mg: 51 40 mg: 50 | M: 75 F: 127 55 (27,86) W: 100% |
| 07-May-2002/ 12-Apr-2003 | Germany | Severe chronic pain of tumor or nontumor origin req opioid or WHO I/II analgesic; OIC | | | | | | | |
| NA | | | | | | | | | |

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Eight Ongoing Studies

| Study ID | Country | Design | Planned No. of Sites | Population/ Age/ Sex | Major Safety Endpoints ¹ | Rx Group | Dose | Freq | | Open-label Rescue or Cover | Planned No. Subjects Enrolled/ Randomized/ Evaluable |
|---------------------------|--------------------------|----------------------------------|--|---|-------------------------------------|---|---------|-----------------------------------|-------------------------------|-------------------------------|--|
| | | | | | | | | Route | Duration | | |
| Ongoing phase 2/3 studies | | | | | | | | | | | |
| 038-002 | Multiple centers Canada | DB, R, CO, ph NR | Chronic noncancer pain req opioid Rx; OIC/ ≥ 18 y/ M & F | AEs, labs, VS, ECG, BFI, CSBM, PAC-SYM, mod SOWS | OLT OXY CR | 20 mg To achieve 60 or 80 mg OXY CR q12h | q12h PO | 14 d | OXY IR, senna/docusate sodium | 80/NR/67 | |
| | | | | | DB (CO) OXN | 20/10 mg To achieve 60/30 or 80/40 mg OXN q12h at end of OLT Conversion using decreasing doses of active OXY CR & increasing doses of PLAC OXY CR & OXN | q12h PO | 5 wk, 2-wk WO between DB periods) | | | |
| | | | | | DB (CO) OXY CR | 20 mg To achieve 60 or 80 mg OXY CR q12h at end of OLT Conversion using stable dose of active OXY CR & increasing doses of PLAC OXN | q12h PO | 5 wk, 2-wk WO between DB periods) | | | |
| ONU3704 | 150 US & other countries | R, DB, DD, PC & AC, PG, ph 3 | Chronic, M/S, nonmalig, NNP, low back pain req opioid Rx; OIC/ ≥ 18 y/ M & F | AEs, labs, VS, PE, ECG, COWS, mod SOWS, BFI, PAC-SYM, CSBM, lax use | OLT OXY CR | 10, 20, 30, &/or 40 mg | q12h PO | ≤28 d | OXY IR, bisacodyl | NR/900/NR | |
| | | | | | DB OXN | 10/5, 20/10, 30/15 (20/10 + 10/5), &/or 40/20 mg DD blinded taper from OLT | q12h PO | 12 wk | | | |
| | | | | | DB OXY CR | 10, 20, 30, &/or 40 mg DD blinded taper from OLT | q12h PO | 12 wk | | | |
| | | | | | DB PLAC | -- DD blinded taper from OLT | q12h PO | 12 wk | | | |
| ONU3705 | 150 US & other countries | R, DB, DD, PC & AC, PG, ph 3 | Chronic, M/S, nonmalig, NNP, low back pain req opioid Rx; OIC/ ≥ 18 y/ M & F | AEs, labs, VS, PE, ECG, COWS, mod SOWS, BFI, PAC-SYM, CSBM, lax use | OLT OXY CR | 10, 20, 30, &/or 40 mg | q12h PO | ≤ 28 d | OXY IR, bisacodyl | NR/900/NR | |
| | | | | | DB OXN | 10/5, 20/10, 30/15 (20/10 + 10/5), &/or 40/20 mg DD blinded taper from OLT | q12h PO | 12 wk | | | |
| | | | | | DB OXY CR | 10, 20, 30, &/or 40 mg DD blinded taper from OLT | q12h PO | 12 wk | | | |
| | | | | | DB PLAC | -- DD blinded taper from OLT | q12h PO | 12 wk | | | |
| OXN2503 | 30 Europe | R, DB, PC, PG, exploratory, ph 2 | Chronic severe pain due to BPS/ ≥ 18 y/ F | AEs, VS, PE, labs, ECG | DB OXN | 5/2.5 (starting dose), 10/5, 15/7.5 (10/5 + 5/2.5), &/or 20/10 mg Allowed titration up to 40/20 mg OXN/d | q12h PO | 8 wk | Current Rx for BPS, ibuprofen | NR/70/60 | |
| | | | | | DB PLAC | --- | q12h PO | 8 wk | | | |
| | | | | | Ext OXN | 5/2.5 (starting dose), 10/5, 15/7.5 (10/5 + 5/2.5), &/or 20/10 mg Allowed titration up to 40/20 mg OXN/d in first 2 wk | q12h PO | 4 wk | | | |

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| | | | | | | | | | | |
|---------|------------------------|--|--|--|----------------------|---|---|----------------|---|-------------|
| OXN2504 | 50 5-7 countries | R, DB, PC, PG, ph 3 | Chronic severe pain associated with Parkinson's disease/ ≥ 25 yr M & F | AEs, labs, VS, PE, ECG | DB OXN | 5/2.5 (starting dose), 10/5, 15/7.5 (10/5+5/2.5), &/or 20/10 mg Allowed titration up to 40/20 mg OXN/d | q12h PO | 16 wk | Levodopa/ benserazide | 250/210/172 |
| | | | | | DB PLAC | --- | q12h PO | 16 wk | Levodopa/ benserazide | |
| | | | | | Ext OXN | 5/2.5 (starting dose), 10/5, 15/7.5 (10/5+5/2.5), &/or 20/10 mg Allowed titration up to 40/20 mg OXN/d in first 2 wk | q12h PO | 4 w | OXY IR | |
| OXN3504 | ~15 NL | OL, ph 3 | M/S nonmalignant pain req ATC opioids/ ≥ 18 yr/ M & F | AEs, BFI, SBMs, lax use | Core OXN | 5/2.5, 10/5 (starting dose), 20/10, &/or 40/20 mg Titration with 5/2.5 mg to achieve 20/10, 40/20, 60/30, 80/40, or 120/60 mg OXN/d | q12h PO | 3 wk | OXY IR; movicolon, bisacodyl, or lactulose per invest | NR/115/100 |
| | | | | | AEs, lax use, BFI | Ext OXN | 5/2.5, 10/5, 20/10, &/or 40/20 mg Allowed titration up to 120/60 mg OXN/d | q12h PO | Until regist | |
| OXN3505 | 150 France | R (strat by pain type), DB, AC, DD, PG, ph 3 | Severe malign or nonmalignant pain adequately managed with opioid Rx, OIC/ ≥ 18 yr/ M & F | AEs, labs, VS, PE, ECG, BFI, PAC-SYM, KESS, lax use | DB OXN | 5/2.5, 10/5, 20/10, &/or 40/20 mg To achieve 20/10-160/80 mg OXN/d | q12h PO | 28 d | OXY IR, bisacodyl | NR/624/284 |
| | | | | | DB OXY CR | 5, 10, 20, &/or 40 mg To achieve 20-160 mg OXY CR/d | q12h PO | 28 d | OXY IR, bisacodyl | |
| | | | | | Ext OXN | 5/2.5, 10/5, 20/10, &/or 40/20 mg Up to a maximum of 160/80 mg OXN/d | q12h PO | Up to 1 yr | OXY IR, bisacodyl | |
| OXN3506 | 80 NR | R, DB, DD, AC, PG, ph 3 | Malig or nonmalignant pain req opioid Rx, OIC/ ≥ 18 yr/ M & F | AEs, labs, VS, PE, ECG, mod SOWS, COWS, BFI | OLT OXY CR | 10, 20, or 40 mg To achieve effective analgesia at 50, 60, 70, or 80 mg q12h | q12h PO | 7-28 d | OXY IR, bisacodyl | NR/270/NR |
| | | | | | DB OXN | 10/5, 20/10, &/or 40/20 mg Starting dose = effective OXY dose at end of OLT Allowed titration up to 80/40 mg q12h (160/80 mg/d) | q12h PO | 5 wk | OXY IR, bisacodyl | |
| | | | | | DB OXY CR | 10, 20, &/or 40 mg Starting dose = effective OXY dose at end of OLT Allowed titration up to 80 mg q12h (160 mg/d) | q12h PO | 5 wk | OXY IR, bisacodyl | |
| | | | | | Ext OXN | 10/5, 20/10, &/or 40/20 mg Stepwise DB, DD conversion from OXY CR to OXN 100/50, 120/60, 140/70, or 160/80 mg/d | q12h PO | Up to 24 wk | OXY IR for first 7 d, then per invest; bisacodyl | |

Abbreviations: AC = active control; AE = adverse event; ATC = around-the-clock; BFI = Bowel Function Index; BPS = bladder pain syndrome; CO = crossover; COWS = Clinical Opiate Withdrawal Scale; CR = controlled-release; CSBM = complete spontaneous bowel movement; d = day; DB = double-blind; DD = double dummy; ECG = electrocardiogram; Ext = extension; F = female subjects; freq = frequency; ID = identification; invest = investigator; IR = immediate release; KESS = Knowles Eccersley Scott Symptom score; labs = clinical laboratory tests; lax = laxative(s); M = male subjects; malig = malignant; mg = milligram; mod = modified; M/S = moderate to severe; NL = Netherlands; no. = number; nonmalignant = nonmalignant; NNP = non-neuropathic; NR = not reported; OIC = opioid-induced constipation; OL = open label; OLT = open-label titration; ONU = studies of OXN in the US clinical development program; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets; OXY IR oxycodone immediate-release; PAC-SYM = Patient Assessment of Constipation Symptoms; PC = placebo control; PE = physical examination; PG = parallel group; ph = phase; PLAC = placebo; PO = by mouth (orally); q12h = every 12 hours; R = randomized; regist = registration; req = requiring; Rx = treatment; SBMS = Spontaneous bowel movement; SOWS = modified Subjective Opiate Withdrawal Scale; strat = stratified; US = United States; VS = vital sign(s); wk = week(s); WO = washout; y = year(s).

¹ Whether considered safety or efficacy endpoints in the actual study, bowel function endpoints were considered safety endpoints in the Integrated Summary of Safety and, therefore, in this table.

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NDA 205-777

Targiniq ER (Oxycodone/Naloxone)

| Study ID Start/End Date Data Pool | No. of Sites Country (ies) | Design | Population | Major Safety Endpts ¹ | Treatment Group | Dose | Frequency Route | Duration | Open- label Rescue | Enrolled/ Randomized/ Completed Safety Pop | No. M & F Median Age (min,max) Predom Race |
|---|---|---|--|---|--------------------|---|--------------------|---|--------------------------------------|--|--|
| 038-001 | 10 Canada | DB, PC, R, CO, ph 3 | Chronic low back pain of at least moderate severity, req opioid Rx | AEs, mod SOWS | OXN | 10/5 (initial), 20/10, &or 40/20 mg Allowed titration to 40/20, 60/30, or 80/40 (max) mg/d at 1-wk intervals | q12h PO | 4 wk 2- to 7-d WO between periods | C/P, senna/ docusate sodium | 100/83/63 Safety: 83 OXN: 74 PLAC: 77 | M: 39 F: 44 51 (mean) (23,88) y Race data not available |
| Dec-2006/ Mar-2008 | NA | | | | PLAC | — | q12h PO | | | | |
| OXN2501 | 35 Czech Rep., Hungary, UK | R, DB, AC, DD, PG, ph 2 explora- tory | Nonmalignant pain req opioid Rx for at least 4 wk; no constipation or lax use in past 3 mo | AEs, labs, VS, PE, ECG, BFI, lax use, other bowel function measures | OXN | 5/2.5, 10/5, &/or 20/10 mg Allowed titration to 40/20 mg/d | q12h PO | 4 wk | OXY IR, bisacodyl | 104/96/66 Safety: 94 OXN: 47 MOR CR: 47 | M: 44 F: 52 61 (28,84) y W: 100% |
| 25-Apr-2008/ 01-Jan-2009 | NA | | | | MOR CR: | 10 &/or 30 mg Allowed titration to 80 mg/d | q12h PO | 4 wk | MOR IR, bisacodyl | | |
| OXN2502 | 29 Czech Rep., Germany, Hungary, Romania | R, DB, PC, single dummy, PG, ph 2 explora- tory | Type 1 or 2 diabetes mellitus; M/S pain due to diabetic/ idopathic poly- neuropathy; on max tolerated dose of pregabalin x 1 mo | AEs, labs, VS, PE, ECG | OXN | 5/2.5, 10/5 (starting dose), 20/10, &/or 40/20 mg Allowed titration to 80/40 mg/d | q12h PO | 12 wk | Para- cetamol, bisacodyl | 117/98/91 Safety: 98 OXN: 48 PLAC: 50 | M: 50 F: 48 60 (38,80) y W: 100% |
| 13-Jul-2009/ 26-Mar-2010 | NA | | | | PLAC | — | q12h PO | | | | |
| Additional postmarketing extension studies | | | | | | | | | | | |
| 038-001S | 10 Canada | OL, ph 3 | Completion of both DB periods of core study | AEs | OXN | 10/5 (starting dose), 20/10, 30/15 (10/5+20/10) &/or 40/20 mg Allowed titration at weekly intervals to 40/20, 60/30, or 80/40 (max) mg/d | q12h PO | 6 mo | C/P, senna/ docusate sodium | 48/NA/40 Safety: 48 | M: 23 F: 25 49 (27,84) y Race NR |
| Dec-2006/ Mar-2008 | NA | | | | | | | | | | |

Abbreviations: AC = active control; AE = adverse event; ATC = around-the-clock; BFI = Bowel Function Index; BUP = buprenorphine; cont = controlled; CO = crossover; COWS = Clinical Opiate Withdrawal Scale; C/P = codeine/paracetamol; CR = controlled-release; CSBM = complete spontaneous bowel movement; d = day; DB = double-blind; DC = discontinuation; DD = double dummy; dissol = dissolution; ECG = electrocardiogram; endpts = endpoints; Ext = extension; F = female subjects; h = hour(s); ID = identification; IN = intranasal(ly); incompl = incomplete; invest = investigator; IR = immediate-release; IV = intravenous(ly); kg = kilogram; lab = laboratory; labs = clinical laboratory tests; lax = laxative(s); liq = liquid; M = male subjects; malig = malignant; max = maximum; MD = multiple dose; med = medication; mg = milligram min = minimum; mod = modified; mo = month; MOR = morphine tablets; M/S = moderate to severe; N = Northern; NA = not applicable; NAL = naloxone; NC = North Carolina; NL = Netherlands; NNP = non-neuropathic; no. = number; nonmalig = nonmalignant; NR = not reported; NTX = naltrexone; O₂ sat = oxygen saturation; OA = osteoarthritis; OIC = opioid-induced constipation; OL = open-label; OLT = open-label titration; omepraz = omeprazole; ONU = studies of OXN in the US clinical development program; OOWS = Objective Opiate Withdrawal Scale; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets; PACOI = patient assessment of opioid-induced constipation summary score; PAC-SYM(b) = Patient Assessment of Constipation Symptoms and bothersomeness; PC = placebo control; PE = physical examination; PG = parallel group; ph = phase; PLAC = placebo; PO = by mouth (orally); pop = population; predom = predominant; prn = as needed; prod = production; q = every; R = randomized; ref = reference; Rep = Republic; req = requiring; Rx = treatment; SD = single dose; seq = sequence; SL = sublingual; SOWS = Subjective Opiate Withdrawal Scale; UK = United Kingdom; uncont = uncontrolled; US = United States; VS = vital sign(s); W = white; WHO = World Health Organization; wk = week; WO = washout; y = year(s).

¹ Whether classified as safety or efficacy endpoints in the actual study, bowel function endpoints were considered safety endpoints in the Integrated Summary of Safety and, therefore, in this table.

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Clinical Review

Elizabeth Kilgore, MD

NDA 205-777

Targiniq ER (Oxycodone/Naloxone)

Clinical Investigator Financial Disclosure Form

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 205-777

Submission Date(s): September 23, 2013

Applicant: Purdue Pharma, LP

Product: Tradename Targiniq ER (oxycodone/naloxone HCL controlled-release) tablets

Reviewer: Elizabeth Kilgore, MD

Date of Review: 6/19/2014

Covered Clinical Study (Name and/or Number): ONU3701

| | | |
|---|---|--|
| Was a list of clinical investigators provided: | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: 152 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): All of the following sections are not applicable | | |
| 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 sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> N/A | No <input type="checkbox"/> (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes <input type="checkbox"/> N/A | No <input type="checkbox"/> (Request information from applicant) |

Clinical Review

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NDA 205-777

Targiniq ER (Oxycodone/Naloxone)

| | | |
|---|-------------------------------------|--|
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u> | | |
| Is an attachment provided with the reason: | Yes <input type="checkbox"/> N/A | No <input type="checkbox"/> (Request explanation from applicant) |

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

The Applicant submitted the Financial Certification and Disclosure in accordance with 21 CFR 54.4. According to the form, Purdue certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangement with the listed clinical investigators and that the value of compensation to the investigator could not have been affected by the outcome of the study as defined in 21 CFR 54.2(a). They also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no investigators disclosed any such interests. Further, Purdue certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f) as shown below:

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The Applicant also included a statement that no investigator was a full or part-time employee of Purdue.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH M KILGORE

06/19/2014

ELLEN W FIELDS

06/19/2014



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Medical Officer Review
Pediatric Study Plan

| | |
|----------------------------|--------------------------------|
| NDA: | NDA 205-777 |
| Drug Name: | Oxycodone/Naloxone (OXN) |
| Sponsor: | Purdue |
| Type of Submission: | Pediatric Study Plan |
| Date of Submission: | December 30, 2013 |
| Date of Receipt: | December 30, 2013 (electronic) |
| Review Date: | May 28, 2014 |
| Reviewer: | Elizabeth Kilgore, MD |
| Team Leader: | Ellen Fields, MD, MPH |
| Project Manager: | Lisa Basham |

Background: Oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets (OXN) has been developed by Purdue Pharma L.P. (Purdue) in the United States (U.S.) in dosage strengths of 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg intended for twice-daily (every 12 hours [q12h]) dosing for the indication of treatment of (b) (4) pain (b) (4) around the clock (b) (4)

Each OXN tablet contains 2 parts oxycodone hydrochloride and 1 part naloxone hydrochloride (2:1 ratio) on an anhydrous, assay corrected, mg/mg basis.

OXN has been approved in Europe since 2006 and is currently approved for use in adults in the European Union, Canada, and Australia. OXN is not approved for use in the pediatric patient populations in any country where it has been approved for use in adults.

Sponsor's Pediatric Study Plan

On 12/30/13, the Sponsor submitted the following pediatric requests:

- *Partial Waiver:* The Sponsor has requested a partial waiver for birth to age 6 years with the rationale that the studies are highly impracticable, the use of oxycodone in this age group is already well documented, and there is concern that this age group would be unable to swallow the tablets.

- *Deferral:* The Sponsor has requested deferral for ages 7-17 years, inclusive. The Sponsor plans to conduct one PK, safety and efficacy study for this age group. The protocol synopsis of this study is the subject of this review.

Sponsor's Proposed Pediatric Protocol Synopsis

Title: TBD (Not provided)

Primary Objectives:

- To characterize the safety of OXN in patients ages 7 to 17 years, inclusive, with (b) (4) pain requiring opioid therapy
- To characterize the PK of OXN

Secondary Objective: To characterize the efficacy of OXN in patients ages 7 to 17 years, inclusive, with (b) (4) pain requiring opioid therapy

Design: Phase 2, multicenter, open-label

Population: N=40

Key Inclusion Criteria:

1. Male and female pediatric patients ages 7 to 17 years (inclusive) who require ongoing, around-the-clock opioid treatment equivalent to total daily doses of 20/10 mg to 80/40 mg of OXN for at least 2 weeks for (b) (4) pain
2. Eligible post-operative patients who have met the definition of opioid tolerant cannot be dosed with study drug until at least two days after surgery

Key Exclusion Criterion

1. Patients who have a contraindication to the use of opioids or do not meet screening laboratory and clinical evaluation

Overview: The study will consist of the three periods with eligible subjects to be treated as outpatients or inpatients. There are to be three clinic visits and additional telephone interviews. The three study periods are as follow:

- Screening (0-72 hours)
- Open-label treatment (up to 2-4 weeks)

- Follow-up (7-10 days) [not clear in the protocol synopsis if this is to be performed by phone or in clinic]

Key Procedures

- Patients' current opioid analgesic daily dose is to be converted to an appropriate daily dose of OXN.
- Patients will be titrated a minimum of 2 weeks and up to 4 weeks (including titration to a safe and effective total daily dose of OXN between 20/10 mg and 80/40 mg/day inclusive).
- Dose adjustments (up- or down-titration) of OXN may be made by the investigator as necessary.
- Supplemental immediate release opioid and non-opioid pain medication (with the exception of oxycodone products (or naloxone-containing products) will be permitted during the study as appropriate. The dose of supplemental analgesic medication allowed will be within appropriate dose ranges for age and weight.
- At the end of treatment period with OXN, patients are to be treated with medications by the investigators as appropriate.

PK Assessments

- PK samples are to be collected at Visit 1 (baseline) and Visit 2 and/or Visit 3 during the treatment period

Safety Assessments

- None were provided in the synopsis
- An independent Data Monitoring Committee (DMC) is to be established to review the accumulating safety data from the trial
- Recommendations are to be made by the DMC regarding early stopping of the study, continuation of the study, or modification of the study protocol as needed

Discussion: In general, DAAAP agrees with the Sponsor's proposal. However, the acceptable reason for the waiver in patients from birth to 6 years is that the studies are impracticable because of the small number of patients in this age group treated with long-term around the clock opioid analgesics.

The Sponsor's proposed pediatric plan (see Appendix A of this review) was discussed at a PeRC (Pediatric Review Committee) meeting on May 28, 2014. The Committee was in agreement with the Sponsor's proposed pediatric plan for waiver of 0-6 years, and PK/safety ages 7-17 years (inclusive) with extrapolation for efficacy.

Comments to Sponsor: The final study protocol will require the following modifications which will be conveyed to the Sponsor:

1. Provide the opioid conversion table which will be used during the open-label conversion and titration period of the study.
2. Provide an OXN conversion table and a taper schedule for how patients are to be either transitioned from study drug OXN to pre-study opioid, or tapered off OXN if they no longer require analgesia.
3. Provide a list of acceptable rescue analgesics and how dosing will be determined.
4. Provide details of the safety assessments and their timing.

Regulatory Action: The Sponsor's proposed pediatric plan and timelines are acceptable. There may be additional comments to the Sponsor after the full PK protocol is submitted.

Appendix A

Table 1. Sponsor's Planned Pediatric Clinical Studies

| Planned Pediatric Clinical Studies | | | |
|---|------------------|--|--|
| Pediatric PK Studies | | | |
| Age Group | Type of Study | Comments | Deferral Request Planned for the Study (Y/N) |
| 0 – 6 years | Waiver requested | Studies are highly impracticable | |
| 7 – 17 years | PK/safety study | To characterize the pharmacokinetics (PK) of OXN | Y |
| Clinical Effectiveness and Safety Studies | | | |
| 0 – 6 years | Waiver requested | Studies are highly impracticable | |
| 7 – 17 years | PK/safety study | Primary: To characterize the safety of OXN in patients ages 7 to 17 years, inclusive, with (b) (4) pain requiring opioid therapy. Secondary: To characterize the efficacy of OXN in patients ages 7 to 17 years, inclusive, with (b) (4) pain requiring opioid therapy. | Y |

(Sponsor's submission, Proposed Pediatric Study Plan, p. 8)

Table 2. Sponsor's Proposed Pediatric PK Study Timeline

| | |
|----------------------------------|---------------|
| Submit final protocol to FDA | December 2014 |
| Study initiation | December 2015 |
| Submit final study report to FDA | December 2019 |

(Sponsor's submission, Proposed Pediatric Study Plan, p. 14)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH M KILGORE
05/28/2014

ELLEN W FIELDS
05/28/2014
concur



Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

DCRP Consult NDA 205777

DATE: Desired Completion date: 10 Feb 2014
Date of initial review: 25 January 2014
Date of final revision (follow AC delay): 17 Mar 2014

FROM: Preston M. Dunnmon, M.D., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Lisa Basham, MS, SRPM
Division of Anesthesia, Analgesia, and Addiction Products

NAME OF DRUG: Targiniq ER (oxycodone/naloxone extended-release (OXN))

SPONSOR: Purdue Pharma LP

FORMULATION: Tablet

DOSE: OXN 5/2.5 mg, OXN 10/5 mg, OXN 20/10 mg and OXN 40/20 mg for BID dosing up to a maximum daily dose of OXN 80/40 mg.

DEVELOPMENT INDICATION: This 505(b)(2) NDA seeks approval of OXN for the relief of ^{(b) (4)} pain ^{(b) (4)} around-the-clock ^{(b) (4)}. Reference products are oxycodone (OXY) and naloxone (NAL).

DOCUMENTS AVAILABLE FOR REVIEW:
NDA 205777
NDA 205777 ISS
NDA 205777 Evaluation of CV Events

Background

DAAAP has received NDA 205777 for an Oxycodone/Naloxone (OXN) combination for the treatment of chronic pain. The naloxone is included in the combination as a deterrent to abuse of the oxycodone. The naloxone in this product is an opioid antagonist, a class

NDA 205777

for which the Review Division (DAAAP) and DGIEP (similar products for the treatment of opioid induced constipation) are concerned that there may be a cardiac signal, based on experience with Alvimopan (Entereg, also an opioid antagonist). Accordingly, DAAAP requested that the Sponsor carefully examine, as part of this NDA, the occurrence of CV adverse events in OXN's development program, and assess for a possible association between CV AEs and symptoms of opioid withdrawal, understanding that the cardiac adverse event data was collected as part of routine safety monitoring in the clinical trials, and is not from a dedicated CV outcomes safety study.

Of relevance to this consult is the fact that there has been a long clinical experience with naloxone which is indicated for the reversal of opioid depression. The sections of the naloxone (IV) label that therefore are or may be relevant to the cardiac risk assessment of OXN are as follows:

- *In vitro* evidence suggests that naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the CNS, with the greatest affinity for the mu receptor
- Naloxone is an essentially pure opioid antagonist; i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.
- Naloxone hydrochloride injection should be administered cautiously to persons, including newborns of mothers, who are known or suspected to be physically dependent on opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.
- The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure.
- Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects such as hypotension, ventricular tachycardia or fibrillation and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Of note, immunohistochemical staining demonstrates that mu-, kappa-, and delta- opioid receptors are present in the human heart (Sabanski et al, Heart Vessels Jan 2014, DOI 10.1007/s00380-013-0456-5) (<http://link.springer.com/article/10.1007%2Fs00380-013-0456-5>). While the authors hypothesize a role for these receptors in neural transmission and regulation of myocardial cell function, the clinical consequences of their activation and/or antagonism on the heart are unknown.

Consult Questions

The review division requests that DCaRP provide an evaluation of the cardiac safety of this product, to include:

- An assessment of whether there appears to be a signal for cardiac adverse events associated with the use of OXN (including the type and extent of the signal if present)
- An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

Characteristics of the OXN combination

- Oxycodone (OXY) is a potent opioid agonist with high affinity for mu, kappa, and delta receptors in the brain, spinal cord, and peripheral organs ISS-33
- Naloxone (NAL) is a potent antagonist of the opioid receptors activated by OXY and has been in use since the 1960s as an intravenous preparation to reverse the effects of opioid overdose. NAL provides abuse deterrence in the OXN combination. ISS-33
- The NAL component provides an additional patient benefit that is not a part of the indication proposed in this NDA - Opioid-induced constipation (OIC) ISS-34
- Gastrointestinal effects of opioids are mediated primarily by mu-opioid receptors in the bowel. Opioids decrease the rate of intestinal transit by inhibiting gastric emptying and reducing propulsive peristalsis of the intestine ISS-34
- Although the NAL component in orally administered OXN has low systemic bioavailability – leading to low NAL serum concentrations – the NAL component is an effective mu antagonist for OXY in the gut, and provides important benefit in bowel function, i.e., constipation
- The FDA and EMA have approved Narcan and Narcanti™, respectively, each a single entity NAL-containing product, administered parenterally for acute treatment of opioid overdose, at doses that produce peak plasma concentrations much higher than those observed for the doses of OXN proposed for approval.

Nonclinical Safety Findings (from sponsor's written Toxicology Summary)

The sponsor concludes the following from the preclinical tox program for OXN:

- The nonclinical studies indicate that adverse effects in rats and dogs associated with oral administration of OXY/NAL at a 2:1 ratio were attributable to the OXY component and reflected an extension of, or were considered secondary to, the pharmacologic effects of OXY (e.g., hypoactivity and associated reduction in food consumption and/or body weight parameters).
- The sponsor concludes that no specific target organ of toxicity was identified after administration of OXY and NAL as single entities or the OXN combination in the rat or dog.

Please see the FDA toxicology review for this NDA.

Clinical Trials -- Integrated Safety Data Structure

The sponsor's CV database includes integrated safety analyses from 29 unique studies (33 if open-label extensions are counted separately). The sponsor originally integrated its safety data for the ISS, excluding the safety outcomes of the malignant pain group because of its much higher fatality rate, which was driven by mostly by progression of the underlying disease. For the purpose of evaluating CV safety in the "Evaluation of Cardiovascular Events (ECVE) document, the sponsor has re-integrated its safety data from these 33 studies for OXN into subgroups that use similar nomenclature but are different from the subgroups that were defined in the ISS integration. The ECVE integration differs in that patients with malignant pain are not pulled out a separate group. The groupings and subgroupings from the updated ECVE safety data integration are shown in the table below (from the ECVE, pg 34):

Table 2: Integrated Analysis Groups for Cardiovascular Analysis

| Analysis group/ Period analyzed | Studies included |
|---|--|
| Group A1A Titration Double-blind Double-blind + extension | Placebo-controlled studies involving subjects with nonmalignant chronic pain (2 studies): ONU3701 , OXN3401 |
| Group A1C = A1B^a + OXN2001 Titration Double-blind Double-blind + extension | OXY CR-controlled studies involving subjects with nonmalignant pain and malignant chronic pain (5 studies): OXN3001 , OXN3006 , OXN3401 , OXN3503 , OXN2001 |
| Group A1D = A1B^a + OXN2001 + ONU3701 Titration + double-blind + extension | Studies to compare OXY (OXY CR and OXY IR) and OXN over the longest continuous period of time possible. Subjects who received different treatments during the titration, double-blind, or extension periods are excluded from these analyses (see Table 3) (6 studies): ONU3701 , OXN3001 , OXN3006 , OXN3401 , OXN3503 , OXN2001 |
| Group C Overall (titration, double-blind, extension) | Studies in chronic pain, healthy subjects, abuse liability, and in special populations and situations (29 studies): All studies defined in Group A1A and A1C, including the open-label titration and open-label extension period data. Phase 1 studies involving healthy subjects: ONU1001 , ONU1002 , ONU1009 , OXN1003 , OXN1004 , OXN1005 , OXN1008 , OXN1009 , OXN1011 , OXN1013 , OXN1016 , OXN1018 , OXN1403 , OXN1505 , OXN1506 Studies of abuse deterrence and other special populations and situations: ONU1003 , ONU1004 , ONU1007 , ONU1008 , OXN1006 , OXN1007 and ONU1017 Active medication-controlled phase 4 study in nonmalignant cancer pain: OXN4502 Note that only studies also included in groups A1A and A1C provide long-term data. |

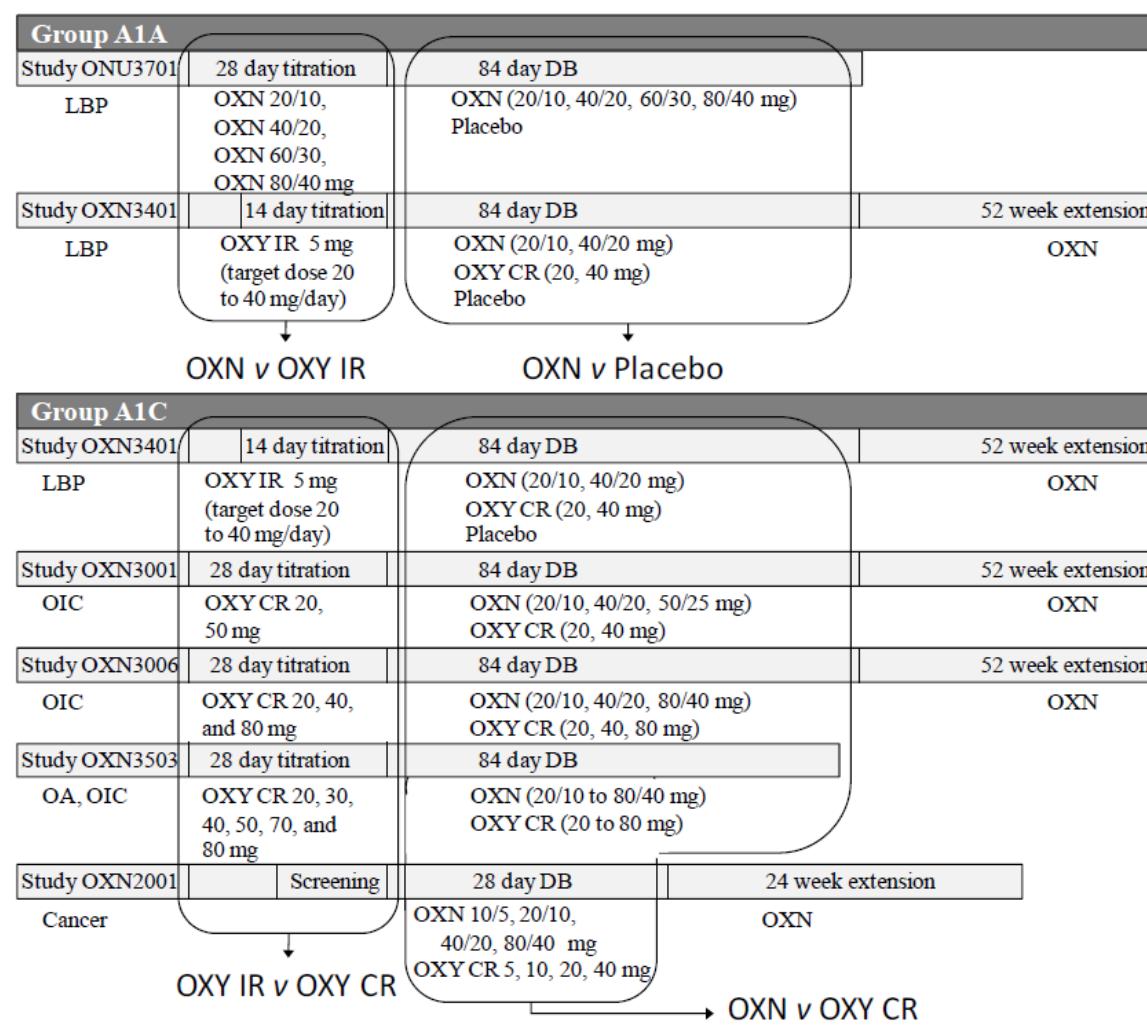
Though high level information for all OXN-treated patients will occasionally be shown (Group C), this review will focus on the controlled data from:

- **Group A1A** – the placebo-controlled trials in subjects with nonmalignant chronic pain
 - 2 placebo-controlled randomized phase 3 studies (ONU3701 and OXN3401)
 - Study ONU3701 utilized a blinded opioid taper during the first 2 to 10 days of the double-blind period for the subjects assigned to the placebo group, depending on the OXN dose at randomization.
 - Study OXN3401 did not utilize an opioid taper during the double-blind period; rather subjects underwent an opioid taper period prior to open-label titration to exclude those demonstrating excessive signs or symptoms of opioid withdrawal.
 - The data from the open-label titration periods in this pool are displayed by treatment (OXY IR in study OXN3401 and OXN in study ONU3701) and

are presented separately from the data collected in the double-blind and open-label extension periods.

- **Group A1C** – the OXY-CR-controlled trials in subjects with nonmalignant chronic pain and malignant chronic pain
 - 5 OXY CR-controlled randomized phase 2 and 3 studies (OXN2001, OXN3001, OXN3006, OXN3401, and OXN3503)
 - no OXN treatment was used during the open-label titration period in this pool
 - The data from the open-label titration periods in this pool are displayed by treatment (OXY IR or OXY CR) and are displayed separately from the data collected in the double-blind and open-label extension periods.

The designs of the trials incorporated into those two Groupings are given in the figure below:



Demographics

In the placebo-controlled trials (Group A1A), the average patient was 54 years old, and most were Caucasian and female. The mean subject weight was approximately 88 kg with a BMI of 31 kg/m². All were suffering low back pain by protocol stipulation. A tabular summary of Group A1A demographics is shown below (source, ECVe Table 9, pg 60):

Table 9: Demographics and Baseline Characteristics of Subjects in Double-Blind and Open-Label Extension Periods: Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A), Randomized Safety Population

| Category | Double-blind | | Open-label extension | Double-blind plus open-label extension OXN |
|---------------------------------|----------------------|------------------|----------------------|--|
| | Placebo (N = 460) | OXN (N = 451) | OXN (N = 379) | (N = 699) |
| Sex, n (%) | | | | |
| Male | 172 (37.4) | 206 (45.7) | 148 (39.1) | 295 (42.2) |
| Female | 288 (62.6) | 245 (54.3) | 231 (60.9) | 404 (57.8) |
| Age (years) | | | | |
| N | 460 | 451 | 379 | 699 |
| Mean (SD) | 54.3 (11.45) | 54.3 (11.42) | 56.3 (10.88) | 55.2 (11.30) |
| Median | 54.0 | 54.0 | 56.0 | 55.0 |
| Min, Max | 20, 85 | 20, 85 | 22, 85 | 20, 85 |
| Age group, n (%) | | | | |
| < 65 years | 379 (82.4) | 373 (82.7) | 295 (77.8) | 561 (80.3) |
| ≥ 65 years | 81 (17.6) | 78 (17.3) | 84 (22.2) | 138 (19.7) |
| ≥ 75 years | 17 (3.7) | 13 (2.9) | 16 (4.2) | 26 (3.7) |
| Race, n (%) | | | | |
| White | 391 (85.0) | 382 (84.7) | 379 (100.0) | 630 (90.1) |
| Non-white | 69 (15.0) | 69 (15.3) | 0 (0.0) | 69 (9.9) |
| Black | 61 (13.3) | 53 (11.8) | 0 (0.0) | 53 (7.6) |
| Asian | 3 (0.7) | 8 (1.8) | 0 (0.0) | 8 (1.1) |
| Other | 5 (1.1) | 8 (1.8) | 0 (0.0) | 8 (1.1) |
| Weight (kg) | | | | |
| N | 458 | 447 | 379 | 695 |
| Mean (SD) | 87.5 (20.88) | 88.1 (21.82) | 83.2 (18.39) | 86.1 (20.54) |
| Median | 86.1 | 86.2 | 82.0 | 84.1 |
| Min, Max | 47, 173 | 45, 191 | 47, 163 | 45, 191 |
| Height (cm) | | | | |
| N | 300 | 294 | | 294 |
| Mean (SD) | 170.7 (10.34) | 169.9 (10.79) | | 169.9 (10.79) |
| Median | 170.2 | 170.2 | | 170.2 |
| Min, Max | 135, 198 | 137, 193 | | 137, 193 |
| BMI (kg/m ²) | | | | |
| N | 300 | 294 | | 294 |
| Mean (SD) | 31.3 (7.48) | 31.2 (7.70) | | 31.2 (7.70) |
| Median | 30.3 | 30.2 | | 30.2 |
| Min, Max | 17, 72 | 15, 62 | | 15, 62 |
| BMI, n (%) | | | | |
| BMI < 25 kg/m ² | 57 (12.4) | 54 (12.0) | | 54 (7.7) |
| 25 ≤ BMI < 30 kg/m ² | 84 (18.3) | 91 (20.2) | | 91 (13.0) |
| BMI ≥ 30 kg/m ² | 159 (34.6) | 149 (33.0) | | 149 (21.3) |
| Type of pain, n (%) | | | | |
| Malignant | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Low back | 460 (100.0) | 451 (100.0) | 379 (100.0) | 699 (100.0) |
| Osteoarthritis knee/hip | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Unspecified | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

In the OXY-CR-controlled studies (Group A1C), patients suffered a variety of different pain-producing ailments including osteoarthritis and cancer, so it is not surprising that the patients were older, and they were also less overweight. Virtually all patients were Caucasian, as seen in the tabular summary below (ECVE Table 10, pg 61):

Table 10: Demographics and Baseline Characteristics of Subjects in Double-Blind and Open-Label Extension Periods: OXY CR-Controlled Studies of Chronic Nonmalignant and Malignant Pain (Group A1C), Randomized Safety Population

| Category | Double-blind | | Open-label extension OXN (N = 970) | Double-blind plus open-label extension OXN (N = 1177) |
|---------------------------------|---------------------|------------------|--|--|
| | OXY CR (N = 646) | OXN (N = 638) | | |
| Sex, n (%) | | | | |
| Male | 250 (38.7) | 244 (38.2) | 387 (39.9) | 455 (38.7) |
| Female | 396 (61.3) | 394 (61.8) | 583 (60.1) | 722 (61.3) |
| Age (years) | | | | |
| N | 646 | 638 | 970 | 1177 |
| Mean (SD) | 59.6 (11.28) | 58.7 (11.23) | 57.5 (11.06) | 58.3 (11.13) |
| Median | 59.0 | 59.0 | 57.0 | 58.0 |
| Min, Max | 25, 87 | 29, 85 | 22, 87 | 22, 87 |
| Age group, n (%) | | | | |
| < 65 years | 414 (64.1) | 448 (70.2) | 706 (72.8) | 833 (70.8) |
| ≥ 65 years | 232 (35.9) | 190 (29.8) | 264 (27.2) | 344 (29.2) |
| ≥ 75 years | 60 (9.3) | 55 (8.6) | 57 (5.9) | 88 (7.5) |
| Race, n (%) | | | | |
| White | 642 (99.4) | 638 (100.0) | 968 (99.8) | 1175 (99.8) |
| Non-white | 4 (0.6) | 0 (0.0) | 2 (0.2) | 2 (0.2) |
| Black | 2 (0.3) | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other | 2 (0.3) | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| Weight (kg) | | | | |
| N | 646 | 637 | 970 | 1176 |
| Mean (SD) | 82.4 (19.59) | 82.2 (18.73) | 82.3 (19.05) | 82.2 (18.90) |
| Median | 80.6 | 80.0 | 80.0 | 80.0 |
| Min, Max | 38, 174 | 39, 163 | 38, 163 | 38, 163 |
| Height (cm) | | | | |
| N | 197 | 191 | 125 | 251 |
| Mean (SD) | 166.8 (9.45) | 166.4 (8.83) | 167.0 (8.83) | 166.3 (8.91) |
| Median | 167.0 | 166.0 | 166.0 | 166.0 |
| Min, Max | 144, 198 | 145, 190 | 144, 188 | 144, 190 |
| BMI (kg/m ²) | | | | |
| N | 197 | 191 | 125 | 251 |
| Mean (SD) | 28.4 (6.25) | 28.1 (6.46) | 25.5 (5.29) | 27.5 (6.24) |
| Median | 28.0 | 27.7 | 25.1 | 26.8 |
| Min, Max | 16, 54 | 15, 46 | 16, 41 | 15, 46 |
| BMI, n (%) | | | | |
| BMI < 25 kg/m ² | 57 (8.8) | 60 (9.4) | 61 (6.3) | 87 (7.4) |
| 25 ≤ BMI < 30 kg/m ² | 71 (11.0) | 54 (8.5) | 39 (4.0) | 77 (6.5) |
| BMI ≥ 30 kg/m ² | 69 (10.7) | 77 (12.1) | 25 (2.6) | 87 (7.4) |
| Type of pain, n (%) | | | | |
| Malignant | 92 (14.2) | 92 (14.4) | 128 (13.2) | 154 (13.1) |
| Low back | 151 (23.4) | 153 (24.0) | 379 (39.1) | 401 (34.1) |
| Osteoarthritis knee/hip | 108 (16.7) | 101 (15.8) | 0 (0.0) | 101 (8.6) |
| Unspecified | 295 (45.7) | 292 (45.8) | 463 (47.7) | 521 (44.3) |

CV Risk at baseline (from ECVE pg 63-64)

The placebo-controlled (Group A1A) population is fairly young as discussed above, but otherwise is certainly an at-risk population for CV events. Approximately half of these patients were hypertensive at baseline, and just under half were diabetic. Approximately 1/3 were hyperlipidemic, and about 1/5 had a history of a CV condition. For the Group A1A population as a whole, approximately 1/2 had at least 2 CV risk factors, and approximately 1/3 had \geq 3 CV risk factors. The most commonly reported CV medical history for both the OXN and placebo trial arms in Group A1A was coronary artery disease (CAD, 3.1% and 3.5%, respectively).

Patients in the OXY CR-controlled studies (Group A1C) were older, so it is not surprising that there was a somewhat higher CV disease rate reported at baseline (approximately 30%), but otherwise, the overall CV risk profile was similar to the Group A1A patients. Commensurate with their more advanced age, the most commonly reported CV medical history for both the OXN and OXY CR arms of Group A1C, myocardial ischemia, occurred at a higher frequency of 8.2% and 7.9%, respectively, compared with CAD in Group A1A .

Disposition of patients (sources, ISS and ECVE)

Because of the fairly high drop-out rate in these trials and the classification of a number of dropouts as “subject’s choice, lost to follow-up, administrative, and lack of therapeutic effect,” the sponsor convened a Discontinuation Reason Adjudication Committee (DRAC) to review the categorization of reasons for dropouts in the trials supporting this NDA. For the principal pivotal trial ONU3701, the DRAC included medical and statistical personnel from an independent party that was contracted for this purpose, and their review was performed retrospectively but prior to the lock of the ONU3701 database. For the other trials, the DRAC was composed of personnel from PPLP and performed retrospectively. The following points summarize patient dispositions across the program:

- A total of 3073 subjects were exposed to OXN in 29 pooled studies in this clinical development program (group C, 33 studies if open-label extensions are counted separately), of which 2396 subjects had nonmalignant or malignant chronic pain and 466 were healthy subjects. Approximately 67% of subjects exposed to OXN in all pooled studies completed treatment.
- Of subjects with chronic nonmalignant pain, the incidence of discontinuation during the 12-week double-blind period was lower in the OXN treatment group (21.5%) compared with the placebo group (31.5%) in the placebo-controlled studies (group A1A) and was slightly lower in the OXN treatment group (13.5%) compared with the OXY CR treatment group (17.1%) in the OXY CR-controlled studies (group A1C).

- The DRAC reviewed key safety and dosing data in the pivotal study ONU3701 prior to database lock. For the other studies, subjects who discontinued due to reasons of subject's choice, administrative reasons, lost to follow-up, or lack of therapeutic effect were reviewed retrospectively and assigned a secondary reason for discontinuation due to AE if this was appropriate. These secondary reasons for discontinuation were subsequently imported into the integrated database and reported as a separate category for discontinuation in the ISS. Thus, the incidence of discontinuation due to AEs is reported for both (1) primary and (2) primary or secondary reasons for discontinuation in ISS tables. Accordingly, a summary disposition table for all subjects exposed to OXN (Group C, N=3073) is as follows (ISS table 5):

Table 5: Subject Disposition and Reasons for Discontinuation of OXN for Subjects Exposed to OXN in All Pooled Studies (Group C, Safety Population)

| Category | OXN (N=3073) |
|--|-----------------|
| | n (%) |
| Completed OXN Medication | 2049 (66.7) |
| Discontinued OXN Medication | 1024 (33.3) |
| Reason for Discontinuation | |
| Adverse Event | 294 (9.6) |
| Subject's Choice | 154 (5.0) |
| Lost to Follow-up | 34 (1.1) |
| Administrative | 112 (3.6) |
| Lack of Therapeutic Effect | 170 (5.5) |
| Suspected Diversion | 21 (0.7) |
| Did not Qualify | 178 (5.8) |
| Subjects With a Secondary Reason Being Discontinuation for Adverse Event | |
| Subject's Choice and Adverse Event | 39 (1.3) |
| Lost to Follow-up and Adverse Event | 4 (0.1) |
| Administrative and Adverse Event | 8 (0.3) |
| Lack of Therapeutic Effect and Adverse Event | 10 (0.3) |

- The most common reasons for discontinuation were AE (9.6% [primary or secondary reason: 11.6%]), did not qualify for the study (5.8%), and lack of therapeutic effect (5.5%).
- For only one of 29 Group C studies were patients who withdrew prematurely encouraged to stay in the trial until its completion, thus limiting CV event ascertainment for the most part to events occurring within 7 days of study drug dosing
- In both placebo-controlled pivotal trials (Group A1A), an open label titration-to-effect phase demonstrated a large and asymmetric premature withdrawal/discontinuation rate (45.1% for OXN versus 21.2% for OXY IR), as seen in the table below:

Table 1.2.1
Subject Disposition and Reasons for Study Drug Discontinuation During Open-label Titration
Population: Safety - Placebo Controlled Studies in Subjects with Non-malignant Chronic Pain (Group A1A)

| Category | OXY IR (N=586) n (%) | OXN (N=1095) n (%) | Total (N=1681) n (%) |
|--|----------------------------|--------------------------|----------------------------|
| Completed Open-label Titration | 462 (78.8) | 601 (54.9) | 1063 (63.2) |
| Discontinued Study Drug | 124 (21.2) | 494 (45.1) | 618 (36.8) |
| Reason for Discontinuation | | | |
| Adverse Event | 22 (3.8) | 95 (8.7) | 117 (7.0) |
| Subject's Choice | 12 (2.0) | 65 (5.9) | 77 (4.6) |
| Lost to Follow-up | 1 (0.2) | 25 (2.3) | 26 (1.5) |
| Administrative | 12 (2.0) | 8 (0.7) | 20 (1.2) |
| Lack of Therapeutic Effect | 52 (8.9) | 107 (9.8) | 159 (9.5) |
| Suspected Diversion | 0 (0.0) | 16 (1.5) | 16 (1.0) |
| Did not Qualify | 0 (0.0) | 178 (16.3) | 178 (10.6) |
| Subject's Choice and Adverse Event | 5 (0.9) | 0 (0.0) | 5 (0.3) |
| Lost to Follow-up and Adverse Event | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Administrative and Adverse Event | 4 (0.7) | 0 (0.0) | 4 (0.2) |
| Lack of Therapeutic Effect and Adverse Event | 16 (2.7) | 0 (0.0) | 16 (1.0) |

Studies in Group A1A: [ONU3701](#) and [OXN3401](#). Only study ONU3701 used OXN and only study OXN3401 used OXY IR during open-label titration.
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Once the controlled phases of the trials in both Groups A1A and A1C began, the incidence of premature withdrawal, though still high in both trial Groups, was lower for patients taking OXN, as can be seen below for controlled phase withdrawal data for Group A1A:

Table 1.2.3
Subject Disposition and Reasons for Study Drug Discontinuation During Double-blind and Open-label Extension
Population: Randomized Safety - Placebo Controlled Studies in Subjects with Non-malignant Chronic Pain (Group A1A)

| Category | Double-Blind | | Open-label Extension OXN (N=379) n (%) | Double-blind plus Open-label Extension OXN (N=699) n (%) |
|--|-----------------------------|-------------------------|---|---|
| | Placebo (N=460) n (%) | OXN (N=451) n (%) | | |
| Completed Study Period | 315 (68.5) | 354 (78.5) | 296 (78.1) | 519 (74.2) |
| Discontinued Study Drug | 145 (31.5) | 97 (21.5) | 83 (21.9) | 180 (25.8) |
| Reason for Discontinuation | | | | |
| Adverse Event | 35 (7.6) | 30 (6.7) | 24 (6.3) | 54 (7.7) |
| Subject's Choice | 13 (2.8) | 14 (3.1) | 25 (6.6) | 39 (5.6) |
| Lost to Follow-up | 1 (0.2) | 4 (0.9) | 1 (0.3) | 5 (0.7) |
| Administrative | 10 (2.2) | 8 (1.8) | 13 (3.4) | 21 (3.0) |
| Lack of Therapeutic Effect | 75 (16.3) | 34 (7.5) | 10 (2.6) | 44 (6.3) |
| Suspected Diversion | 6 (1.3) | 5 (1.1) | 0 (0.0) | 5 (0.7) |
| Subject's Choice and Adverse Event | 1 (0.2) | 1 (0.2) | 6 (1.6) | 7 (1.0) |
| Lost to Follow-up and Adverse Event | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Administrative and Adverse Event | 0 (0.0) | 0 (0.0) | 2 (0.5) | 2 (0.3) |
| Lack of Therapeutic Effect and Adverse Event | 4 (0.9) | 1 (0.2) | 2 (0.5) | 3 (0.4) |

Studies in Group A1A: [ONU3701](#) and [OXN3401](#).
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For all patients in Group C (all studies) who rolled over to open-label OXN therapy in an extension trial, as would be expected, patient that rolled over from placebo to active OXN therapy had the highest discontinuation rate (29.4%, ECV table 1.2.5):

Table 1.2.5
Subject Disposition and Reasons for Study Drug Discontinuation During Open-label Extension
Population: Safety - Studies in Chronic Pain, Healthy Subjects, Abuse Liability and in Special Populations and Situations (Group C)

| Category | Previous Double-blind Treatment Group | | | Total OXN in Extension |
|--|---------------------------------------|----------------------------|-------------------------|-------------------------|
| | Placebo (N=126) n (%) | OXY CR (N=413) n (%) | OXN (N=431) n (%) | OXN (N=970) n (%) |
| Completed Study Period | 89 (70.6) | 327 (79.2) | 338 (78.4) | 754 (77.7) |
| Discontinued Study Drug | 37 (29.4) | 86 (20.8) | 93 (21.6) | 216 (22.3) |
| Reason for Discontinuation | | | | |
| Adverse Event | 11 (8.7) | 35 (8.5) | 40 (9.3) | 86 (8.9) |
| Subject's Choice | 7 (5.6) | 23 (5.6) | 23 (5.3) | 53 (5.5) |
| Lost to Follow-up | 0 (0.0) | 2 (0.5) | 2 (0.5) | 4 (0.4) |
| Administrative | 6 (4.8) | 13 (3.1) | 12 (2.8) | 31 (3.2) |
| Lack of Therapeutic Effect | 6 (4.8) | 2 (0.5) | 6 (1.4) | 14 (1.4) |
| Suspected Diversion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subject's Choice and Adverse Event | 4 (3.2) | 8 (1.9) | 6 (1.4) | 18 (1.9) |
| Lost to Follow-up and Adverse Event | 0 (0.0) | 0 (0.0) | 2 (0.5) | 2 (0.2) |
| Administrative and Adverse Event | 2 (1.6) | 1 (0.2) | 1 (0.2) | 4 (0.4) |
| Lack of Therapeutic Effect and Adverse Event | 1 (0.8) | 2 (0.5) | 1 (0.2) | 4 (0.4) |

Studies in Group C with an open label extension: OXN2001, OXN3001, OXN3006 and OXN3401.
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Exposure

- Group C (all pooled studies)
 - A total of 3073 subjects were exposed to total daily doses of OXN ranging from 10/5 mg to > 100/50 mg
- Group A1A (placebo controlled)
 - A total of 1680 subjects received at least 1 dose of study drug during the open-label titration period. Of the 1680 subjects, 1095 subjects (study ONU3701 only) received OXN and 585 subjects (study OXN3401 only) received OXY IR. The subject-years of exposure were higher in the OXN group (55 subject-years) compared with the OXY IR group (23 subject-years), primarily due to the higher number of subjects treated with OXN during titration and protocol differences (from ECVE Table 13, not shown).
 - During the double-blind period, a total of 911 subjects received at least 1 dose of study drug (ECVE Table 14, below). Of the 911 subjects, 451 subjects received OXN and 460 subjects received placebo. The subject-years of exposure were slightly higher in the OXN group (86 subject-years) compared with placebo (79 subject-years).
 - A total of 379 subjects received at least 1 dose of OXN during the open-label extension.

Table 14: Summary of Cumulative Exposure During Double-blind and Open-label Extension Periods: Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A), Randomized Safety Population

| Exposure | Double-blind | | Open-label extension | | Double-blind plus open-label extension | |
|---------------------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|---|--|
| | Placebo (N = 460) n (%) | OXN (N = 451) n (%) | OXN (N = 379) n (%) | OXN (N = 699) n (%) | label extension OXN (N = 699) n (%) | |
| Subjects with any exposure | 460 (100.0) | 451 (100.0) | 379 (100.0) | | 699 (100.0) | |
| Cumulative exposure categories (n, %) | | | | | | |
| < 1 week | 27 (5.9) | 19 (4.2) | 5 (1.3) | | 23 (3.3) | |
| ≥ 1 week | 433 (94.1) | 432 (95.8) | 374 (98.7) | | 676 (96.7) | |
| ≥ 2 weeks | 397 (86.3) | 423 (93.8) | 372 (98.2) | | 665 (95.1) | |
| ≥ 3 weeks | 372 (80.9) | 405 (89.8) | 372 (98.2) | | 647 (92.6) | |
| ≥ 4 weeks | 353 (76.7) | 397 (88.0) | 370 (97.6) | | 638 (91.3) | |
| ≥ 8 weeks | 326 (70.9) | 361 (80.0) | 358 (94.5) | | 596 (85.3) | |
| ≥ 12 weeks | 168 (36.5) | 172 (38.1) | 349 (92.1) | | 430 (61.5) | |
| ≥ 3 months (90 days) | 21 (4.6) | 24 (5.3) | 346 (91.3) | | 363 (51.9) | |
| ≥ 6 months (180 days) | 0 (0.0) | 0 (0.0) | 330 (87.1) | | 333 (47.6) | |
| ≥ 12 months (360 days) | 0 (0.0) | 0 (0.0) | 279 (73.6) | | 291 (41.6) | |
| Cumulative days of exposure | | | | | | |
| N | 460 | 451 | 379 | | 699 | |
| Mean (SD) | 62.8 (30.46) | 69.9 (24.98) | 321.3 (104.93) | | 219.3 (166.16) | |
| Median | 81.0 | 82.0 | 365.0 | | 123.0 | |
| Min, Max | 1, 99 | 1, 123 | 1, 492 | | 1, 492 | |
| Subject-years of exposure | 79 | 86 | 333 | | 420 | |

- Group A1C

- A total of 1707 subjects received at least 1 dose of study drug during the open-label titration period. Of the 1707 subjects, 1122 subjects received OXY CR and 585 subjects received OXY IR. The subject-years of exposure were higher in the OXY CR group (47 subject-years) compared with the OXY IR group (23 subject-years), primarily due to the higher number of subjects treated with OXY CR during titration (from ECV Table 15, not shown).
- During the double-blind period, a total of 1284 subjects received at least 1 dose of study drug (Table 16). Of the 1284 subjects, 638 subjects received OXN and 646 subjects received OXY CR. The mean cumulative duration and the subject-years of exposure were similar for the OXN and OXY CR treatment groups. A total of 970 subjects received at least 1 dose of OXN during the open-label extension; a total of 1177 subjects received OXN during the double-blind and open-label extension periods (Table 16).

Table 16: Summary of Cumulative Exposure During Double-blind and Open-label Extension Periods: OXY CR-Controlled Studies of Chronic Nonmalignant and Malignant Pain (Group A1C), Randomized Safety Population

| Exposure | Double-blind | | Open-label extension | Double-blind plus open-label extension OXN |
|---------------------------------------|---------------------|------------------|----------------------|--|
| | OXY CR (N = 646) | OXN (N = 638) | OXN (N = 970) | (N = 1177) n (%) |
| Subjects with any exposure | 646 (100.0) | 638 (100.0) | 970 (100.0) | 1177 (100.0) |
| Cumulative exposure categories (n, %) | | | | |
| < 1 week | 10 (1.5) | 22 (3.4) | 17 (1.8) | 35 (3.0) |
| ≥ 1 week | 636 (98.5) | 616 (96.6) | 953 (98.2) | 1142 (97.0) |
| ≥ 2 weeks | 612 (94.7) | 596 (93.4) | 941 (97.0) | 1116 (94.8) |
| ≥ 3 weeks | 595 (92.1) | 578 (90.6) | 936 (96.5) | 1098 (93.3) |
| ≥ 4 weeks | 571 (88.4) | 555 (87.0) | 926 (95.5) | 1082 (91.9) |
| ≥ 8 weeks | 483 (74.8) | 485 (76.0) | 890 (91.8) | 1040 (88.4) |
| ≥ 12 weeks | 386 (59.8) | 385 (60.3) | 866 (89.3) | 989 (84.0) |
| ≥ 3 months (90 days) | 62 (9.6) | 39 (6.1) | 859 (88.6) | 893 (75.9) |
| ≥ 6 months (180 days) | 0 (0.0) | 0 (0.0) | 756 (77.9) | 794 (67.5) |
| ≥ 12 months (360 days) | 0 (0.0) | 0 (0.0) | 523 (53.9) | 621 (52.8) |
| Cumulative days of exposure | | | | |
| N | 646 | 638 | 970 | 1177 |
| Mean (SD) | 69.7 (27.47) | 69.5 (27.97) | 296.4 (118.50) | 281.9 (158.22) |
| Median | 84.0 | 84.0 | 361.0 | 362.0 |
| Min, Max | 1, 107 | 1, 123 | 1, 492 | 1, 492 |
| Subject-years of exposure | 123 | 121 | 787 | 908 |

CV Adverse Events

Definitions

In order to evaluate the CV risk of OXN uniformly across this somewhat diverse clinical development program, the sponsor analyzed CV outcome events using 4 different (post hoc) definitions as follows:

- FDA cMACE (FDA custom Major Adverse Cardiac Event) - an event which has been coded to 1 of the preferred terms included in the following table:

Table 4: Preferred Terms Included in the FDA-Defined Custom Major Adverse Cardiac Events

| | |
|---------------------------------------|---|
| Acute myocardial infarction | Embolic cerebral infarction |
| Myocardial infarction | Embolic stroke |
| Coronary artery thrombosis | Haemorrhagic cerebral infarction |
| Papillary muscle infarction | Haemorrhagic stroke |
| Post procedural myocardial infarction | Haemorrhagic transformation stroke |
| Silent myocardial infarction | Ischemic cerebral infarction |
| Basilar artery thrombosis | Ischemic stroke |
| Brain stem infarction | Lacunar infarction |
| Brain stem stroke | Lateral medullary syndrome |
| Brain stem thrombosis | Moyamoya disease |
| Carotid arterial embolus | Post procedural stroke |
| Carotid artery thrombosis | Stroke in evolution |
| Cerebellar infarction | Thalamic infarction |
| Cerebral artery embolism | Thrombotic cerebral infarction |
| Cerebral artery thrombosis | Thrombotic stroke |
| Cerebral infarction | Wallenberg syndrome |
| Cerebral thrombosis | Cardiovascular death (see definition below) |
| Cerebrovascular accident | |

CV Death in the cMACE definition set was defined as death associated with the following conditions:

- AE in the SOC OF Cardiac Disorders
- AE contained in the SMQ for Central Nervous System Hemorrhages and Cerebrovascular Condition
- Clinical scenario suggestive of sudden death, or
- Other vascular events (including pulmonary embolism, peripheral arterial occlusive disease, and peripheral arterial reocclusion)
- SMQ-based MACE - any AE which had been coded to a preferred term in 1 of the following SMQs:
 - Myocardial Infarction (sub-SMQ)
 - Central Nervous System Hemorrhages and Cerebrovascular Conditions (sub-SMQ) CV death
- SMQ-based CV SAEs/AEs – any SAE/AE that was coded to a preferred term in 1 of the following SMQs:
 - Cardiac Arrhythmias
 - Cardiac Failure
 - Cardiomyopathy
 - Central Nervous System Hemorrhages and Cerebrovascular Conditions (sub-SMQ)
 - Embolic and Thrombotic Events
 - Hypertension
 - Ischemic Heart Disease
 - Torsade de Pointes/QT Prolongation.

MACE – Open-Label Titration Period

- Group A1A
 - 1 subject (0.2%) in the OXY IR group experienced an FDA cMACE of sudden cardiac death (OXN3401-0710A-0071003). No subjects treated with OXN during the open-label titration period experienced an FDA cMACE. This same patient was also identified as the only SMQ-MACE event during the open-label titration phase.
- Group A1C
 - 1 subject (0.2%) in the OXY IR group experienced an FDA cMACE of sudden cardiac death (OXN3401-0710A-0071003) and 1 subject (0.1%) in the OXY CR group experienced an FDA cMACE of cerebrovascular accident (OXN3503-0749A-0074905). This is the same patient as in Group A1A as study 3401 is common to both groups.
 - 2 subjects (0.2%) in the OXY CR group (1 dysarthria [OXN3001-0956A-0095603] and 1 cerebrovascular accident [OXN3503-0749A-0074905]) experienced at least 1 SMQ-based MACE

MACE – Double-Blind Period

A summary of incidence rate and relative risk of FDA cMACE, SMQ-based MACE, SMQ-based CV SAEs, and SMQ-based CV AEs for Group A1A and Group A1C are shown in the below (Table 17 from the ECVE):

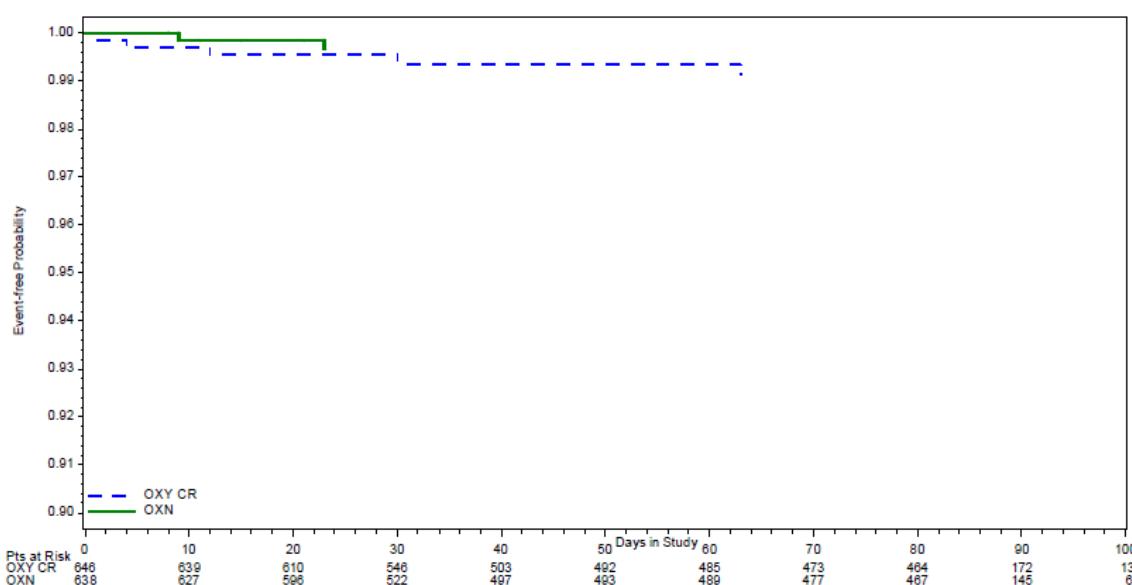
Table 17: Summary of Incidence Rate and Relative Risk of FDA-Defined Custom Major Adverse Cardiac Events, SMQ-Based Major Adverse Cardiac Events, SMQ-Based Cardiovascular Serious Adverse Events, and SMQ-Based Cardiovascular Adverse Events During the Double-Blind Period, Randomized Safety Population

| | Placebo N = 460 | OXN N = 451 | Relative Risk ^a | 95% CI | P-value |
|------------------|--|----------------|----------------------------|----------------------|---------|
| | n (Rate) | n (Rate) | | | |
| Group A1A | | | | | |
| | At least 1 FDA cMACE | 2 (2.3) | 0 | - | - |
| | At least 1 SMQ-based MACE ^b | 2 (2.3) | 0 | - | - |
| | At least 1 SMQ-based CV SAE | 2 (2.3) | 4 (4.2) | 1.85 (0.35, 9.83) | 0.4727 |
| Group A1C | At least 1 SMQ-based CV AE | 18 (20.3) | 20 (20.8) | 1.03 (0.58, 1.81) | 0.9310 |
| | OXY CR N = 646 | OXN N = 638 | | | |
| | | | | | |
| | n (Rate) | n (Rate) | Relative Risk ^a | 95% CI | P-value |
| | At least 1 FDA cMACE | 3 (2.4) | 1 (0.8) | 0.34 (0.04, 3.22) | 0.3464 |
| | At least 1 SMQ-based MACE ^b | 5 (3.9) | 2 (1.6) | 0.41 (0.08, 2.06) | 0.2773 |
| | At least 1 SMQ-based CV SAE | 8 (6.3) | 9 (7.2) | 1.15 (0.46, 2.87) | 0.7728 |
| | At least 1 SMQ-based CV AE | 48 (37.7) | 44 (35.1) | 0.93 (0.67, 1.29) | 0.6775 |

The following observations, by Group, are noted:

- Group A1A
 - MACE events occurring during the double-blind period of both the placebo-controlled and the active-controlled groups were more frequent in the comparator arms, though other CV SAEs were numerically more common in the OXN arms, regardless of the definition set used
 - Low rate of CV events affects the power to detect differences in the occurrence of CV-related events between treatment groups
 - Both the FDA cMACE and SMQ-based MACE definition sets identified two subjects in the placebo group (0.4%) that experienced acute MIs.
- Group A1C
 - 3 subjects (0.5%) in the OXY CR group (2 cerebrovascular accident [OXN2001-0206A-0020601, OXN3001-0962A-0096219] and 1 MI [OXN2001-0408A-0040807]) and 1 subject (0.2%) in the OXN group (1 cardiac failure [OXN2001-0409A-0040902]) experienced at least 1 FDA cMACE
 - SMQ-based MACE analysis identified all the above-listed FDA cMACE events, but also identified dysarthria (1 subject [0.2%], OXN2001-0602A-0060202), and paraparesis (1 subject [0.2%], OXN2001-0507A-0050703) in the OXY CR group, and hemiparesis (1 subject [0.2%], OXN2001-0502A-0050205) in the OXN group
 - Using the more comprehensive SMQ-based MACE analysis to examine time to first event, there was no discernable temporal pattern to the occurrence of these events as seen in the K-M curves below, but the number of events, even using this definition set, was small:

Figure 4.3.6.2
Kaplan-Meier Curves of Time to First Occurrence for SMQ-based MACE During Double-blind
Population: Randomized Safety - OXY Controlled Studies in Subjects with Non-malignant and Malignant Chronic Pain (Group A1C)



Group A1C: OXN2001, OXN3001, OXN3006, OXN3401 and OXN3503.

Cross-reference: Table 4.3.3.2

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Deaths

Across the OXN development program, 57 total deaths are known to have occurred. 51 of the 57 deaths occurred in study OXN2001 that included malignant pain, most of which were the result of tumor progression. None was considered by the investigator to be related to treatment. The following table summarizes all-cause deaths across both Group A1A and Group A1C according to study phase and relationship to treatment emergent adverse events (ECVE pg 79):

Table 20: Incidence of Adverse Events Leading to Death by Treatment-Emergent Status in Open-Label Titration, Double-Blind, and Open-Label Extension Periods: Placebo and OXY CR-Controlled Studies of Chronic Malignant and Nonmalignant Pain (Group A1A and Group A1C Combined), Safety Population

| Category | Open-label Titration | | | Double-Blind | | | Extension Period |
|--|------------------------------|-------------------------------|----------------------------|-------------------------------|------------------------------|---------------------------|---------------------------|
| | OXY IR (N = 586) n (%) | OXY CR (N = 1122) n (%) | OXN (N = 1095) n (%) | Placebo (N = 460) n (%) | OXY CR (N = 646) n (%) | OXN (N = 936) n (%) | OXN (N = 970) n (%) |
| All-cause deaths | 1 (0.2) | 1 (0.1) | 0 | 1 (0.2) | 12 (1.9) | 16 (1.7) | 26 (2.7) |
| Treatment-emergent AE with outcome death | 1 (0.2) | 1 (0.1) | 0 | 1 (0.2) | 9 (1.4) | 10 (1.1) | 25 (2.6) |
| Non-treatment-emergent AE with outcome death | 0 | 0 | 0 | 0 | 3 (0.5) | 6 (0.6) | 1 (0.1) |
| CV deaths | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) | 2 (0.2) | 2 (0.2) |
| Treatment-emergent AE with outcome death | 1 (0.2) | 0 | 0 | 0 | 1 (0.2) | 1 (0.1) | 2 (0.2) |
| Non-treatment-emergent AE with outcome death | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 |

Details for the deaths occurring in studies involving subjects with nonmalignant pain and subjects who died in study OXN2001 for reasons other than malignant disease progression are provided in ISS Table 37 as shown below:

Table 37: Subjects With Adverse Events Leading to Death (Excluding Subjects Who Died Because of Disease Progression in Study OXN2001) (Group C)

| MedDRA System Organ Class Preferred Term Verbatim Term | AE Onset Date Study Period (Study Day/Period Day) | Study Drug at AE Onset Date | Subject ID |
|--|---|-----------------------------------|-----------------------|
| Cardiac Disorders | | | |
| Cardiac failure HEART AND CIRCULATION FAILURE | (b) (6) Double-Blind/ (b) (6) | OXN | OXN2001-0409A-0040902 |
| Pericarditis PERICARDITIS | (b) (6) | OXN | OXN2001-0802A-0080201 |
| Cardiac arrest CARDIAC ARREST | (b) (6) Extension/ (b) (6) | OXN | OXN2001-0807A-0080707 |
| General Disorders and Administration Site Conditions | | | |
| Multi-organ failure MULTIPLE ORGAN FAILURE | (b) (6) Run-in/ (b) (6) | OXY CR | OXN3503-1676A-0167602 |
| Sudden cardiac death SUDDEN CARDIAC DEATH | (b) (6) Run-in/ (b) (6) | OXY IR | OXN3401-0710A-0071003 |
| Infections and Infestations | | | |
| Necrotising fascitis NECROTISING FASCIITIS | (b) (6) Extension/ (b) (6) | OXN | OXN3001-0938A-0093803 |
| Sepsis SEPSIS | (b) (6) Extension/ (b) (6) | OXN | OXN3006-1097A-0019706 |
| Septic shock SEPTIC SHOCK | (b) (6) Run-in/ (b) (6) | OXY CR | OXN3503-1676A-0167602 |
| Urinary tract infection URINARY TRACT INFECTION | (b) (6) Run-in/ (b) (6) | OXY CR | |
| Urosepsis UROSEPSIS | (b) (6) Run-in/ (b) (6) | OXY CR | |
| Injury, Poisoning and Procedural Complications | | | |
| Gunshot wound GUNSHOT WOUND | (b) (6) Double-Blind/ (b) (6) | Placebo | ONU3701-0390A-0136003 |
| Chest crushing CHEST CRUSHING | (b) (6) Extension/ (b) (6) | OXN | OXN3401-0670A-0067009 |
| Road traffic accident QUADRICYCLE ACCIDENT | (b) (6) Extension/ (b) (6) | OXN | |
| Vascular Disorders | | | |
| Circulatory collapse HEART AND CIRCULATION FAILURE | (b) (6) Double-Blind/ (b) (6) | OXN | OXN2001-0409A-0040902 |
| Respiratory, Thoracic and Mediastinal Disorders | | | |
| Asphyxia SUFFOCATION | (b) (6) Extension/ (b) (6) | OXN | OXN3401-0670A-0067009 |
| Pulmonary embolism LUNG EMBOLISM | (b) (6) Extension/ (b) (6) | OXN | OXN2001-0504A-0050401 |

AE = adverse event; ID = identification; OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets; OXY IR = oxycodone immediate-release.

Note: MedDRA Version 15.0 was used to code adverse events.

Study day is relative to the day of first dose in the study; period day is relative to the first dosing day in the corresponding study period. The first dosing day is Day 1.

Studies in group C: Studies in groups A and B and studies ONU1003, ONU1004, ONU1007, ONU1008, OXN1006, OXN1007, and OXN1017. Note: subjects with more than one adverse event leading to death will listed for each event.

Source: ISS Appendix 17.4 Post-text Table 4.7.1.1.

Of these deaths, six were adjudicated to be CV deaths, four of which occurred on OXN, two of which occurred on comparators. Details of the four OXN deaths are as follows, (according to the sponsor's narratives, with cross-check against the CRF):

- Subject OXN2001-0802A-0080201, a 60-year-old male subject with history of esophageal cancer, treated with OXN during the double-blind period, experienced adverse event of opioid withdrawal on Day 2 and withdrew from study on that day. The patient subsequently experienced the SAE of pericarditis on (b) (6), Day

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(b) (6) of the double-blind period. The subject died as a result of the SAE of pericarditis on [REDACTED] (b) (6). Related ongoing CV medical conditions included hypertension. The SAE of pericarditis was considered not related to study drug.

Reviewer's note: patients with esophageal cancer can develop pericarditis due to direct spread of their disease to the pericardium, or due to radiation therapy. Pericardial effusions associated with this condition can be inflammatory, malignant, or purulent.

- Subject OXN2001-0409A-0040902, a 61-year-old male subject with squamous cell carcinoma treated with OXN during the double-blind period experienced an SAE of cardiac failure on [REDACTED] (b) (6), Day (b) (6) of the double-blind period. Study drug was stopped permanently and the subject died as a result of the SAE on [REDACTED] (b) (6). The subject did not have any CV-related medical history or ongoing CV conditions. The SAE was considered not related to study drug but rather related to pulmonary embolism and intracerebral bleeding.

Reviewer's note: We cannot find documentation of the pulmonary embolism or the intracranial bleeding in the FSR or the CRF. The FSR notes that this patient experienced heart and circulatory failure (b) (6) days after screening.

- Subject OXN2001-0807A-0080707, a 78 yo with h/o MI, PTCA, ICD implantation, V-tach, and DM, and lung cancer. The subject experienced the AE of constipation, and discontinued the study due to this event on 26-Jun-2009 (Day 10). On the same day, the subject re-entered the study, entered the extension period, and began open-label treatment. The subject died suddenly at home on [REDACTED] (b) (6); no hospital report or postmortem was available. The event of constipation was ongoing at the time of death (attributed to cardiac arrest). Only the constipation AE was felt to be probably related to study drug.
- Subject OXN2001-0504A-0050401, a 55 yo with h/o ischemic heart disease, hyperlipidemia, hypertension, COPD, bilateral leg amputations, and bladder cancer metastatic to bone. On [REDACTED] (b) (6), the subject experienced the SAE of lung embolism and died due to the event on the same day.

Reviewer's note: This patient was certainly at risk for a fatal pulmonary embolism, but the sponsor's narrative could not be corroborated because this patient's CRF was not found in the submission files.

SMQ-based CV SAEs – Open-Label Titration Period

- Group A1A
 - 2 subjects (0.3%) in the OXY IR group (1 chest pain [OXN3401-0750A-0075019] and 1 sudden cardiac death [OXN3401-0710A-0071003]) and no subjects in the OXN group experienced at least 1 SMQ-based CV SAE

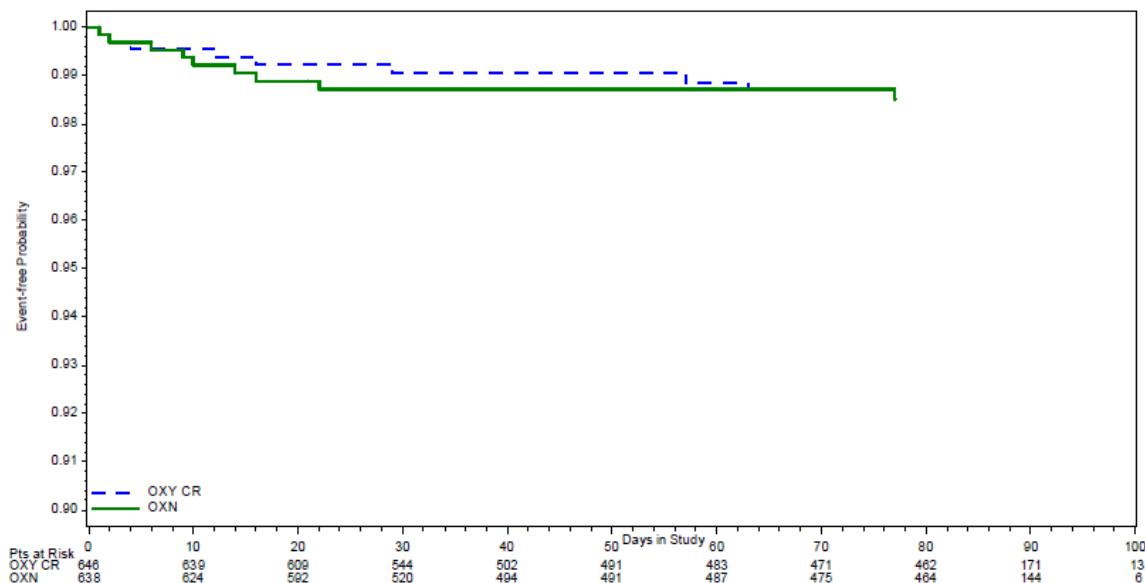
- Group A1C
 - 2 subjects (0.3%) in the OXY IR group (1 chest pain and 1 sudden cardiac death) and 3 subjects (0.3%) in OXY CR group experienced at least 1 SMQ-based CV SAE. Out of 3 subjects in OXY CR group, 1 subject (OXN3001-0664A-0066404) experienced both angina pectoris and coronary artery stenosis; 1 subject each had cerebrovascular accident and dyspnea.

SMQ-based CV SAEs – Double-Blind Period

- Group A1A
 - In Group A1A during the double-blind period, 2 subjects (0.4%) in the placebo group and 4 subjects (0.9%) in OXN group experienced at least 1 SMQ-based CV SAE.
 - Both subjects in the placebo group had acute MIs (ONU3701-0755A-0039002 and ONU3701-1175A-0070013). These were the same patients who were counted as placebo MACE events above.
 - Out of 4 subjects in OXN group, 2 subjects experienced atrial fibrillation (ONU3701-0513A-0076013 and OXN3401-0750A-0075003); and 1 subject each had angina pectoris (ONU3701-2335A-0142013) and syncope (ONU3701-2208A-0090018).
- Group A1C
 - 8 subjects (1.2%) in the OXY CR group and 9 subjects (1.4%) in OXN group experienced at least 1 SMQ-based CV SAE.
 - Out of 8 subjects in the OXY CR group, 2 subjects had cerebrovascular accident; 1 subject each had MI, palpitations, metabolic syndrome, paraparesis, and hypertension; 1 subject (OXN2001-0408A-0040807) had both edema peripheral and dyspnea; 1 subject (OXN2001-0602A-0060220) had both dyspnea and pulmonary embolism.
 - Out of 9 subjects (1.4%) in the OXN group, 2 subjects had dyspnea; 1 subject each had angina pectoris, atrial fibrillation, cardiac failure, ECG change, hypertensive crisis; 1 subject (OXN3006-1161A-0016104) had both CV disorder and myocarditis; 1 subject (OXN3006-0809A-0080903) had both thrombosis and thrombophlebitis superficial.
 - K-M analysis as shown below demonstrates that most of these events occurred within the first three weeks of therapy, but interpretation is limited by the small number of events (ECVE pg 4821):

Reviewer's comment: SAEs for OXN-treated patients do not seem to have a common theme (manifestation/etiology/pathophysiology).

Figure 4.4.8.2
 Kaplan-Meier Curves of Time to First Occurrence of SMQ-based Cardiovascular SAE During Double-blind
 Population: Randomized Safety - OXY Controlled Studies in Subjects with Non-malignant and Malignant Chronic Pain (Group A1C)



SMQ-based CV AEs – Open-Label Titration Period

- Group A1A
 - 3 subjects (0.5%) in the OXY IR group (2 chest pain and 1 sudden cardiac death) and 20 subjects (1.8%) in the OXN group experienced at least 1 SMQ-based CV AE, as shown below:

Table 4.5.2.1
 Incidence Rate of SMQ-based Cardiovascular Adverse Events by System Organ Class and Preferred Term During Open-label Titration
 Population: Safety - Placebo Controlled Studies in Subjects with Non-malignant Chronic Pain (Group A1A)

| MedDRA System Organ Class Preferred Term | OXY IR (N=586) n (Rate) | OXN (N=1095) n (Rate) |
|--|-------------------------------|-----------------------------|
| At least one SMQ-based Cardiovascular AE | 3 (12.1) | 20 (29.9) |
| Cardiac disorders | 0 (0.0) | 1 (1.5) |
| Tachycardia | 0 (0.0) | 1 (1.5) |
| General disorders and administration site conditions | 3 (12.1) | 9 (13.4) |
| Oedema peripheral | 0 (0.0) | 7 (10.5) |
| Chest pain | 2 (8.1) | 1 (1.5) |
| Oedema | 0 (0.0) | 1 (1.5) |
| Sudden cardiac death | 1 (4.0) | 0 (0.0) |
| Investigations | 0 (0.0) | 3 (4.5) |
| Blood pressure increased | 0 (0.0) | 1 (1.5) |
| Electrocardiogram QT prolonged | 0 (0.0) | 1 (1.5) |
| Electrocardiogram ST segment depression | 0 (0.0) | 1 (1.5) |

Reviewer's comment: It is unclear how many of these subjects withdrew from the trial prematurely, but this may have had the effect of "sanitizing" the double-blind CV event rate data by including only patients tolerant of OXN. Note the increased incidence of

edema for OXN-treated patients above during Group A1A up-titration and compare to the Group A1C up-titration CV AEs below, which also show an increased incidence of edema for OXY CR-treated patients. In Table 25 on page 24 of this review, OXN-treated patients also had slightly more edema than placebo-treated patients during the double-blind phase for Group A1A.

- Group A1C

- 3 subjects (0.5%) in the OXY IR group and 31 subjects (2.8%) in OXY CR group experienced at least 1 SMQ-based CV AE per the following summary table (ECVE pg 4824):

Table 4.5.1.2
Incidence of SMQ-based Cardiovascular Adverse Events by System Organ Class and Preferred Term During Open-label Titration
Population: Safety - OXY Controlled Studies in Subjects with Non-malignant and Malignant Chronic Pain (Group A1C)

| MedDRA System Organ Class Preferred Term | OXY IR (N=586) n (%) | OXY CR (N=1122) n (%) |
|--|----------------------------|-----------------------------|
| At least one SMQ-based Cardiovascular AE | 3 (0.5) | 31 (2.8) |
| Cardiac disorders | 0 (0.0) | 8 (0.7) |
| Angina pectoris | 0 (0.0) | 1 (0.1) |
| Cardiovascular disorder | 0 (0.0) | 1 (0.1) |
| Coronary artery stenosis | 0 (0.0) | 1 (0.1) |
| Palpitations | 0 (0.0) | 4 (0.4) |
| Tachycardia | 0 (0.0) | 1 (0.1) |
| Ventricular extrasystoles | 0 (0.0) | 1 (0.1) |
| General disorders and administration site conditions | 3 (0.5) | 5 (0.4) |
| Chest pain | 2 (0.3) | 0 (0.0) |
| Sudden cardiac death | 1 (0.2) | 0 (0.0) |
| Oedema peripheral | 0 (0.0) | 5 (0.4) |
| Investigations | 0 (0.0) | 3 (0.3) |
| Blood pressure increased | 0 (0.0) | 1 (0.1) |
| Electrocardiogram abnormal | 0 (0.0) | 2 (0.2) |
| Nervous system disorders | 0 (0.0) | 3 (0.3) |

Note: Percentages are based on N. Adverse events are sorted alphabetically by system organ class. AE=adverse event. Counts are based on 8 selected SMQs. Multiple occurrences of the same adverse event in one subject are counted only once. MedDRA Version 15.0 was used to code adverse events.

Reviewer's Comment: The disposition of these subjects is unclear. If they withdrew from the trials, then the double-blind CV safety dataset is essentially reflecting those patients who tolerated a narcotic. The reason for the prevalence of cardiac disorders with OXY CR is unknown.

SMQ-based CV AEs – Double-Blind Period

- Group A1A

- In Group A1A during the double-blind period, 18 subjects (3.9%) in the placebo group and 20 subjects (4.4%) in the OXN group experienced at least 1 SMQ-based CV AE. The relative risks for all the SMQ-based CV AEs were less than 1 for OXN, with the exception of atrial fibrillation (relative risk: 1.85; 95% CI: 0.17, 20.00) and edema peripheral (relative risk: 1.85; 95% CI: 0.35, 9.83).

Table 25: Incidence Rate and Relative Risk of SMQ-Based Cardiovascular Adverse Events by System Organ Class and Preferred Term During the Double-Blind Period: Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A), Randomized Safety Population

| MedDRA SOC Preferred Term | Placebo N = 460 n (Rate) | OXN N = 451 n (Rate) | Relative Risk* | 95% CI | P-value |
|---|--------------------------------|----------------------------|-------------------|---------------|---------|
| At least 1 SMQ-based CV AE | 18 (20.3) | 20 (20.8) | 1.03 | (0.58, 1.81) | 0.9310 |
| Cardiac Disorders | 11 (12.4) | 4 (4.2) | 0.34 | (0.11, 1.02) | 0.0533 |
| Atrial fibrillation | 1 (1.1) | 2 (2.1) | 1.85 | (0.17, 20.00) | 0.6142 |
| Angina pectoris | 2 (2.3) | 1 (1.0) | 0.46 | (0.04, 5.00) | 0.5247 |
| Tachycardia | 3 (3.4) | 1 (1.0) | 0.31 | (0.03, 2.90) | 0.3033 |
| Acute myocardial infarction | 2 (2.3) | 0 | - | - | - |
| Cardiovascular disorder | 1 (1.1) | 0 | - | - | - |
| Coronary artery disease | 1 (1.1) | 0 | - | - | - |
| Ventricular extrasystoles | 1 (1.1) | 0 | - | - | - |
| General Disorders and Administration Site Conditions | 3 (3.4) | 5 (5.2) | 1.54 | (0.38, 6.25) | 0.5472 |
| Oedema peripheral | 2 (2.3) | 4 (4.2) | 1.85 | (0.35, 9.83) | 0.4727 |
| Chest pain | 2 (2.3) | 1 (1.0) | 0.46 | (0.04, 5.00) | 0.5247 |
| Investigations | 0 | 3 (3.1) | - | - | - |
| Blood pressure increased | 0 | 1 (1.0) | - | - | - |
| Electrocardiogram abnormal | 0 | 1 (1.0) | - | - | - |
| Heart rate increased | 0 | 1 (1.0) | - | - | - |
| Nervous System Disorders | 0 | 1 (1.0) | - | - | - |
| Syncope | 0 | 1 (1.0) | - | - | - |
| Renal and Urinary Disorders | 0 | 1 (1.0) | - | - | - |
| Nocturia | 0 | 1 (1.0) | - | - | - |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 2 (2.1) | - | - | - |
| Pulmonary congestion | 0 | 2 (2.1) | - | - | - |
| Vascular Disorders | 7 (7.9) | 6 (6.2) | 0.79 | (0.28, 2.26) | 0.6622 |
| Hypertension | 7 (7.9) | 5 (5.2) | 0.66 | (0.22, 2.00) | 0.4621 |
| Venous thrombosis | 0 | 1 (1.0) | - | - | - |

AE = adverse event; CI = confidence interval; CV = cardiovascular; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; SOC = system organ class.

Note: incidence rates are expressed as cases per 100 subject-years of exposure time. A case is a subject with at least 1 occurrence of the event during the exposure time in treatment arm or dose. Exposure time is defined as: last dose - first dose + 7 days. Counts are based on 8 selected SMQs.

Reviewer's Comment: large confidence intervals for relative risk all crossing 1.0

- Group A1C
 - 48 subjects (7.4%) in the OXY CR group and 44 subjects (6.9%) in OXN group experienced at least 1 SMQ-based CV AE, per the following summary table (ECVE pg 92):

Table 26: Incidence Rate and Relative Risk of SMQ-Based Cardiovascular Adverse Events by System Organ Class and Preferred Term During the Double-Blind Period: OXY CR-Controlled Studies of Chronic Nonmalignant and Malignant Pain (Group A1C), Randomized Safety Population

| MedDRA SOC Preferred Term | OXY CR N = 646 n (Rate) | OXN N = 638 n (Rate) | Relative Risk ^a | 95% CI | P-value |
|--|-------------------------------|----------------------------|-------------------------------|---------------|---------|
| At least 1 SMQ-based CV AE | 48 (37.7) | 44 (35.1) | 0.93 | (0.67, 1.29) | 0.6775 |
| Cardiac Disorders | 9 (7.1) | 11 (8.8) | 1.24 | (0.53, 2.90) | 0.6127 |
| Angina pectoris | 3 (2.4) | 2 (1.6) | 0.68 | (0.12, 3.99) | 0.6681 |
| Atrioventricular block first degree | 0 | 2 (1.6) | - | - | - |
| Atrial fibrillation | 0 | 1 (0.8) | - | - | - |
| Atrioventricular block | 0 | 1 (0.8) | - | - | - |
| Bradycardia | 0 | 1 (0.8) | - | - | - |
| Bundle branch block left | 0 | 1 (0.8) | - | - | - |
| Cardiac failure | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Cardiac failure chronic | 0 | 1 (0.8) | - | - | - |
| Cardiovascular disorder | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Myocarditis | 0 | 1 (0.8) | - | - | - |
| Ventricular extrasystoles | 0 | 1 (0.8) | - | - | - |
| Myocardial infarction | 1 (0.8) | 0 | - | - | - |
| Palpitations | 1 (0.8) | 0 | - | - | - |
| Sinus tachycardia | 1 (0.8) | 0 | - | - | - |
| Supraventricular extrasystoles | 1 (0.8) | 0 | - | - | - |
| General Disorders and Administration Site Conditions | 20 (15.7) | 14 (11.2) | 0.71 | (0.38, 1.35) | 0.2970 |
| Oedema peripheral | 16 (12.6) | 10 (8.0) | 0.64 | (0.30, 1.35) | 0.2376 |
| Chest pain | 3 (2.4) | 4 (3.2) | 1.36 | (0.31, 5.94) | 0.6852 |
| Oedema | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Oedema due to cardiac disease | 0 | 1 (0.8) | - | - | - |
| Investigations | 3 (2.4) | 4 (3.2) | 1.36 | (0.31, 5.94) | 0.6852 |
| Blood pressure increased | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Electrocardiogram QT prolonged | 0 | 1 (0.8) | - | - | - |
| Electrocardiogram change | 0 | 1 (0.8) | - | - | - |
| Heart rate increased | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Electrocardiogram abnormal | 1 (0.8) | 0 | - | - | - |
| Heart rate decreased | 1 (0.8) | 0 | - | - | - |
| Metabolism and Nutrition Disorders | 1 (0.8) | 0 | - | - | - |
| Metabolic syndrome | 1 (0.8) | 0 | - | - | - |
| Nervous System Disorders | 5 (3.9) | 2 (1.6) | 0.41 | (0.08, 2.06) | 0.2773 |
| Hemiparesis | 0 | 1 (0.8) | - | - | - |
| Syncope | 1 (0.8) | 1 (0.8) | 1.02 | (0.06, 16.10) | 0.9899 |
| Cerebrovascular Accident | 2 (1.6) | 0 | - | - | - |

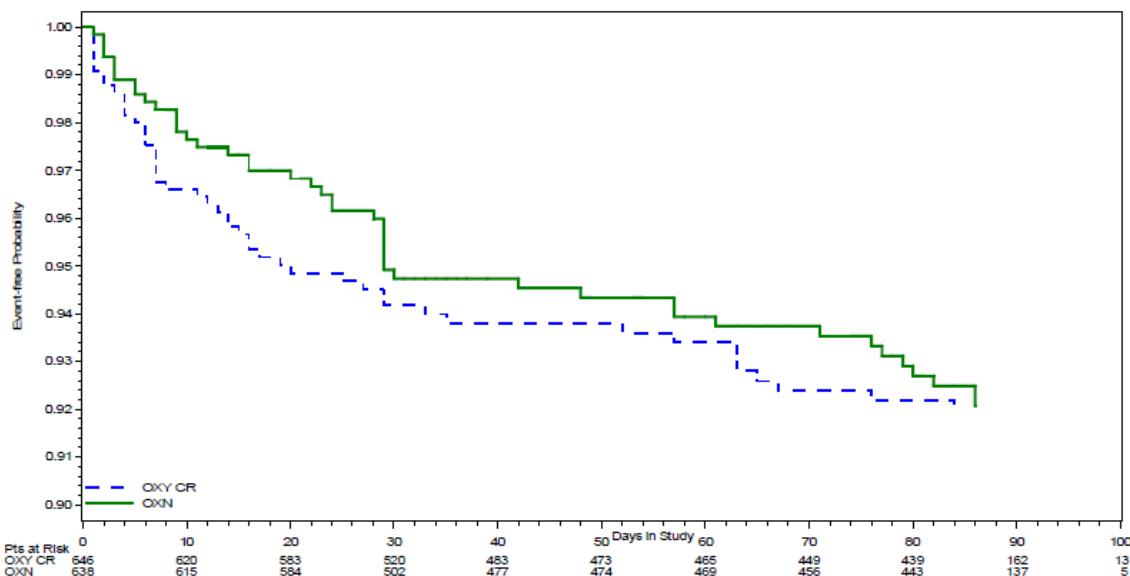
| MedDRA SOC Preferred Term | OXY CR N = 646 n (Rate) | OXN N = 638 n (Rate) | Relative Risk ^a | 95% CI | P-value |
|---|-------------------------------|----------------------------|-------------------------------|--------------|---------|
| Dysarthria | 1 (0.8) | 0 | - | - | - |
| Paraparesis | 1 (0.8) | 0 | - | - | - |
| Respiratory, Thoracic and Mediastinal Disorders | 4 (3.1) | 7 (5.6) | 1.78 | (0.53, 5.93) | 0.3471 |
| Dyspnoea | 4 (3.1) | 7 (5.6) | 1.78 | (0.53, 5.93) | 0.3471 |
| Pulmonary embolism | 1 (0.8) | 0 | - | - | - |
| Vascular Disorders | 9 (7.1) | 13 (10.4) | 1.47 | (0.65, 3.32) | 0.3529 |
| Hypertension | 9 (7.1) | 6 (4.8) | 0.68 | (0.25, 1.85) | 0.4487 |
| Hypertensive crisis | 0 | 2 (1.6) | - | - | - |
| Thrombosis | 0 | 2 (1.6) | - | - | - |
| Accelerated hypertension | 0 | 1 (0.8) | - | - | - |
| Thrombophlebitis | 0 | 1 (0.8) | - | - | - |
| Thrombophlebitis superficial | 0 | 1 (0.8) | - | - | - |
| Venous thrombosis | 0 | 1 (0.8) | - | - | - |

AE = adverse event; CI = confidence interval; CV = cardiovascular; MedDRA = Medical Dictionary for Regulatory Activities; OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; OXY CR = oxycodone hydrochloride controlled-release tablets; SOC = system organ class.

Note: incidence rates are expressed as cases per 100 subject-years of exposure time. A case is a subject with at least 1 occurrence of the event during the exposure time in treatment arm or dose. Exposure time is defined as: last dose – first dose + 7 days. Counts are based on 8 selected SMQs.

Reviewer's Comment: large confidence intervals for relative risk all crossing 1.0

- K-M analysis as shown below demonstrates no discernable clustering of events for OXN treated patients during the double-blind phase (ECVE pg 96):



OXN = oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets; OXY CR = oxycodone hydrochloride controlled-release tablets.
Studies in Group A1C: OXN2001, OXN3001, OXN3006, OXN3401, and OXN3503.

Source: Appendix 9.6 Post-text Figure 4.5.8.2.

Figure 3: Time to First Occurrence of SMQ-based Cardiovascular Adverse Event During the Double-blind Period: OXY CR-Controlled Studies of Chronic Nonmalignant and Malignant Pain (Group A1C), Randomized Safety Population

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Concomitant CV AEs and Opioid Withdrawal Symptoms

The concomitant occurrence of withdrawal symptoms as determined by the DRAC was correlated with the occurrence of CV AEs/SAEs within 28 days of opioid withdrawal symptoms, for both Group A1A and Group A1C, as summarized in Table 32 and Table 33, respectively, below:

Table 32: Cardiovascular Adverse Events Following Opioid Withdrawal Symptoms During the Double-Blind Period: Placebo-Controlled Studies of Chronic Nonmalignant Pain (Group A1A), Randomized Safety Population

| Variable | Placebo (N = 460) | OXN (N = 451) |
|---|----------------------|------------------|
| | n (%) | n (%) |
| Subjects with opioid withdrawal symptoms (n%) | 9 (2.0) | 11 (2.4) |
| Subjects with FDA cMACE | 2 (0.4) | 0 (0.0) |
| Subjects with FDA cMACE and opioid withdrawal symptoms (at any time in DB) | 0 (0.0) | 0 (0.0) |
| Subjects with FDA cMACE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based MACE | 2 (0.4) | 0 (0.0) |
| Subjects with SMQ-based MACE and opioid withdrawal symptoms (at any time in DB) | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based MACE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based CV SAE | 2 (0.4) | 4 (0.9) |
| Subjects with SMQ-based CV SAE and opioid withdrawal symptoms (at any time in DB) | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based CV SAE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based CV AE | 18 (3.9) | 20 (4.4) |
| Subjects with SMQ-based CV AE and opioid withdrawal symptoms (at any time in DB) | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based CV AE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |

Table 33: Cardiovascular Adverse Events Following Opioid Withdrawal During the Double-Blind Period: OXY CR-Controlled Studies of Chronic Nonmalignant and Malignant Pain (Group A1C), Randomized Safety Population

| Variable | OXY CR (N = 646) | OXN (N = 638) |
|---|---------------------|------------------|
| | n (%) | n (%) |
| Subjects with opioid withdrawal symptoms (n%) | 10 (1.5) | 17 (2.7) |
| Subjects with FDA cMACE | 3 (0.5) | 1 (0.2) |
| Subjects with FDA cMACE and opioid withdrawal symptoms (at any time in DB) | 1 (0.2) | 0 (0.0) |
| Subjects with FDA cMACE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based MACE | 5 (0.8) | 2 (0.3) |
| Subjects with SMQ-based MACE and opioid withdrawal symptoms (at any time in DB) | 1 (0.2) | 0 (0.0) |
| Subjects with SMQ-based MACE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 0 (0.0) |
| Subjects with SMQ-based CV SAE | 8 (1.2) | 9 (1.4) |
| Subjects with SMQ-based CV SAE and opioid withdrawal symptoms (at any time in DB) | 1 (0.2) | 2 (0.3) |
| Subjects with SMQ-based CV SAE within 28 days after opioid withdrawal symptoms | 0 (0.0) | 2 (0.3) |
| Subjects with SMQ-based CV AE | 48 (7.4) | 44 (6.9) |
| Subjects with SMQ-based CV AE and opioid withdrawal symptoms (at any time in DB) | 2 (0.3) | 3 (0.5) |
| Subjects with SMQ-based CV AE within 28 days after opioid withdrawal symptoms | 1 (0.2) | 3 (0.5) |

According to the DRAC's assessment, co-occurrence of withdrawal symptoms and CV symptoms did not occur for Group A1A, and occurred with a low frequency in Group A1C.

In Group A1C, no MACE events occurred coordinately with withdrawal symptoms in OXN-treated patients. While the of CV AEs and SAEs occurring within 28 days of withdrawal symptoms in Group A1C was numerically higher in OXN treated patients as compared to OXY CR patients (by one or two subjects, depending on the category), the numbers of these events were exceptionally small. That being said, the following two subjects' courses would be typical of scenarios that would be concern for naloxone-induced physiologic stress in an at-risk patient (from ECVE page 111):

Subject OXN3503-1704A-0170401, an 84-year-old female subject treated with OXY CR during the open-label titration period and OXN during the double-blind period experienced an SAE of drug withdrawal syndrome on [REDACTED]^{(b) (6)}, Day [REDACTED]^{(b) (6)} of the double-blind period. On the same day, the subject experienced an SAE of hypertensive crisis (blood pressure: 200/100 mm Hg; reference: 90 - 140 /40 - 90 mm Hg) and AEs of anxiety, sweating, and abdominal pain. The SAE of drug withdrawal syndrome was severe in severity and the SAE of hypertensive crisis was moderate in severity and study drug was stopped permanently as a result of both SAEs on 04-Dec-2009. Ongoing CV conditions included hypertension. The SAEs of drug withdrawal syndrome and hypertensive crisis were considered probably related to study drug.

Subject OXN3001-0962A-0096217, a 76-year-old female subject treated with OXN, experienced an SAE of drug withdrawal syndrome on 06-Oct-2006, Day 3 of the double-blind treatment period. On [REDACTED]^{(b) (6)} (Day [REDACTED]^{(b) (6)} of the double-blind period), she experienced an SAE of ECG change. The SAE of ECG change was moderate in severity and study drug was stopped permanently on [REDACTED]^{(b) (6)}. The investigator reported that the subject's T-wave was different from the previous ECG. The subject showed no other signs of cardiac pathology and cardiac enzymes were not increased; subsequently the ECG abnormality was classified as a disturbance of repolarization. The subject also experienced an AE of social avoidant behavior on 05-Oct-2006, AEs of hyperhidrosis, hot flush, chills, tremor, myalgia, nausea, diarrhea, and asthenia on 05-Oct-2006 and 06-Oct-2006, and AEs of weight decreased and blood phosphorus decreased on 09-Oct-2006. Related CV medical history included hypertension. The SAE of ECG change was considered probably related to study drug.

Though the numbers of subjects in which a CV AE/SAE occurred within 28 days of withdrawal symptoms was small, the hazard ratio for the time to first CV SAE was 14 times higher in patients with opioid withdrawal symptoms within 28 days ($p=0.0006$), and 5 times higher for the time to first non-serious CV AE ($p=0.0014$), regardless of treatment, per the following table (ECVE pg 5717):

Table 4.7.2.2
Cox Regression Model Analysis for Time to First Cardiovascular Adverse Event During Double Blind
Population: Randomized Safety – OXY Controlled Studies in Subjects with Non-malignant and Malignant Chronic Pain (Group A1C)

| Event of Interest | Parameter | Hazard Ratio | 95% CI | p-value |
|--|---|--------------|---------------|---------|
| Time to first FDA custom MACE | Treatment (OXN vs OXY CR) | 0.34 | (0.04, 3.29) | 0.3526 |
| | Opioid Withdrawal Symptoms within 28 days (yes vs no) | -- | -- | -- |
| Time to first SMQ-based MACE | Treatment (OXN vs OXY CR) | 0.41 | (0.08, 2.14) | 0.2926 |
| | Opioid Withdrawal Symptoms within 28 days (yes vs no) | -- | -- | -- |
| | Gender (M vs F) | 4.05 | (0.79, 20.90) | 0.0943 |
| Time to first SMQ-based Cardiovascular SAE | Treatment (OXN vs OXY CR) | 1.09 | (0.42, 2.85) | 0.8641 |
| | Opioid Withdrawal Symptoms within 28 days (yes vs no) | 14.14 | (3.11, 64.22) | 0.0006 |
| | Age (years) | 1.04 | (1.00, 1.09) | 0.0663 |
| Time to first SMQ-based Cardiovascular AE | Treatment (OXN vs OXY CR) | 0.91 | (0.61, 1.38) | 0.6665 |
| | Opioid Withdrawal Symptoms within 28 days (yes vs no) | 5.23 | (1.90, 14.42) | 0.0014 |
| | Age (years) | 1.02 | (1.00, 1.04) | 0.0210 |

Hazard ratios, 95% CI and p-values are found using a Cox proportional hazards model with treatment as a covariate and opioid withdrawal symptoms within 28 days before the event as a time-dependent covariate. Treatment*Opioid Withdrawal Symptoms (within 28 days) interaction is included if significant at the 10% level. Age, gender, race and number of CV risk factors were also included in the model if they were significant at the 10% level. Treatment*opioid symptoms interaction and demographic factors are only shown in the table if they had <10% significance level and were included in the final model.

--: not reported if no events within one treatment group or no events within 28 days after opioid withdrawal symptoms.

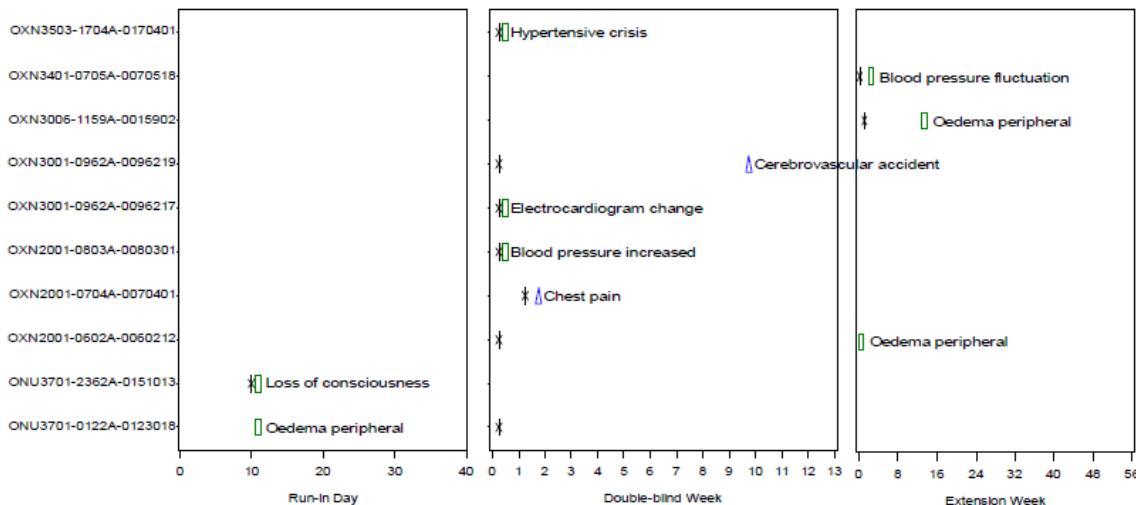
AE=adverse event, CI=confidence interval, CV=cardiovascular, SAE=serious adverse event. Group A1C: [OXN2001](#), [OXN3001](#), [OXN3006](#), [OXN3401](#) and [OXN3503](#).

About these results, the sponsor states the following:

The high hazard ratio was due to 2 subjects (OXN3503-1704A-0170401 and OXN3001-0962A-0096217... (*the patient above with the hypertensive crisis and the patient with T-wave changes*). Since the proportion of censored observations was high (> 95%), the wide CI reflects more uncertainty.

Reviewer's comment: I assume that the sponsor's comment about censoring observations is related to the fact that patients who withdrew due to an AE were censored at the time of withdrawal. Patients in study 3701 were encouraged to stay in the study after premature discontinuation according to the study stat plan, but it is unclear how adverse events were collected for patients that did in fact stay in the study.

The sponsor points out that, “Although some events were clinically important, (e.g., hypertensive crisis), many of these CV AEs were minor, (e.g., edema peripheral).” (ECVE pg 113, data not shown). However, review of the narratives and descriptions from other patients having withdrawal symptoms and CV AEs demonstrates what appear to be asymptomatic blood pressure elevations, syncope, and chest pain of unclear etiology, as well as a CVA (ECVE pg 113-115). The three occurrences of edema which the sponsor specifically points to as being “minor” were also events for which there was relatively poor temporal correlation between the withdrawal symptoms and the CV AE, as shown in the figure below (ECVE pg 115):



Note: Period day/week = relative to the first dosing day in the corresponding study period. The first dosing day is day 1.

Note: red = placebo (diamond); blue = OXY (triangle); green = OXN (square); black = opioid withdrawal symptoms (star).

Studies in Group C: studies in Groups A1A and A1C and studies ONU1001, ONU1002, ONU1009, OXN1003, OXN1004, OXN1005, OXN1008, OXN1009, OXN1011, OXN1013, OXN1016, OXN1018, OXN1403, OXN1505, OXN1506, ONU1003, ONU1004, ONU1007, ONU1008, OXN1006, OXN1007, OXN1017, and OXN4502.

Source: Appendix 9.6 Post-text Figure 4.7.3.4.

Figure 4: Timeline of SMQ-based Cardiovascular Adverse Events and Opioid Withdrawal Symptoms for Subjects Who Reported Both in Any Study Period: All Studies (Group C), Safety Population

Vital Signs

Vital sign shifts were not reanalyzed according to the ECVE re-integration. Therefore, the heart rate and blood pressure effects of OXN were assessed from the original ISS integration, Group A1, which included all controlled and open label studies of patients with nonmalignant pain (excluded studies 2001 and 2001 of malignant pain).

The sponsor evaluated mean changes in vital signs for the population as well as categorical shifts to “clinical notable” ranges. These “notable” ranges were somewhat wide and crude, but for the purposes of these studies, likely identify the more worrisome categorical shifts, as defined below (ISS page 469):

Appendix 17.3 Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

| Vital Sign Variable | Value ¹ | Change From Baseline ¹ |
|--------------------------|--|--|
| Systolic blood pressure | ≥ 180 mm Hg ≤ 90 mm Hg | Increase of ≥ 20 mm Hg Decrease of ≥ 20 mm Hg |
| Diastolic blood pressure | ≥ 105 mm Hg ≤ 50 mm Hg | Increase of ≥ 15 mm Hg Decrease of ≥ 15 mm Hg |
| Heart rate | ≥ 120 bpm ≤ 50 bpm | Increase of ≥ 15 bpm Decrease of ≥ 15 bpm |
| Respiratory rate | < 12 breaths per minute > 20 breaths per minute | NA NA |
| Temperature | NA | NA |
| Weight | NA | Increase > 5% Decrease > 5% |

bpm = beats per minute; mm Hg = millimeters of mercury; NA = not applicable.

¹ To qualify as having a clinically notable vital sign abnormality, a subject had to meet at least one of the criteria, ie, the value and/or the change from baseline.

According to these definitions of categorical shifts, categorical shifts of HR, SBP, and DBP were similar across the treatment groups, with the exceptions of somewhat higher incidences of respiratory rate excursions in all narcotic exposed groups as compared to placebo, as seen in ISS table 85 below:

Table 85: Incidence of Clinically Notable Vital Sign Outliers During Double-blind Treatment in Subjects With Chronic Nonmalignant Pain (Group A1)

| Parameter Outlier ¹ | Placebo | | OXY CR | | Codeine/ Paracetamol | | OXN | |
|---|---------|----------|--------|-----------|-------------------------|----------|-----|-----------|
| | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Pulse rate, bpm | | | | | | | | |
| Abnormally low or high | 441 | 9 (2.0) | 533 | 9 (1.7) | 115 | 4 (3.5) | 926 | 18 (1.9) |
| Abnormally low | 441 | 7 (1.6) | 533 | 9 (1.7) | 115 | 4 (3.5) | 926 | 16 (1.7) |
| Abnormally high | 441 | 2 (0.5) | 533 | 0 (0.0) | 115 | 0 (0.0) | 926 | 2 (0.2) |
| Systolic blood pressure, mm Hg | | | | | | | | |
| Abnormally low or high | 441 | 9 (2.0) | 523 | 5 (1.0) | 115 | 4 (3.5) | 922 | 10 (1.1) |
| Abnormally low | 441 | 8 (1.8) | 523 | 3 (0.6) | 115 | 1 (0.9) | 922 | 6 (0.7) |
| Abnormally high | 441 | 1 (0.2) | 523 | 2 (0.4) | 115 | 3 (2.6) | 922 | 4 (0.4) |
| Diastolic blood pressure, mm Hg | | | | | | | | |
| Abnormally low or high | 441 | 8 (1.8) | 523 | 2 (0.4) | 115 | 2 (1.7) | 922 | 9 (1.0) |
| Abnormally low | 441 | 2 (0.5) | 523 | 2 (0.4) | 115 | 1 (0.9) | 922 | 3 (0.3) |
| Abnormally high | 441 | 6 (1.4) | 523 | 0 (0.0) | 115 | 1 (0.9) | 922 | 6 (0.7) |
| Respiratory rate, breaths per minute | | | | | | | | |
| Abnormally low or high | 297 | 19 (6.4) | 135 | 29 (21.5) | 115 | 11 (9.6) | 537 | 73 (13.6) |
| Abnormally low | 297 | 6 (2.0) | 135 | 5 (3.7) | 115 | 5 (4.3) | 537 | 19 (3.5) |
| Abnormally high | 297 | 14 (4.7) | 135 | 24 (17.8) | 115 | 6 (5.2) | 537 | 54 (10.1) |
| Weight, kg | | | | | | | | |
| Abnormal decrease from prerandomization | 408 | 20 (4.9) | 517 | 63 (12.2) | 115 | 4 (3.5) | 879 | 85 (9.7) |
| Abnormal increase from prerandomization | 408 | 26 (6.4) | 517 | 25 (4.8) | 115 | 4 (3.5) | 879 | 35 (4.0) |

bpm = beats per minute; kg = kilogram; mmHg = millimeters of mercury; N = number of subjects with measurement; n = number of subjects with at least one outlier assessment during treatment period;

OXN = oxycodone/naloxone controlled-release tablets; OXY CR = oxycodone controlled-release tablets.

Note: The criteria for identifying clinically notable vital signs abnormalities are provided in [ISS appendix 17.3](#).

Note: The clinically notable outliers are defined in the SAP ([ISS appendix 17.1](#)).

Percentages are based on N as the denominator.

Studies in group A1: [ONU3701](#), [OXN3001](#), [OXN3006](#), [OXN3401](#), [OXN3503](#), and [OXN4502](#).

¹ At any week.

Source: [ISS Appendix 17.4 Post-text Table 6.2.2](#)

The sponsor claims no substantial shifts in mean HR/SBP/DBP as determined by comparison of percentage changes of the difference between mean screening and mean follow-up values, as follows:

- Mean changes in vital signs from screening to the end of open-label titration were small across all treatment groups ($\pm 2.4\%$) and not clinically relevant for subjects in group A1 treated with OXN, OXY CR, and OXY IR.
- Across all treatment groups, mean changes from pre-randomization to the end of the double-blind period for pulse rate, SBP, DBP, respiratory rate, temperature, and body weight were small ($\pm 2.2\%$) and not clinically relevant. Overall mean changes in vital signs at the end of double-blind treatment with OXN were similar to OXY CR and placebo for all of the study groups.

Reviewer's Comment: This analysis somewhat obscures what is happening to the patients at most risk for vital sign shifts – those patients who have been previously treated with medications (I assume for hypertension, as opposed to pain – not clear from the ISS). Accordingly, the raw data tables were extracted from the appendices of the ISS

to examine this group. There were no important HR changes noted. However, blood pressure elevations were evident in patients previously treated for this condition, both for the SBP and the DBP, as shown below respectively for the up-titration phase of all non-malignant pain trials (ISS pg 14988-14989):

Table 6.1.1
Summary of Changes in Vital Signs from Screening to End of Open-label Titration by Treatment
Population: Safety – Studies in Subjects with Non-malignant Chronic Pain (Group A1)

| Parameter/ Period/ Statistic | OXY CR (N=1122) | OXY IR (N=586) | Previous Prescribed Medication (N=297) | OXN (N=1095) |
|------------------------------------|--------------------|-------------------|--|-----------------|
| Systolic Blood Pressure (mmHg) | | | | |
| Screening | | | | |
| n | 1122 | 584 | 297 | 1095 |
| Mean (SD) | 132.5 (16.44) | 133.0 (16.26) | 138.8 (15.81) | 125.9 (14.49) |
| Median | 130.0 | 130.0 | 140.0 | 125.0 |
| Min, Max | 90, 207 | 90, 200 | 100, 187 | 80, 197 |
| End of Open-label Titration | | | | |
| n | 432 | 560 | 25 | 963 |
| Mean (SD) | 132.7 (15.21) | 131.0 (15.77) | 148.4 (12.10) | 125.1 (14.44) |
| Median | 132.0 | 130.0 | 144.0 | 125.0 |
| Min, Max | 90, 203 | 90, 187 | 123, 174 | 80, 180 |
| Change from Screening | | | | |
| n | 432 | 558 | 25 | 963 |
| Mean (Std. Error) | -0.3 (0.65) | -1.7 (0.61) | -1.0 (3.64) | -0.8 (0.43) |
| Percentage change | -0.2 | -1.3 | -0.7 | -0.6 |
| Median | 0.0 | 0.0 | -2.0 | 0.0 |
| Min, Max | -50, 40 | -55, 47 | -45, 28 | -55, 41 |
| 95% CI | (-1.6, 1.0) | (-2.9, -0.5) | (-8.5, 6.5) | (-1.6, 0.1) |

Table 6.1.1
Summary of Changes in Vital Signs from Screening to End of Open-label Titration by Treatment
Population: Safety – Studies in Subjects with Non-malignant Chronic Pain (Group A1)

| Parameter/ Period/ Statistic | OXY CR (N=1122) | OXY IR (N=586) | Previous Prescribed Medication (N=297) | OXN (N=1095) |
|------------------------------------|--------------------|-------------------|--|-----------------|
| Diastolic Blood Pressure (mmHg) | | | | |
| Screening | | | | |
| n | 1122 | 584 | 297 | 1095 |
| Mean (SD) | 78.5 (9.46) | 80.5 (9.01) | 79.5 (9.15) | 78.3 (9.33) |
| Median | 80.0 | 80.0 | 80.0 | 79.0 |
| Min, Max | 50, 131 | 49, 115 | 40, 108 | 41, 120 |
| End of Open-label Titration | | | | |
| n | 432 | 560 | 25 | 963 |
| Mean (SD) | 78.5 (9.51) | 79.8 (9.15) | 83.5 (8.41) | 77.3 (9.65) |
| Median | 80.0 | 80.0 | 84.0 | 78.0 |
| Min, Max | 49, 137 | 45, 133 | 67, 101 | 43, 114 |
| Change from Screening | | | | |
| n | 432 | 558 | 25 | 963 |
| Mean (Std. Error) | -0.6 (0.43) | -0.5 (0.37) | -0.2 (2.13) | -0.9 (0.29) |
| Percentage change | -0.7 | -0.6 | -0.2 | -1.2 |
| Median | 0.0 | 0.0 | 1.0 | -1.0 |
| Min, Max | -30, 33 | -30, 34 | -20, 17 | -30, 36 |
| 95% CI | (-1.4, 0.3) | (-1.2, 0.2) | (-4.6, 4.2) | (-1.5, -0.4) |

Unfortunately, the sponsor did not include a breakout of previously treated patients for the double-blind/controlled phase of the trials.

Electrocardiographic findings

TQT – not done

In the pivotal study ONU3701, ECGs were reviewed and assessed by a central evaluator, and all abnormal findings were classified by the following prespecified main categories:

- Arrhythmia findings
- Conduction findings
- Morphology findings
- Myocardial infarction findings
- Rhythm findings
- ST segment findings
- T wave findings
- U wave findings
- Overall interpretation.

For other studies, the ECGs were assessed by the investigator, and the clinically abnormal findings were recorded but not mapped to the same prespecified categories as used by the central ECG vendor.

Incidence shift tables for all clinically relevant abnormal assessments were analyzed for ISS Group A1 (double-blind exposure) and for overall OXN exposure. Because of different methodologies as described above, study ONU3701 was excluded from this analysis.

Each ECG was classified as to whether a category finding was present or absent in the readings at baseline and during the study. A subject was counted in the shift table in 1 of the 4 combinations for each subcategory finding:

- normal at screening / normal during treatment period
- normal at screening / abnormal during treatment period
- abnormal at screening / normal during treatment period
- abnormal at screening / abnormal during treatment period

This somewhat coarse assessment yielded similar frequencies of baseline normal ECGs shifting to follow-up abnormal tracings during the double-blind phase of the studies, though the incidence of this was numerically higher for OXN, as seen below (ISS table 90):

Table 90: Shift Summary of Clinically Significant Electrocardiogram (ECG) Abnormalities During Double-blind Treatment in Subjects With Chronic Nonmalignant Pain (Group A1: Randomized Safety Population)

| Parameter Period/Outlier | Placebo n (%) | OXY CR n (%) | Codeine/Paracetamol n (%) | OXN n (%) |
|------------------------------|---------------|--------------|---------------------------|------------|
| Baseline normal, N | 127 | 505 | 109 | 596 |
| Normal during double-blind | 126 (99.2) | 500 (99.0) | 108 (99.1) | 585 (98.2) |
| Abnormal during double-blind | 1 (0.8) | 5 (1.0) | 1 (0.9) | 11 (1.8) |
| Baseline abnormal, N | 12 | 16 | 1 | 26 |
| Normal during double-blind | 9 (75.0) | 12 (75.0) | 1 (100.0) | 17 (65.4) |
| Abnormal during double-blind | 3 (25.0) | 4 (25.0) | 0 (0.0) | 9 (34.6) |

A more detailed interval analysis from pivotal study 3701 demonstrated no important changes from baseline in HR, QT, QTcB, or QTcF comparing OXN to placebo, either during the up-titration phase or the double blind phase, per table 89 and table 88 below, respectively:

Table 89: Mean Change in QT and QTc From Screening to the End of the Open-label Titration Period (Study ONU3701 Safety Population)

| ECG Parameter (Unit) | OXN (N=947) Mean (SD) Change |
|----------------------|------------------------------------|
| QT (msec) | -2.9 (21.59) |
| QTcB (msec) | 1.6 (14.50) |
| QTcF (msec) | -0.0 (12.26) |

Table 88: Mean Change in Heart Rate, QT, and QTc From Screening to the End of the Double-blind Period (Study ONU3701 Randomized Safety Population)

| ECG Parameter (Unit) | Placebo (N=302) Mean (SD) Change / n | OXN (N=298) Mean (SD) Change / n |
|----------------------|--|--|
| Heart Rate (bpm) | 4.7 (11.15) / 180 | 0.4 (9.65) / 216 |
| QT (msec) | -10.3 (25.27) / 180 | -0.2 (21.86) / 216 |
| QTcB (msec) | 3.1 (16.32) / 180 | 0.8 (16.57) / 216 |
| QTcF (msec) | -1.6 (13.70) / 180 | 0.4 (13.56) / 216 |

Assessment

This was a challenging analysis for the sponsor that encompassed an ISS integration of 33 studies (counting open label studies separately), and then a complete E CVE (Evaluation of Cardiovascular Events) reintegration in order to attempt to get an interpretable integrated assessment of cardiac safety for OXN. We recognize the herculean effort involved, because of the some of the more important, fundamental limitations of the datasets as follow:

- Distinct populations – with the A1C population being older, including malignant pain, and other non-back pain conditions
- Distinct run-in protocols – with placebo controlled trials (Group A1A) including an OXN run-in arm for which there was a staggering 45.1% premature discontinuation rate. 95 of the 494 patients who dropped out prematurely during the run-in (19%) dropped out due to adverse events. It is unclear how many of these patients dropped out before having a follow up ECG (QTc analyses were only performed on study 3701 patients who had one post-baseline ECG). Extracting these 494 patients during the run-in essentially “sanitized” the results of the Group A1A double-blind safety data because only patients tolerant to OXN during the run-in were randomized. Of note, from the Group A1A run-in, 3 subjects (0.5%) in the OXY IR group and 20 subjects (1.8%) in the OXN group experienced at least 1 SMQ-based CV AE.
- The stat plan states that only in trial 3701 were patients who prematurely discontinued study drug encouraged to stay in the trial for follow up until the end of the trial. All other patients were censored following premature withdrawal. Indeed, the sponsor states the following during their analysis of concomitant withdrawal and CV adverse events: *“Since the proportion of censored observations was high (> 95%), the wide CI reflects more uncertainty.”*
- Multiple small studies with different dosing algorithms, run-ins, and follow-up schedules have been integrated. None were sized or powered to assess CV outcomes, and ascertainment of CV events was undoubtedly sub-optimal. Evidence for this ascertainment limitation includes but is not limited to the retrospective reclassification of premature withdrawal reasons by the Discontinuation Reason Adjudication Committee (DRAC), the relatively small number of CV events that were recorded, and the fact that assessment of CV safety was the objective of none of these trials.
- Given the relative high baseline CV risk of the trial populations, especially the Group A1C population, CV events could reasonably have been expected to occur. The small number of CV events that were recorded was undoubtedly effected by the short duration of the trials themselves, the very large dropout rates in these trials (run-in and double-blind phases), the large percentage of censored observations (and so I assume censored observation days), as well as the challenges noted for ascertainment even before censoring.

It is also noted that in addition to the structural limitations of the data, there seems to be a basic misconception by the sponsor regarding the patients in which CV adverse outcomes

occurred. Specifically, with respect to the MACE analysis, the sponsor states that: “Overall, the small number of cases involving an SMQ-based cardiovascular AE, SMQ-based cardiovascular SAE, major adverse cardiac events (MACE) SMQ, or FDA custom MACE SMQ event for OXN primarily involved patients with pre-existing disease and/or risk factors or contained multiple confounding factors.” It should be understood by those assessing cardiac safety the pre-existing CV disease and/or risk factors for CV disease are not confounders for the occurrence of CV events. Indeed, CV safety studies in high risk patients with known disease or risks for CV disease involve higher baseline event rates from which to interpret CV outcomes on experimental therapy.

With these limitations in mind, DCaRP's responses to your consult questions are as follows:

1. Assessment of whether there appears to be a signal for cardiac adverse events associated with the use of OXN (including the type and extent of the signal if present), the following are relevant:

MACE events were more frequent in the comparator arms as compared to the OXN treatment arms of both pooled Group A1A (placebo controlled trials) and Group A1C (OXY CR-controlled trials). Exposure-corrected non-MACE cardiovascular adverse event rates were similar between OXN and comparator-treated patients. (See table 17, page 16 of this review). These observations are limited by the very high percentages of antecedent dropouts in the run-in periods, high censoring rate of premature withdrawals, sub-optimal CV event ascertainment in all trials, and the brief duration of follow-up in these short studies.

While no TQT study was performed with the OXN combination, ECG interval analysis from pivotal trial 3701 does not demonstrate a clinically meaningful prolongation of the QT, QTcB, or QTcF.

While there were numerically more occurrences of atrial fibrillation in OXN-treated patients (by one or two cases, depending on the analysis), the numbers are too small to draw any conclusions.

Thus, no signals for excess MACE, non-MACE CV AEs, or repolarization/conduction system toxicity with OXN are identified from these studies.

2. An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

OXN appears to be associated with elevations of both SBP and DBP in patients previously treated (presumably for hypertension, see table page 33 of this review), and hypertensive AEs occurred. Of the nine patients experiencing an SMQ-based CV AE and opioid withdrawal symptoms in the overall population (Group C) during any study period, three of the nine experienced blood pressure elevations in close

proximity to OXN dosing, one of which was a hypertensive crisis. There were no concomitant AEs involving BP elevation with withdrawal symptoms in any comparator group. Though the numbers of subjects in which a CV AE/SAE occurred within 28 days of withdrawal symptoms was small, the hazard ratio for the time to first CV SAE was 14 times higher in patients with opioid withdrawal symptoms within 28 days ($p=0.0006$), and 5 times higher for the time to first non-serious CV AE in patients with opioid withdrawal symptoms within 28 days ($p=0.0014$), regardless of treatment (see page 28 of this review).

From a mechanistic point of view, the above observations should be interpreted in the context of an understanding of the determinants of myocardial oxygen demand. Opioid withdrawal induces physiologic stress in some patients. This physiologic stress will increase myocardial work and myocardial oxygen demand. Any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease (these are not “confounders”). These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important. In the overall target populations of all of these therapies, however, this risk is small.

Other DCaRP Comments/Recommendations

It is unclear what if any relevance that the side effect profile of IV naloxone has to the clinical safety profile of this oral oxycodone + naloxone combination. However, given the lack of clinical experience with OXN in post-operative patients, it would be reasonable to at least reference the warning about these patients from the IV naloxone label (i.e., that several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients treated with IV naloxone).

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/s/

PRESTON M DUNNMON
03/20/2014

THOMAS A MARCINIAK
03/20/2014

NORMAN L STOCKBRIDGE
03/20/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205777

Applicant: Purdue

Stamp Date: September 23, 2013
(Electronic submission)

Drug Name: Targiniq ER **NDA Type:** Priority
(Oxycodone/Naloxone) Abuse Deterrent 505(b)(2)

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---------------------------------------|--|------------|-----------|-----------|---|
| FORMAT/ORGANIZATION/LEGIBILITY | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | X | | | Electronic |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | X | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | X | | | |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)? | X | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | X | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | X | | | |
| LABELING | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | X | | | |
| SUMMARIES | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (<i>i.e.</i> , Module 2 summaries)? | X | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | X | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | X | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | X | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? 505(b)(2) Reference: Narcan (naloxone NDA 016636) Cross Reference: OxyContin (NDA 020553) and Reformulated OxyContin (NDA 022272) | X | | | |
| DOSE | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)? Study Number:OXN2401 Study Title: Optimization of Naloxone-Oxycodone | X | | | Dose proportionality study OXN1506 and dose finding study OXN2401 |

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-----------------|---|------------|-----------|-----------|--|
| | Ratio in Pain Patients Sample Size: 202 Arms: Naloxone 10/ 20/40 or Placebo Location in submission: Clinical Studies | | | | |
| EFFICACY | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 ONU3701 Indication: Management of (b) (4) pain (b) (4) around-the-clock (b) (4) | X | | | 1 AWC trial as per Agency advice |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | Average pain over the last 24 hours score at Week 12 on 11-point NRS |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | | | X | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? Of the 2396 subjects with chronic nonmalignant or malignant pain, 1084 subjects (45.2%) were exposed to OXN for ≥ 3 months, 794 subjects (33.1%) were exposed to OXN for ≥ 6 months, and 621 subjects (25.9%) were exposed to OXN for ≥ 12 months across all study periods. | X | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|--------------------------|--|------------|-----------|-----------|---|
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | 1) Abuse Liability Studies 2) Opioid withdrawal assessments 3) Cardiovascular assessments |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | X | | | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | X | | | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | X | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | (See Stats filing review as needed) |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse | | | X | |

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|------------|-----------|-----------|-------------------|
| | drop-outs) as previously requested by the Division? | | | | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | Key study ONU3701 |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH M KILGORE
11/18/2013

ELLEN W FIELDS
11/18/2013