

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205777Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	July 7, 2014
<b>From</b>	Ellen Fields, MD, MPH
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	205777
<b>Applicant</b>	Purdue Pharma
<b>Date of Submission</b>	September 23, 2013
<b>PDUFA Goal Date</b>	July 23, 2014
<b>Proprietary Name / Established (USAN) names</b>	TARGINIQ ER/ oxycodone HCl and naloxone HCl extended-release tablets
<b>Dosage forms / Strength</b>	ER tablets: 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg
<b>Proposed Indication(s)</b>	the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
<b>Recommended:</b>	Approval

## Cross Discipline Team Leader Review

### 1. Introduction

Purdue Pharma (the Applicant) submitted this 505(b)(2) NDA for TARGINIC ER (oxycodone hydrochloride/naloxone hydrochloride controlled-release) Tablets for oral administration every 12 hours, in dosage strengths (oxycodone/naloxone mg) 10/5 mg, 20/10 mg, and 40/20 mg. TARGINIC ER is a fixed-dose combination drug in which oxycodone, a Schedule II opioid analgesic, and naloxone, a mu opioid antagonist intended to decrease the abuse-potential of oxycodone, are combined. The NDA references the listed drug Narcan, naloxone HCl (NDA 016636) and cross-references both the original OxyContin (NDA 20553) and reformulated OxyContin (NDA 22272), as both are the Applicant's products. TARGINIC ER was developed in accordance with 21 CFR 300.50(a), "Fixed-combination prescription drugs for humans", which states that "...Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects...". It further states that "Special cases of this general rule are where a component is added "...To minimize the potential for abuse of the principal active component."

TARGINIC ER falls within the class of drugs that are part of the Extended-Release/Long-Acting (ERLA) Opioid Risk Evaluation and Mitigation Strategy (REMS), and the proposed indication is the same as that for other ERLA products, "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

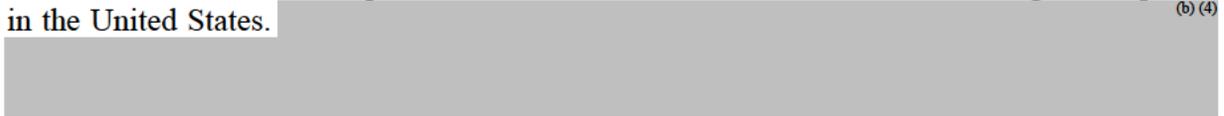
The NDA submission includes the results of one adequate and well-controlled study in patients with chronic low back pain, and a safety database of over 3,000 subjects that supports the safety of TARGINIC ER in the intended population.

The Applicant is seeking abuse-deterrent label claims for intravenous (IV) and intranasal (IN) routes of abuse conveyed by the naloxone component. They have submitted data that they believe supports the notion that the presence of naloxone will attenuate or abolish the euphoric effects of oxycodone if TARGINIC ER is crushed and inhaled intranasally, or dissolved and injected IV, due to the high bioavailability of naloxone via both of these routes of abuse.

The Applicant requested a Priority Review based on the abuse-deterrent (AD) properties of TARGINIC ER, however because OxyContin (NDA 22272) already has AD claims in the label, and the TARGINIC ER application did not include any comparative data with OxyContin in regards to AD properties, the Priority Review request was denied and the application was reviewed under a standard 10-month review cycle.

### 2. Background

TARGINIC ER was developed under IND 070851 and was called OXN during development in the United States. (b) (4)



(b) (4)

Oxycodone is a mu opioid agonist with the primary therapeutic action of analgesia. It has been marketed for over 80 years, and is the active ingredient in several marketed drug products used for the treatment of pain, as a single-entity (IR oxycodone, OxyContin) and in combination with acetaminophen and non-steroidal anti-inflammatory drugs (Percocet, Percodan). It is a Schedule II opioid under the Controlled Substance Act, which is defined as a drug that has therapeutic utility, and has a “high potential for abuse which may lead to severe psychological or physical dependence.”

Naloxone is an opioid-receptor antagonist and can exert an effect anywhere there are opioid receptors such as 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. When administered orally, the absolute bioavailability is less than 2% due to extensive first-pass metabolism. It is approved for parenteral use to reverse the effects of opioid overdose (Narcan, Evizio). It is also approved in combination with buprenorphine under the tradename Suboxone, which is administered sublingually for maintenance treatment for opioid dependence. Talwin NX (pentazocine/naloxone) is also an approved product to which naloxone was added to deter parenteral abuse.

At the EOP2 meeting in November, 2010, the Applicant discussed with the Agency the possibility of developing OXN as an abuse-deterrent formulation of extended-release oxycodone. The Applicant then chose to pursue the analgesic indication for OXN with AD claims in the US (b) (4).

As a 505(b)(2) application relying on prior findings of safety and efficacy for Narcan, and cross-referencing these findings for OxyContin, the Division agreed with the Applicant that one positive, adequate and well-controlled clinical trial would be sufficient to support efficacy. The key study is a Phase 3, randomized, double-blind, placebo-controlled, enriched, randomized-withdrawal study (ONU3701) in opioid-experienced patients with chronic low back pain, that assessed the analgesic efficacy and tolerability of TARGINIC ER compared to placebo. The Applicant also submitted data from a large safety database made up of multiple studies conducted outside the US that included more than 3,000 subjects exposed to TARGINIC ER. The ex-US studies were conducted for the EU indication (analgesia and OIC), however, they included a similar population of patients with chronic pain.

The Applicant submitted data from nine in vitro and four in vivo abuse liability studies in order to demonstrate the AD features of TARGINIC ER as they relate to the intravenous (IV)

and intranasal (IN) routes of abuse. These studies have been reviewed by the Controlled Substance Staff (CSS) and are discussed in detail later in this review. As stated earlier, reformulated OxyContin, also owned by the Applicant, is labeled as an AD formulation for the IV and IN routes of administration, due to physicochemical properties that make abuse by these routes difficult.

The Applicant's proposal for the upper dose limit of TARGINIC ER as 80/40 mg per day is discussed in this review. OxyContin is titrated to effect and tolerability, and prescribed to some patients at doses above 80 mg per day, without a maximum dosage recommendation. Also discussed is the occurrence of adverse events related to naloxone, including opioid withdrawal, in study subjects taking TARGINIC ER. Naloxone is present in the product to mitigate abuse, however adverse effects due to naloxone on patients taking TARGINIC ER as directed must be assessed.

### 3. CMC/Device

The CMC review was conducted by Eugenia Nashed, Ph.D., with secondary concurrence by Julia Pinto, Ph.D. They have not identified any issues that would preclude approval of TARGINIC ER.

There are two drug substances in TARGINIC ER, oxycodone hydrochloride and naloxone hydrochloride. The oxycodone drug substance is supported by DMF [REDACTED] (b) (4) which has an adequate status. The naloxone hydrochloride drug substance is supported by DMF [REDACTED] (b) (4) which has an adequate status, and DMF [REDACTED] (b) (4) which has an inadequate status, based on review by the Office of Generic Drugs (OGD) completed June 3, 2014. The deficiency in DMF [REDACTED] (b) (4) is regarding the modification [REDACTED] (b) (4)

[REDACTED] In her review, Dr. Nashed recommended not approving TARGINIC ER based on the issue with the [REDACTED] (b) (4) DMF. However, following additional discussion, Dr. Pinto entered a review into DARRTS on June 26, 2014 stating the following:

Under GDUFA, the (OGD) reviewer recommended the processes be split into two DMFs. Therefore, since the deficiency is not safety or quality related, and since sufficient data is provided within the NDA to support the naloxone drug substance obtained [REDACTED] (b) (4) under this DMF, NDA 205777 is recommended for approval from the CMC perspective.

Several information requests were sent to the Applicant to tighten the acceptance specifications to the ICH Q3A-recommended levels for drug substance impurities, [REDACTED] (b) (4)

[REDACTED] Dr. Nasheed wrote that while the proposed acceptance criteria may be adequate for a maximum daily dose (MDD) of TARGINIC ER 80/40 mg, it is not adequate for higher MDDs. At the time of completion of Dr. Nasheed's review, the MDD had not been confirmed by the Division. However, since then the maximum daily dose has been designated as 80/40 mg (see NonClinical and Clinical Pharmacology sections of this review), and therefore, the Applicant has provided sufficient data to support the acceptance criteria.

Dr. Nasheed describes the drug product manufacturing as follows:



The Sponsor is seeking an expiry period of 24 months for each drug product presentation. The provided stability data indicate that all batches are within the currently proposed specification limits. However, the currently proposed specifications were proposed based on MTDD of NMT (b) (4) which was not adequately assessed and justified by the Applicant. Possible future change of the MTDD may require changing of the acceptance criteria for impurities and reassessment of the data supporting the proposed expiry period. Refer to Agreements provided by the Applicant on April 30, 2014, regarding the drug product specifications and stability data, as listed on page 8 of this review (item #2 and #3).

The proposed expiry of 24 months is acceptable based on the maximum recommended dose of 80/40 mg.

The current EER recommendation from the Office of Compliance is Acceptable.

Microbiology safety controls were found adequate per review by Steven Donald, Ph.D., microbiology reviewer.

#### **4. Nonclinical Pharmacology/Toxicology**

The nonclinical review was conducted by BeLinda Hayes, Ph.D., with secondary concurrence by R. Daniel Mellon, Ph.D. They did not identify any issues that would preclude approval.

The following is taken from Dr. Hayes' review:

To support the safety of the drug product, the Applicant submitted the full standard battery of nonclinical toxicology studies for naloxone and resubmitted the oxycodone toxicology studies previously completed to support the OxyContin program. In addition, the Applicant submitted 3-month general toxicology studies evaluating the combination of oxycodone and naloxone.

The relative safety of oxycodone alone has been established in the development programs for OxyContin and via post-marketing experience. Characterization of

the toxicologic potential of naloxone at the proposed doses and duration required additional studies to support this program. Although the general toxicology studies suggested that high doses of naloxone can produce convulsions in animals, there is an adequate safety margin (>60-fold) for the proposed maximum recommended daily dose of naloxone via this drug product.

The standard ICH battery of genetic toxicology studies were conducted for oxycodone HCl and naloxone HCl. Genetic toxicology studies submitted for oxycodone HCl was previously submitted to support the NDAs for Oxycontin. Oxycodone tested negative in the in vitro bacterial reverse mutation assay for mutagenicity and the in vivo bone marrow micronucleus assay. However, oxycodone was positive in the in vitro chromosomal aberration assay for mutagenicity in the presence of metabolic activation. Likewise, naloxone tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay. However, naloxone also tested positive in the L5178Y mouse lymphoma assay.

No reproductive studies and developmental studies were conducted using the oxycodone and naloxone combination. However, reproductive toxicology studies were performed with naloxone hydrochloride (b) (4). Embryo-fetal developmental studies conducted in pregnant rats treated with 50, 200, and 800 mg/kg/day naloxone hydrochloride by oral gavage during organogenesis. No remarkable treatment-related maternal toxicity was observed at doses up to 800 mg/kg/day. The maternal NOAEL was established at 800 mg/kg/day (192-fold human systemic exposure based on a mg/m<sup>2</sup> comparison. No developmental toxicity was observed at doses up to 800 mg/kg/day; the NOAEL for developmental toxicity was established at 800 mg/kg/day (192-fold human systemic exposure based on mg/m<sup>2</sup>).

Embryo-fetal developmental studies were conducted in New Zealand White rabbits treated with 20, 100, or 400 mg/kg/day naloxone hydrochloride by oral gavage during organogenesis. Naloxone was not teratogenic under the conditions of the assay; no significant malformations (external, soft tissue, or skeletal) were noted at doses up to 400 mg/kg/day. The maternal NOAEL was established at 100 mg/kg/day based on a non-statistical decrease in implantation rate, mean number of females per litter, and number of live fetus per dams. The developmental NOAEL is established at > 400 mg/kg/day based on lack of developmental toxicity (192-times the maximum recommended daily dose of 40 mg naloxone, on a body surface area basis).

Pre- and post-natal studies were conducted in pregnant rats treated with 50, 200, and 800 mg/kg/day naloxone hydrochloride by oral gavage from organogenesis through weaning. Evidence of maternal toxicity was indicated by treatment-related mortalities at the 800 mg/kg/day level and decreased body weight gain at the 200 mg/kg/day. The maternal NOAEL was established at 50 mg/kg/day (estimated exposure approximately 192-fold on a mg/m<sup>2</sup> basis). The

developmental NOAEL was established at 200 mg/kg/day based on reduced viability index and newborns per litter from dams orally administered 800 mg/kg/day naloxone.

Collectively, although the existing oxycodone reproductive and developmental toxicology data do not suggest concern for the maximum recommended daily dose of oxycodone via this formulation, and there is an adequate safety margin for any naloxone-mediated effects, there appears to be little reproductive and developmental toxicology risk with this product. However, as there are not studies with the combination, we recommend that the drug product be given a Pregnancy Category C.

No carcinogenicity studies were conducted using the oxycodone and naloxone combination. However, carcinogenicity studies were performed with naloxone hydrochloride. Naloxone was negative in a 26-week Tg.rasH2 mouse carcinogenicity study and in a 2-year dietary rat carcinogenicity study at doses of 4, 20, or 100 mg/kg/day naloxone HCl showed no evidence of treatment-related tumors (24-times the human dose of 40 mg/day on a mg/m<sup>2</sup> basis). Carcinogenicity data on oxycodone do not exist and based on OND policy, these studies will not be required for this drug product since the exposures to oxycodone via this formulation do not result in novel exposures compared to the cross-referenced OxyContin drug product.

Adequate safety data for the excipients in the drug has been provided for the maximum recommended daily dose of up to 80 mg oxycodone and 40 mg naloxone for this drug product. The proposed drug substance and drug product specifications are acceptable for approval at this time. The drug substance impurity (b)(4) which contains a structural alert for mutagenicity, has historically been limited to not more than (NMT) (b)(4)% for existing drug product formulations largely based on the relatively low daily exposures to naloxone. However, this drug product results in greater exposure to naloxone, therefore, the Applicant was asked to reduce the level to NMT (b)(4) (b)(4). This would require a specification of NMT (b)(4)%. To date, the drug substance manufacturers are able to reach (b)(4)% for this impurity, but are not able to reduce it further at this time. Therefore, although not an approval issue, since this is as low as technically feasible, a PMR should be issued to either reduce the levels to NMT (b)(4) or to adequately qualify the impurity for safety. This would require an in vivo micronucleus assay and an in vivo comet assay testing both stomach and liver tissue.

It should be noted that this maximum recommended daily dose (MRDD) is not acceptable for single entity controlled release oxycodone drug products, which are taken at much higher levels due to the development of tolerance. This MRDD is based on the presence of the naloxone in the drug product, which is believed to limit the drug product's utility at higher doses. However, should the drug product be deemed appropriate for dosing above the MRDD of 80 mg oxycodone

hydrochloride and 40 mg naloxone hydrochloride, further safety justification for the levels of excipients, drug substance impurities, and drug product degradants will be required.

The following nonclinical post-marketing requirement (PMR) should be issued:

Conduct a combination in vivo micronucleus and comet assay for (b) (4) (b) (4). The comet assay portion of the study should include assessment of both stomach and liver tissue and include doses of the drug substance that would be obtained at the maximum recommended daily dose of the drug product and result in adequate toxicity to ensure assay validity. Alternatively, you may reduce the levels of (b) (4) to NMT (b) (4) (b) (4).

The nonclinical review team recommended labeling language for Sections 8 and 13, which was included in the label. Please refer to the nonclinical review and final label for details.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Srikanth Nallani, Ph.D., with secondary concurrence by Yun Xu, Ph.D. There were no issues identified that would preclude approval from the clinical pharmacology perspective.

As summarized by Dr. Nallani in his review:

For this 505(b)(2) NDA, Purdue has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Tradename (oxycodone and naloxone) to approved NDA products, OxyContin (oxycodone extended release NDA 022272 and its predecessor NDA 020553) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan since Narcan is not available on the market).

A total of 23 Phase 1 clinical studies and 1 Phase 2 clinical study were conducted as part of the Tradename clinical pharmacology program to support the Tradename dosage regimen proposed for US registration. These studies characterized the PK and PD properties, effect of age, sex, special populations, drug interaction potential, abuse deterrence, and GI motility effects associated with Tradename. The results of these studies support the proposed BID dosing regimen and dosage range, within which the exposures to oxycodone from Tradename are bioequivalent to those from the oxycodone CR marketed products including reformulated OxyContin and Oxygesic, the European marketed product. Eighteen of the clinical studies were reviewed. The main goal of the clinical pharmacology review is to focus on the clinical and clinical pharmacology studies with regard to impact of naloxone on clinical safety and efficacy.

### *Oxycodone Pharmacokinetics*

Purdue Pharma conducted a randomized crossover study (ONU1009) in healthy volunteers (n=27) to assess the relative bioavailability of Tradename (Oral

Oxycodone 20 mg and Naloxone 10 mg) as compared to IV naloxone 0.4 mg and oral OxyContin 20 mg. Oxycodone C<sub>max</sub> and AUC were bioequivalent between Tradename and Oxycontin. In a separate study (OXN1506) pharmacokinetics of oxycodone were observed to be dose-proportional for Tradename strengths proposed 10/5 mg, 20/10 mg and 40/20 mg. Food-effect study (OXN1003) revealed a 25% increase in C<sub>max</sub> and a 17% increase in AUC for oxycodone following administration of Tradename (40/20 mg) with high-fat meal compared to fasting. Following multiple dose administration (BID) systemic exposure of oxycodone was similar to that noted with a controlled release oxycodone (similar to OxyContin) on Day 4.

### *Naloxone Pharmacokinetics*

Observations from the relative bioavailability study ONU1009 also provide a context for the plasma naloxone levels. Parenteral (IV, IM or SC) naloxone is commonly used in the treatment of reversing opioid overdose with a dose range from 0.4 mg to 2 mg based on Narcan label. Additionally, parenteral (0.2 to 0.6 mg IM or IV) naloxone challenge test is used to screen for subjects claiming to be recreational users of opioids. Absolute bioavailability of naloxone from Tradename was <1% as measured by dose-normalized AUC. The first noted plasma concentrations of naloxone (at 30 min) following IV administration were 1.26 ± 0.37 ng/mL (Range 0.725 to 2 ng/mL).

As mentioned before, [REDACTED] (b) (4) because of low oral bioavailability plasma levels of naloxone are very low. Under normal circumstances, systemic levels of naloxone in majority of the subjects were observed to be low (<0.725 ng/mL, the lower end of the observed concentration at T= 30 min) and highly variable. Dose-proportionality in naloxone PK is **not** noted with increased doses of TARGINIC ER .

Administration of TARGINIC ER with food resulted in higher plasma levels of naloxone compared to fasted state. Four different food-effect studies were conducted where a worst case of 75% increase in plasma levels of naloxone was noted with TARGINIC ER 40/20 mg (Study OXN1003). This observed increase in plasma naloxone levels may not be clinically significant.

Of note, plasma levels of naloxone following administration of a single dose of 40/20 mg of TARGINIC ER in the fed state, are highly variable, with a range of concentrations between 0.05 ng/mL to 1.034 ng/mL.

Treatment	N	Mean (ng/mL)	SD	Median (ng/mL)	Min (ng/mL)	Max (ng/mL)
-----------	---	-----------------	----	-------------------	----------------	----------------

**Study OXN 1003 (Food Effect Study)**

<b>Targiniq 10/5 Fast</b>	27	0.025	0.024	0.016	0	0.103
<b>Targiniq 10/5 Fed</b>	26	0.051	0.046	0.032	0.016	0.205
<b>Targiniq 40/20 Fast</b>	25	0.074	0.044	0.054	0.03	0.177
<b>Targiniq 40/20 Fed</b>	26	0.14	0.19	0.085	0.05	1.034

During the NDA review cycle, the nonclinical team required that the Applicant address the safety of excipients used in the TARGINIC ER formulation, which is typically done by determining the maximum theoretical daily dose (MTDD) a patient could take and using that to compare the levels of excipients to the inactive ingredient safety database. The Applicant has proposed a maximum daily dose of TARGINIC ER of 80/40 mg administered as 40/20 mg BID. They based this on clinical experience in Study ONU3701 where this was the highest dose studied, and postmarketing experience outside the US. The Applicant was asked to provide a justification for the proposed MTDD, and data to support why patients would not take more than 80/40 mg per day.

*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 TARGINIC 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.*

The Applicant was not able to address this information request satisfactorily.

To assist in answering whether 80/40 mg is the appropriate MTDD for TARGINIC ER, Dr. Nallani performed pharmacokinetic simulations utilizing the naloxone C<sub>max</sub> as a limitation to the use of higher doses of TARGINIC ER. The relevant question here is what dose of TARGINIC ER would result in a naloxone exposure level high enough to block efficacy or trigger opioid withdrawal in a substantial number of patients when TARGINIC ER is taken as directed.

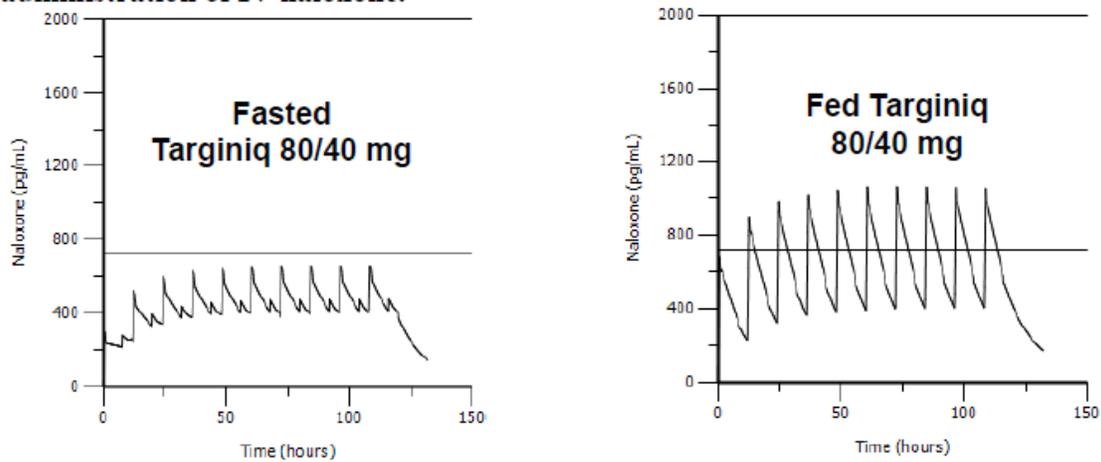
Dr. Nallani stated in his review:

IM or IV injection of naloxone 0.4 mg is commonly used in the naloxone challenge test. Plasma naloxone concentrations were noted to be 1.26 ng/mL (range 0.725 – 2 ng/mL) at 30 minutes following IV bolus administration.

In the PK simulations, Dr. Nallani used a systemic naloxone concentration of 725 pg/ml as the lowest level at which opioid withdrawal may occur, based on the data from the single 0.4 mg dose of naloxone that is used to reverse opioid overdose symptoms. He noted the following:

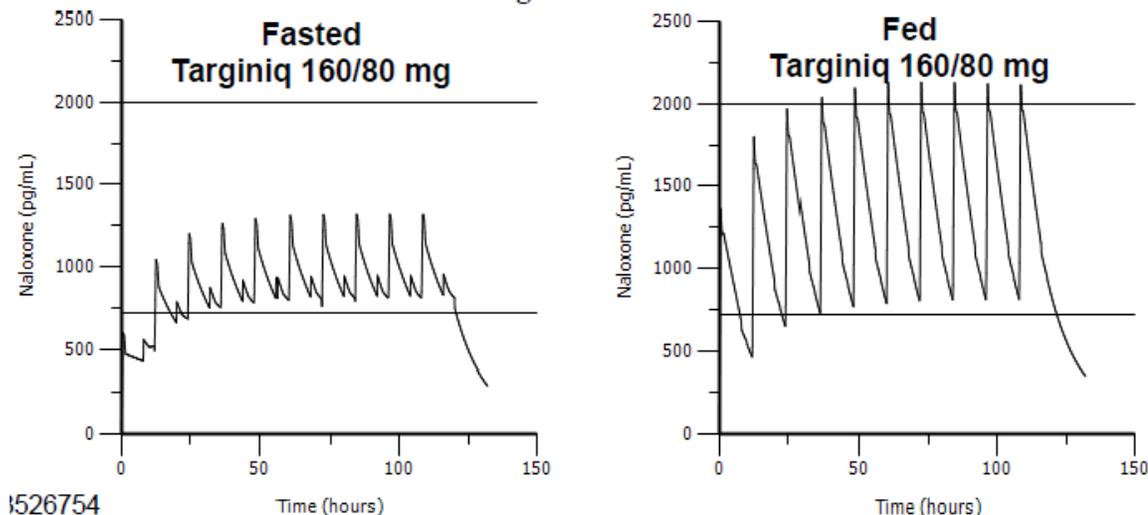
1. Simulated plasma naloxone levels for TARGINIC ER 80/40 mg BID (total daily dose 160/80 mg)

**Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 80/40 mg strength with a total daily dose of 160/80 mg (based on data from OXN1505). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.**



2. Simulated plasma naloxone levels for TARGINIC ER 160/80 mg BID (total daily dose 320/160 mg)

**Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 160/80 mg strength with a total daily dose of 320/160 mg (based on data from OXN1505 and assumed dose-proportional PK). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.**



The total daily dose of 160/80 mg results in naloxone plasma levels that are greater than 750 pg/ml for the fed state only, and for total daily dose of 320/160 mg, plasma levels are above 750 pg/ml for both fed and fasted. Referring back to the results of Study OXN1003 above, the Cmax levels for a single dose of TARGINIC ER 40/20 mg are very variable, with a mean of Cmax of 140 pg/ml in the fed state (below the 725ng/ml cutoff), and a maximum Cmax in the fed state is well above the 725 pg/ml level at 1034 pg/ml.

In Dr. Nallani's review, page 8, he states that:

“...simulated plasma naloxone levels that are more likely to produce opioid-blockade or opioid-withdrawal in dependent subjects may occur under following circumstances:

- TARGINIQ ER 160/80 mg dose administered twice daily under fasted or fed condition (total daily dose of 320/160 mg) or,
- TARGINIQ ER 80/40 mg dose administered under fed condition (high-fat meal consumption) twice daily (total daily dose of 160/80 mg under fed condition)

Based on the fact that TARGINIC ER may be administered without regard to food intake, the high intersubject variability in systemic exposure, and that the PK modeling showed that the 160/80 mg total daily dose taken with food results in a plasma level of naloxone higher than 750 pg/ml, the level at which opioid withdrawal may occur, I recommend that the maximum dose be designated as 80/40 mg (40/20 mg BID). Please refer to the nonclinical section of this review for additional information.

#### TARGINIC ER Pharmacokinetics under Conditions of Abuse and Misuse

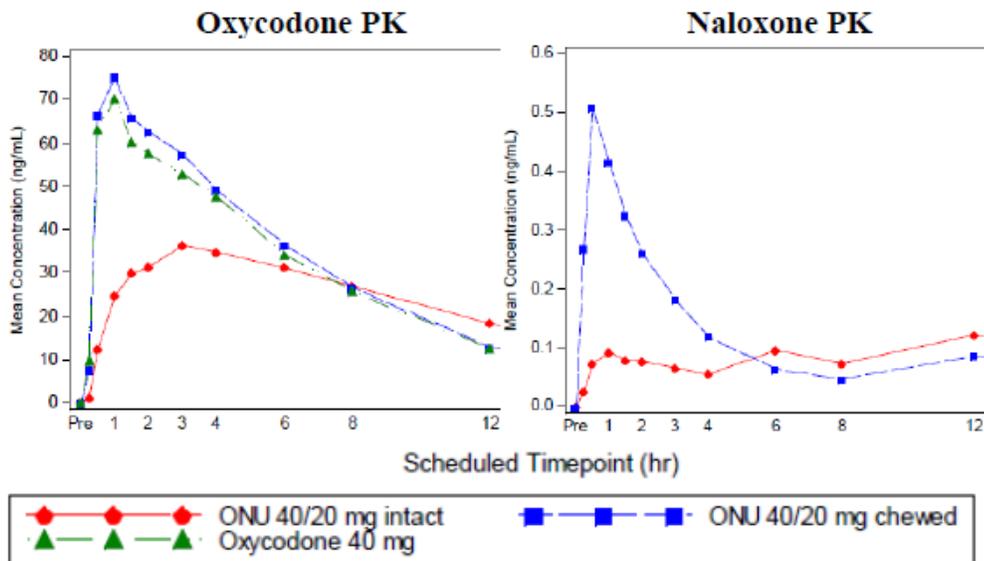
Dr. Nallani also reviewed TARGINIC ER pharmacokinetics and pharmacodynamics under conditions of abuse and misuse. The following summary from his review focuses on the

pharmacokinetic data obtained under conditions of abuse. The pharmacodynamic data is discussed later in this review as part of the Controlled Substance Staff review:

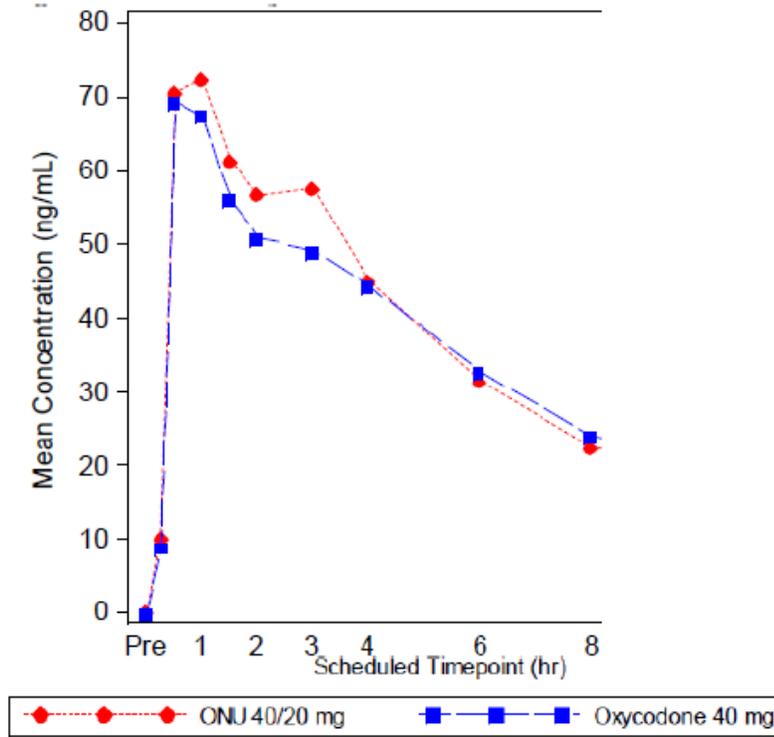
Purdue conducted study ONU1007 evaluating drug liking of Targiniq ER 40/20 mg following oral abuse and intranasal abuse in healthy non-dependent recreational opioid users. Purdue also conducted study ONU1003 where pharmacokinetics and pharmacodynamics of Targiniq ER 40/20 mg were evaluated following common methods/conditions of opioid ER product abuse in healthy non-dependent recreational users of opioids. In addition, drug liking studies were also conducted in methadone-dependent subjects where PK and PD of Targiniq ER was evaluated following oral abuse (Study ONU1004 and Study ONU1008).

Oral abuse following Chewing: Study ONU1007, ONU1003, ONU1004 and ONU1008 all demonstrated that Targiniq ER loses extended release characteristics following oral administration after chewing. Both naloxone and oxycodone pharmacokinetic parameters indicated significant increase immediately after oral administration of chewed product. However, the systemic concentrations of naloxone were not significant enough to block the drug liking effects of oxycodone in recreational drug users (like non-methadone maintained patients).

**Figure: Mean plasma oxycodone (left) and naloxone (right) profile over time following administration of intact Targiniq ER (or ONU 40/20 mg-Circles), chewed Targiniq (Squares) and oxycodone API (oxycodone profile only- Triangles) in Study ONU1007.**

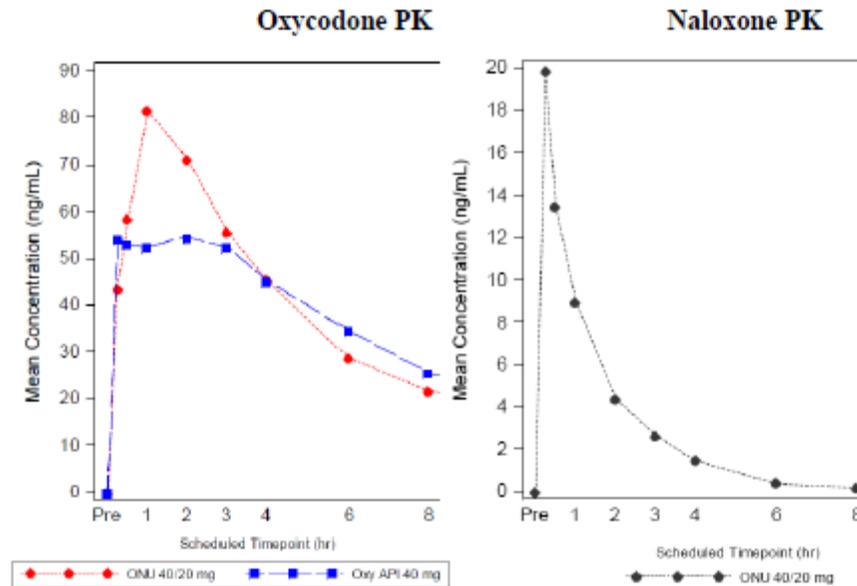


**Figure: Mean Oxycodone Plasma Concentrations over Time following oral abuse (chewing) (Group 1 – PK Population Study ONU1003) compared to oxycodone oral solution.**



Intranasal administration of crushed product: As noted with oral abuse, extended release characteristics of oxycodone and naloxone are defeated following crushing of Targiniq ER followed by intranasal administration. However, systemic absorption of both oxycodone and naloxone is noted. Peak exposure (C<sub>max</sub>) of oxycodone was higher following administration of crushed OXN compared to OXY API. Total exposure to naloxone via the IN route was much higher than that observed via the oral route (C<sub>max</sub>: 19.3 vs. 0.336 ng/mL; AUC<sub>0-t</sub>: 27.4 vs. 1.24 hr\*ng/mL).

**Figure: Plasma oxycodone (left) and naloxone (right) profile following intranasal administration (Study ONU1003) of crushed Targiniq ER (Circles) and oxycodone powder (Squares, left only).**

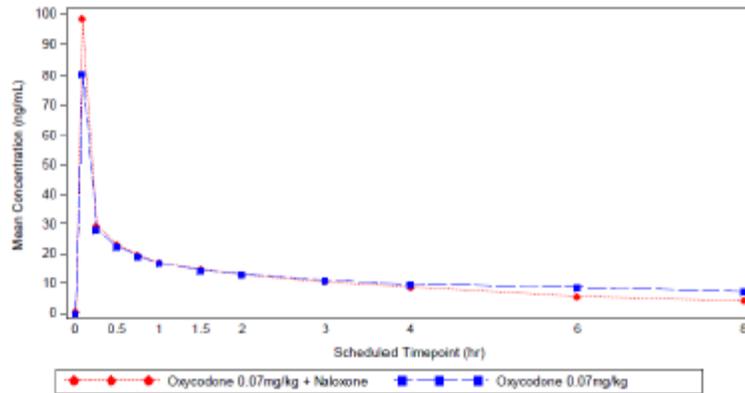


Because of the significant plasma concentrations of naloxone following intranasal administration of crushed Targiniq 40/20 mg, significant number of recreational opioid users did not experience the drug liking as compared to oxycodone powder (See Figure below).

See Dr. Nallani's review for figure mentioned above.

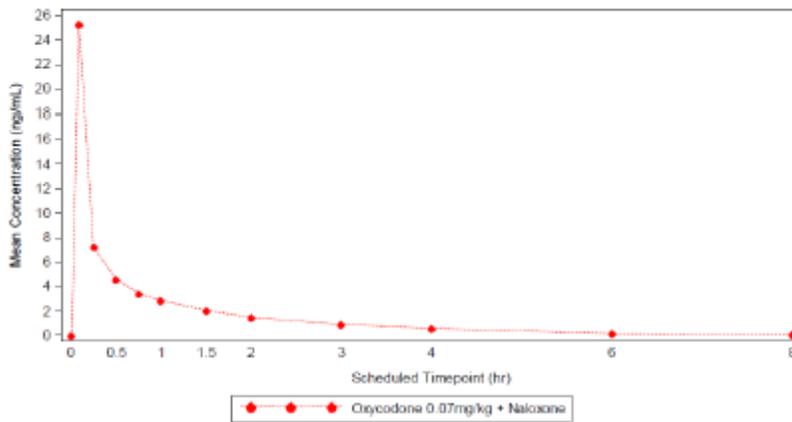
IV administration simulating parenteral abuse: Because it is unsafe to administer particulate matter intravenously, sponsor evaluated drug abuse of intravenously administered clear solution of oxycodone with and without concomitant naloxone administration. Mean plasma oxycodone concentration profiles were similar between IV doses of oxycodone with and without concomitant naloxone, as also evidenced by the almost identical AUC values of oxycodone between.

**Figure: Mean Plasma Concentrations of Oxycodone vs Time in Study ONU1003 Following Intravenous Oxycodone Solution With and Without Concomitant Naloxone.**



Plasma levels of naloxone were significantly higher following IV administration (0.035 mg/kg, or 2.5 mg for a 70 kg subject) compared to that following oral administration of Targiniq 40/20 mg.

**Figure: Mean Plasma Concentrations of Naloxone vs Time in Study ONU1003 Following Intravenous Administration of Naloxone Solution.**



### TARGINIC ER Pharmacokinetics in Special Populations

The Applicant conducted dedicated studies to evaluate the effect of age, renal impairment, and hepatic impairment on the PK of oxycodone and naloxone from TARGINIC ER.

Study OXN1006 evaluated the effect of mild, moderate, and severe hepatic impairment on the pharmacokinetics of oxycodone and naloxone following TARGINIC ER 10/5 mg administration compared to healthy subjects. Study OXN1007 evaluated the effect of mild, moderate, and severe renal impairment on the pharmacokinetics of oxycodone and naloxone

following 10/5 mg administration compared to healthy subjects. The results are summarized below (as well as the food effect) in the table from Dr. Nallani's review.

**Table: Summary table indicating observed percentage change in Cmax and AUC for oxycodone and naloxone following single Targiniq 10/5 mg administration.**

	Oxycodone		Naloxone	
	Percent Change in Cmax	Percent Change in AUC	Percent Change in Cmax	Percent Change in AUC
Food Effect (Study OXN1003)				
Food Effect	↑25%	↑15%	↑75%	↑25 – 65 %
Hepatic Impairment (HI) (Study OXN1006)				
Mild HI	↑20%	↑43%	↑93%	↑311%
Moderate HI	↑100%	↑219%	↑5192%	↑11418%
Severe HI	↑91%	↑210%	↑5152%	↑10566%
Renal Impairment (RI) (Study OXN1007)				
Mild RI	↑10%	↑53%	↑976%	↑2750%
Moderate RI	↑35%	↑66%	↑758%	↑3910%
Severe RI	↑67%	↑124%	↑1575%	↑7512%

There was no significant effect of age, race, and gender on the PK of oxycodone following administration of TARGINIC ER. Plasma levels of naloxone were low in healthy volunteers of different age, race and gender following TARGINIC ER administration. Compared to the low and variable levels of naloxone in young adults, a higher steady state naloxone AUC (82% increase) was noted in the elderly. Dr. Nallani notes that this increase is not expected to be clinically significant.

Based on the above results, Dr. Nallani recommended the following language for the label:

### **Labeling Recommendations:**

**Hepatic Impairment:** Lower starting dose may be recommended in patients with mild hepatic impairment with regard to oxycodone PK changes noted. This recommendation is consistent with the described caution in Section 8.6 of OxyContin label.

Use of Targiniq in patients with moderate to severe hepatic impairment should be contraindicated. This recommendation is due to the potential for high naloxone concentrations in moderate to severe renal impairment.

**Renal Impairment:** Patients with renal impairment (mild, moderate or severe) should be monitored and followed up by a conservative approach to dose initiation and adjust to the clinical situation. This recommendation is also consistent with that described in Section 8.7 of OxyContin label.

There is a typographical error in the second paragraph above, the second sentence should read, "This recommendation is due to the potential for high naloxone concentrations in moderate to severe hepatic impairment.

These labeling recommendations will be incorporated into the TARGINIC ER label.

A Biopharmaceutics review was conducted by Kareen Riviere, Ph.D., with secondary concurrence by Tapash Ghosh, Ph.D., and Richard Lostritto, Ph.D. They did not identify any issues that would preclude approval of TARGINIC ER.

Their review focused on the evaluation and acceptability of the proposed dissolution method, the proposed dissolution acceptance criteria, information and data on alcohol dose dumping, data supporting the bioequivalence of the proposed product manufactured in the US and Europe for each strength, and data supporting the in vitro in vivo relationship (IVIVR) for the oxycodone component of the proposed drug product.

In summary, the dissolution method and proposed acceptance criteria are acceptable. The Applicant provided in vitro data demonstrating no potential for alcohol dose-dumping. Adequate data was provided to demonstrate the bioequivalence of the proposed product manufactured in the US and Europe. Thus clinical and clinical pharmacology data generated with the European product may be used to support approval of the US product. The Applicant attempted to establish a model with the relationship between in vitro tablet dissolution rates and in vivo absorption/bioavailability for the oxycodone component of the proposed product. However, the submitted report lacked detailed information on the assumptions and procedures taken to develop and validate this model. Therefore, it serves no regulatory purposes to implement any possible change that will affect oxycodone alone in this combination controlled release product.

### **3. Clinical Microbiology**

TARGINIC ER is not an antimicrobial, therefore this section is not relevant.

### **4. Clinical/Statistical- Efficacy**

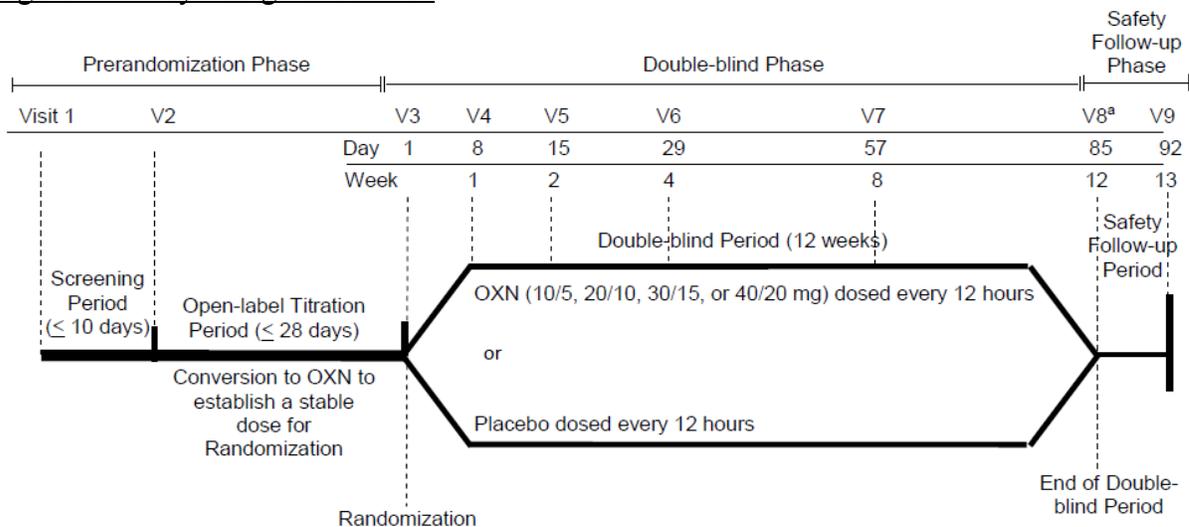
The clinical review was conducted by Elizabeth Kilgore, MD, and the statistical review by Feng Li, Ph.D., with secondary concurrence by Janice Derr, Ph.D.

As a 505(b)(2) application, referencing the Listed Drug, Narcan, with cross-reference to the original OxyContin and reformulated OxyContin NDAs, the Division advised the Applicant that a clinical trial demonstrating efficacy would be needed if detectable levels of naloxone in systemic circulation were noted, and agreed with the Applicant that one positive adequate and well-controlled clinical trial was necessary to support a finding of efficacy for the proposed indication was sufficient. The Division also advised the Applicant that the primary efficacy endpoint must measure pain over a 12-week treatment period to support a chronic pain indication, and a landmark analysis was the preferred approach. Discussions were also conducted regarding the use of imputation methods to account for missing data.

### Study Design ONU3701

Study ONU3701, conducted in opioid-experienced subjects with chronic low back pain, was submitted to support the efficacy of OXN administered twice daily compared to placebo. It was a double-blind, placebo-controlled, parallel group, randomized withdrawal study of OXN in subjects with moderate-to-severe chronic low back pain. The study consisted of three phases: the pre-randomization phase including a screening period and an open-label titration period (up to 28 days), the 12-week double-blind phase, and the safety follow-up phase. Subjects who demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period were eligible for entering the double-blind phase.

Figure X Study Design ONU3701



Source: Applicant's CSR3701, p. 23

In order for subjects to enter the open-label titration period, they must have had an average pain over the prior 24 hours of at least 5 on an 11-point NRS, and a total average daily opioid dose over the screening period of 20 to 160 mg morphine equivalents of an opioid analgesic, or tramadol with dose of at least 100 mg daily. At entry into the open-label titration, all subjects were converted from their current opioid to OXN at an oxycodone dose

approximately equivalent to their current therapy. A conversion table was supplied to the investigators, however, they were allowed to use their own discretion regarding the dose of OXN selected. OXN doses could be adjusted up or down based on effectiveness and tolerability, the maximum allowed dose being OXN 40/20 mg BID. Subjects entering the double-blind phase were required to have demonstrated analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period. Subjects were then randomized to receive either OXN or matching placebo every 12 hours, based on their OXN dose at the end of the open-label titration period. Supplemental pain medication (IR oxycodone) for breakthrough low back pain was allowed except during the 30 hours preceding study visits. The first 10 days of the double-blind period constituted a randomized withdrawal phase where subjects randomized to placebo were tapered off OXN in a blinded fashion. The double-blind phase comprised six visits: visit 3 (randomization), visit 4 (Week 1  $\pm$  2 days), visit 5 (Week 2  $\pm$  2 days), visit 6 (Week 4  $\pm$  3 days), visit 7 (Week 8  $\pm$  3 days), and visit 8 (Week 12  $\pm$  3 days). A seven-day follow up visit was conducted following completion of the double-blind phase or early discontinuation.

At scheduled study visits, efficacy assessments included “average pain over the last 24 hours” using an 11-point NRS, Brief Pain Inventory-Short Form (BPI-SF), the Clinical Opioid Withdrawal Scale (COWS), the modified Subjective Opioid Withdrawal Scale (SOWS), and Medical Outcomes Study (MOS) sleep scale.

The primary efficacy outcome was the “average pain over the last 24 hours” at Week 12. The secondary efficacy outcomes included Patient Global Impression of Change (PGIC) and MOS Sleep Disturbance Subscale score at Week 12. Safety assessments included collection of adverse events, Clinical Opioid Withdrawal Scale (COWS), modified Subject Opioid Withdrawal Scale (SOWS), clinical laboratory tests, vital signs and ECGs. Pharmacokinetic assessments were also conducted at Visit 3 and Visit 6, and clinic visits where the subject had a COWS score  $\geq$ 13 or an adverse event of opioid withdrawal.

### **Results ONU3701**

Study design and conduct were reviewed by Dr. Kilgore. The Applicant determined that 10% of subjects in both the OXN and placebo groups had major protocol violations that could have affected efficacy analyses. These subjects were excluded from the per protocol analyses. All subjects (n=17) from one study site (2214A-9015) were excluded from analysis due to allegations that the investigator was involved in writing prescriptions illegally for purposes of abuse. There did not appear to be protocol amendments or protocol deviations that would be expected to affect the efficacy results.

There were 1095 subjects who received open-label titration treatment, and 600 subjects who entered the double-blind phase of the study (placebo-302, OXN-298). During the open-label titration, 45% of subjects discontinued the study, approximately 9% due to adverse events, 10% due to lack of efficacy, and 16% did not qualify for entry into the double-blind phase. Of the 600 subjects entering the double-blind phase, 399 completed it, with the most common reason for early discontinuation being lack of therapeutic effect (17%), followed by adverse events (8%). Discontinuation due to lack of efficacy was more common in the placebo group (24%) compared to OXN (10%) as would be expected. Discontinuation due to adverse events

was similar in both groups (10%). The Applicant's table below shows the disposition of patients in detail.

Table X: Subject Disposition-Number (%) of Patients

	Placebo	OXN	Total
<b>Randomized</b>	<b>302</b>	<b>299</b>	<b>601</b>
<b>Randomized and treated (full analysis population)</b>	<b>302</b>	<b>298</b>	<b>600</b>
<b>Completed period on study drug</b>	181 (60%)	218 (73%)	399 (67%)
<b>Discontinued study drug during double-blind period</b>	121 (40%)	80 (27%)	201 (34%)
Adverse event	23 (8%)	24 (8%)	47 (8%)
Subject's choice	8 (3%)	10 (3%)	18 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	73 (24%)	31 (10%)	104 (17%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
<b>Discontinued study drug and study simultaneously</b>	62 (21%)	48 (16%)	110 (18%)
Adverse event	14 (5%)	15 (5%)	29 (5%)
Subject's choice	8 (3%)	8 (3%)	16 (3%)
Lost to follow-up	1	4 (1%)	5 (1%)
Lack of therapeutic effect	23 (8%)	10 (3%)	33 (6%)
Confirmed or suspected diversion	6 (2%)	5 (2%)	11 (2%)
Administrative	10 (3%)	6 (2%)	16 (3%)
<b>Discontinued study drug and stayed in study</b>	59 (20%)	32 (11%)	91 (15%)
Completed Week 12	49 (16%)	25 (8%)	74 (12%)
Discontinued study prior to Week 12	10 (3%)	7 (2%)	17 (3%)
Adverse event	0	7 (2%)	7 (1%)
Subject's choice	8 (3%)	0	8 (1%)
Lost to follow-up	2 (1%)	0	2

Source: Clinical Study Report, Table 14.1.1.4 and Table 14.1.1.5

In the double-blind phase, subjects were distributed among the OXN dose groups as follows: 10/5 mg: n = 59, 20/10 mg: n = 78, 30/15 mg: n = 69, 40/20 mg: n = 92.

Demographic and baseline characteristics were similar between the treatment groups. The average age was 54 years for both groups, and both groups were predominantly female and Caucasian. The mean pre-randomization pain intensity was 3/10 on the NRS for both treatment groups.

#### Rescue medication use

During the double-blind period, the percentage of subjects who took, on average, up to two rescue pills per day (oxycodone IR 5 mg) was greater for the placebo group (35%) than the OXN group (28%). Four percent of placebo-treated subjects took more than two rescue pills per day compared to 2% of OXN treated subjects.

#### **Statistical Analysis**

As stated in Dr. Li's statistical review:

The primary efficacy outcome was the “average pain over the last 24 hours” at Week 12. The protocol stated that the causal estimand was the difference in the primary efficacy outcome between the placebo and OXN treatment groups at Week 12 for all randomized subjects regardless of study drug compliance. The primary analysis was based on a mixed-model repeated measures analysis (MMRM) and an adaption of a hybrid imputation approach for handling missing data due to dropouts, which assigns high pain scores to discontinuations due to adverse events. The primary efficacy population included the subjects who were randomized and received study drug. The primary analysis only included data while subjects were taking study drug.

Dr. Li was able to replicate the Applicant’s statistical analysis of the primary endpoint, which showed that the difference between OXN and placebo at Week 12 for average pain in the last 24 hours was statistically significant.

Table X: 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

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

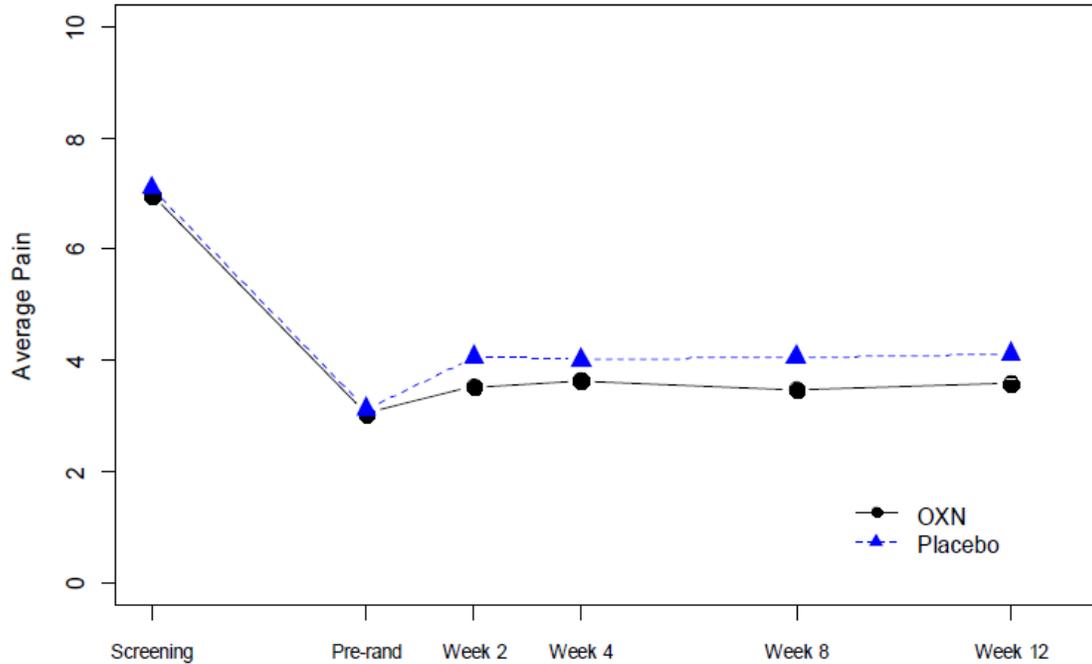
Dr. Li also replicated a number of sensitivity analyses conducted by the Applicant and conducted one additional sensitivity analysis using all observed data including those collected after discontinuation of study drug. The sensitivity analysis results were similar to the primary analysis. Refer to Dr. Li’s review for details regarding the sensitivity analyses.

Dr. Li’s analyses of the primary endpoint by subgroups; gender, age, and race, did not result in any major or important differences within the groups.

The study was not powered to determine differences in the primary endpoint by dose group, however, there was no clear relationship of the mean “average pain over the last 25 hours” and dose.

Dr. Li constructed a pain curve showing the average pain intensity over time for OXN compared to placebo. It appears that the study effect was roughly maintained from Week 2 to Week 12.

**Figure 1: Average Pain Intensity on Study Drug Over Time**

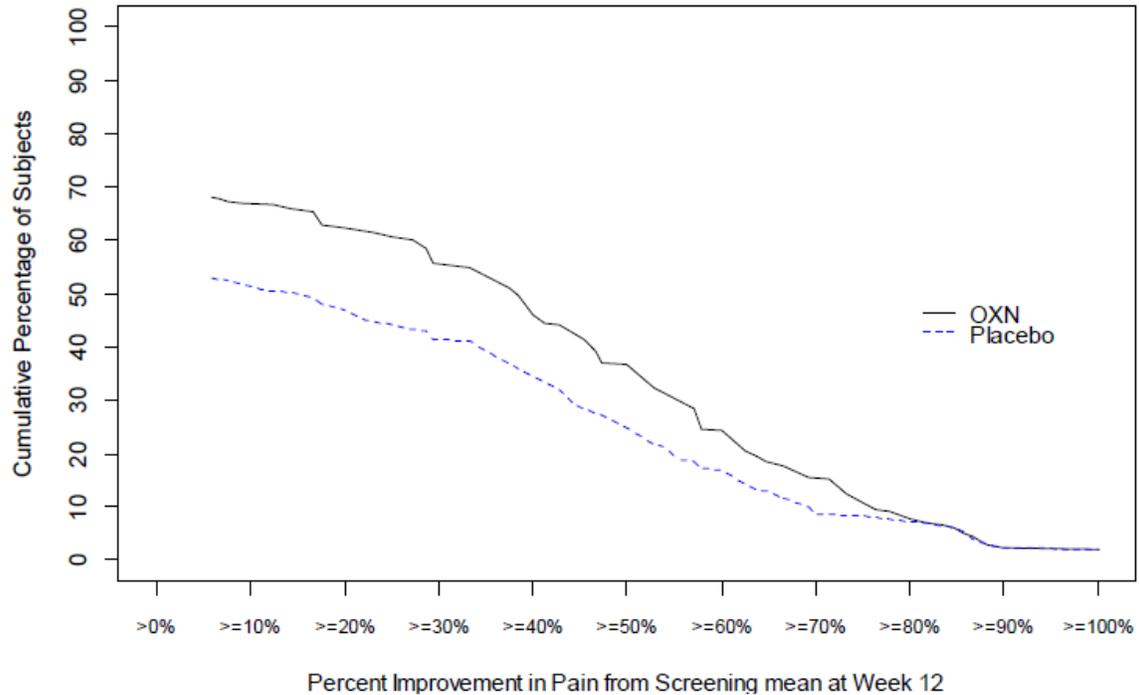


Source: Dr. Li's review, p. 14

Dr. Li also constructed a continuous responder curve, as follows from his review:

The OXN group also had a better continuous responder curve than the placebo group (Figure 2). For example, about 55% of the subjects in the OXN group had at least 30% improvement from screening. In contrast, approximately 41% of placebo group had at least 30% improvement from screening. Subjects who discontinued study drug were considered as non-responders in the calculations. There was no notable difference between the two treatment groups in the percentages of subjects who achieved more than 80% improvement.

**Figure 2: Continuous Responder Curve**



Source: Dr. Li's review, p. 15

### Secondary Endpoints

The Applicant's analyses of the secondary endpoints, MOS Sleep Scale and PGIC, and additional exploratory endpoints also favored OXN over placebo. These results are supportive, and the Applicant did not request inclusion of these results in the label. Refer to Dr. Kilgore's review for a more detailed discussion of the secondary endpoints.

I am in agreement with Dr. Kilgore's and Dr. Li's findings regarding efficacy for Study ONU3701. Based on review of the conduct of the study and the results of the primary endpoint analysis, with support from the responder analysis and other secondary and exploratory endpoints, this study supports the efficacy of TARGINIC ER in an enriched study population of adults with chronic low back pain requiring treatment with extended-release opioids for a prolonged period of time. This population of patients is representative of the target population of patients with chronic pain, to which these findings may be generalized.

## **5. Safety**

The safety review was conducted by Elizabeth Kilgore, MD. The following is a summary of Dr. Kilgore's findings.

The Applicant's Integrated Summary of Safety (ISS) was comprised of a complex pooling of 33 clinical studies based on patient population, study design (double-blind vs open-label), study phase, and comparator arms. The majority of the studies, other than the key efficacy study ONU3701, three Phase 1 PK studies, and four abuse liability studies, were conducted outside the US to support registration of OXN in the EU for the indication of the treatment of

pain and OIC. Please refer to Dr. Kilgore's review for additional details regarding the pooling strategy. The most informative pooling for the purposes of this NDA review is what the Applicant refers to as Group A1A which includes two placebo-controlled studies in patients with chronic non-malignant pain (ONU3701 and OXN3401). These studies were similar in design (randomized double-blind, placebo-controlled) and are a subgroup of Group A which includes subjects with chronic nonmalignant or malignant pain. Study OXN3401 was conducted outside the US. Dr. Kilgore reviewed the data from the large pool of 33 studies, as well as Groups A and A1A. Phase 1 studies and the abuse liability studies were reviewed as separate groups.

#### Exposure

The overall exposure to OXN, in terms of duration of exposure and dose levels appears adequate to inform the safety profile of this product. In the large pool of 33 studies, a total of 3,073 study subjects were exposed to total daily doses of OXN ranging from 10/5 mg to more than 100/50 mg. The average total daily dose of OXN (as oxycodone) was approximately 40 mg. Seven-hundred-ninety-four subjects (26%) were exposed for at least 6 months, and 621(20%) for at least 12 months.

Of the 2396 subjects with chronic nonmalignant or malignant pain (group A), 1084 subjects (45.2%) were exposed to OXN for  $\geq 3$  months, 794 subjects (33.1%) were exposed to OXN for  $\geq 6$  months, and 621 subjects (25.9%) were exposed to OXN for  $\geq 12$  months across all study periods. Of the 2396 exposures, 142 (6%) were exposed to total daily doses of OXN greater than 80/40 mg.

Of the 911 subjects with chronic nonmalignant pain (Group A1A), 460 were exposed to OXN during the double-blind phase of the studies, 168 (37%) for at least 12 weeks. The distribution of exposure by dose in this group is shown in the following Applicant's table. The most common dose was OXN 40/20 mg.

Table 3.3.3  
 Summary of Cumulative Exposure to OXN During Double-blind by Randomized Total Daily OXN Dose  
 Population: Randomized Safety – Placebo Controlled Studies in Subjects with Non-malignant Chronic Pain (Group A1A)

Exposure Variable	Total OXN (N=451)	OXN 20/10 (N=124)	OXN 40/20 (N=166)	OXN 60/30 (N=69)	OXN 80/40 (N=92)
Cumulative Exposure Categories, n (%)					
Any Exposure	451 (100.0)	124 (100.0)	166 (100.0)	69 (100.0)	92 (100.0)
>= 1 Week	432 (95.8)	120 (96.8)	163 (98.2)	64 (92.8)	85 (92.4)
>= 2 Weeks	423 (93.8)	119 (96.0)	160 (96.4)	62 (89.9)	82 (89.1)
>= 4 Weeks	397 (88.0)	116 (93.5)	152 (91.6)	57 (82.6)	72 (78.3)
>= 6 Weeks	380 (84.3)	111 (89.5)	148 (89.2)	53 (76.8)	68 (73.9)
>= 8 Weeks	361 (80.0)	107 (86.3)	140 (84.3)	50 (72.5)	64 (69.6)
>= 10 Weeks	335 (74.3)	103 (83.1)	127 (76.5)	47 (68.1)	58 (63.0)
>= 12 Weeks	172 (38.1)	60 (48.4)	71 (42.8)	17 (24.6)	24 (26.1)
Cumulative Days of Exposure					
n	451	124	166	69	92
Mean (SD)	69.9 (24.98)	75.3 (21.59)	72.8 (22.01)	64.4 (27.99)	61.8 (29.09)
Median	82.0	83.0	83.0	79.0	78.0
Min, Max	1, 123	4, 123	1, 93	4, 89	1, 92
Average Total Daily Oxycodone Dose (mg)					
n	298	59	78	69	92
Mean (SD)	49.5 (22.36)	19.7 (0.51)	37.4 (8.22)	56.9 (7.61)	73.5 (14.36)
Median	53.3	19.9	39.7	59.5	79.4
Min, Max	10, 80	17, 20	19, 80	20, 60	10, 80

Note: Cumulative exposure is defined as the total number of days the subject is exposed to OXN during double-blind. OXN dose is presented as total daily oxycodone dose in mg. Studies in Group A1A: ONU3701 and OXN3401. Study OXN3401 is excluded from average total daily dose calculation due to the inconsistent recording of dose in this study.

Disposition

Of the 3073 subjects exposed to OXN, 33% discontinued treatment at some point during the studies. The most common reason for discontinuation was adverse event (10%), followed by lack of therapeutic effect (6%). There were no unexpected findings in terms of disposition of patients in the safety database.

Demographics

Dr. Kilgore constructed a table in her review that compared the demographics of the integrated pool of 33 studies with the key efficacy study ONU3701, and showed that the key demographic features are quite similar between the groups. This is important particularly because the majority of the studies were conducted outside the US, and provides support that the safety findings from these studies are applicable to the US population.

Table X: Key Demographics of Subjects in ONU3701 vs Integrated Studies

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

Adapted from Dr. Kilgore’s review, p. 66

Deaths

Across the studies of chronic nonmalignant or malignant pain (Group A study pool), there were 57 deaths; a total of 42 deaths occurred in 2,396 subjects during or after exposure to OXN. There were 13 deaths that occurred in patients treated with oxycodone controlled-release, one treated with oxycodone IR, and one in a placebo patient. Fifty-one of the 57 deaths occurred in Study OXN2001 and were mainly the result of tumor progression in cancer patients. One death occurred in the key efficacy study ONU3701 in a patient randomized to placebo treatment.

Dr. Kilgore reviewed all of the narratives, and noted two deaths may have possibly been related to study drug. One was a 61 year old male with metastatic cancer who after (b) (6) days of treatment with OXN (titrated from 30/15 mg to 90/45 mg during that period) complained of headache and dizziness, followed by death later in the day. The death was coded as heart and circulation failure, and the narrative also stated the patient had a pulmonary embolism and intracerebral bleed (timing not clear). However, the pulmonary embolism and intracerebral bleed appear to have been the cause of death, not the study drug.

The second death occurred in a 55 year old male with metastatic lung cancer who died after treatment with OXN for (b) (6) days at increasing doses up to 80/40 mg total daily dose. Dr. Kilgore felt that contribution of the study drug to death could not be ruled out.

Three deaths on OXN occurred in non-cancer patients, and all appear unrelated. Causes of deaths were traffic accident, necrotizing faciitis, and sepsis.

#### Nonfatal Serious Adverse Events

Dr. Kilgore reviewed the nonfatal SAEs and noted that 7% of the 3,073 subjects exposed to OXN experienced at least one event, the most common being neoplasms, gastrointestinal, and connective tissue disorders, all at 1%. In the double-blind, placebo-controlled studies in nonmalignant pain patients, the incidence of SAEs was 6% in OXN-treated subjects, and 3% in placebo subjects. Drug screen positive and abdominal pain were the only SAE terms that occurred in more than two subjects in either treatment group. Of note, there were two MIs in the OXN group compared to none in the placebo group. An in depth review of the cardiac safety findings for OXN was conducted by the Division of Cardiorenal Products and no cardiac safety signal was identified. The consult response is discussed later in this section.

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

Source: Applicant's ISS, p. 176

In Study ONU3701, the incidence of SAEs during the open-label titration period where all subjects were treated with OXN was 1% (9 subjects with 16 events), and in the double-blind period was 4% in placebo subjects and 6% in OXN treated subjects. For nine of the 11 subjects in the open-label titration period, abuse-related terms were reported, e.g., drug screen positive, drug abuse, and drug overdose. For the remaining subjects, Dr. Kilgore determined that two events (dehydration/vomiting, and worsening esophageal stricture) may have been related to OXN. In the double-blind period, 4% of placebo and 6% of OXN treated subjects experienced SAEs. One SAE of rectal perforation was determined by the investigator not to be related to OXN, however, Dr. Kilgore could not rule out an association with study drug. While the subject had a long-term history of constipation, OXN may have contributed to both the continued constipation and hence the SAE.

Overall there were no trends or unexpected findings in the review of the SAEs that would require the addition of labeling language not already proposed by the Applicant.

#### Discontinuations due to AEs

Overall, the pattern of discontinuations due to adverse events was consistent with the known safety profile of opioid analgesics observed in clinical trials.

Of the 3073 subjects exposed to OXN, 280 (9%) discontinued treatment due to AEs. The most common types of AEs were in the System Organ Class (SOC) for Gastrointestinal Disorders (3%) and Nervous System Disorders.

In the double-blind, placebo-controlled studies in subjects with non-malignant pain (Group A1A), rates of discontinuation due to AEs were similar in the OXN-treated (6%) and placebo-treated (7%) subjects. Types of adverse events were similar to those in the larger database, however the GI disorders occurred slightly more commonly in the placebo group (2%) compared to OXN-treated subjects (1.3%). Also, 3% of subjects in the OXN group discontinued due to drug screen positive, compared to 1% in the placebo-treated group.

In Study ONU3701 during the open-label titration) period, the incidence of discontinuation adverse events was higher in the non-randomized (18%) compared to randomized (<1%). The study was designed so 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%). Of note, one subject treated with OXN discontinued treatment because of angioedema after (b)(6) days of treatment.

In the double-blind period, adverse events leading to discontinuation 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.

#### Common Adverse Events

The table of common adverse events proposed by the Applicant for the label is as follows:

Table X: TEAES in  $\geq 2$  % of Subjects in Study ONU3701

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 (b) (4)			(b) (4)
			(b) (4)
Pruritus	2	1	2
Vomiting	2	2	5
Abdominal pain (b) (4)		2	(b) (4)
Anxiety	1	0	3
			(b) (4)
Insomnia	1	1	2
			(b) (4)
Back pain	0	1	3
			(b) (4)

These events are consistent with the adverse event profile of OxyContin. The proposed table will be modified in the label. Events that occur less frequently in study drug than in placebo will be removed (b) (4) and abdominal pain will be added together to make one category. Additionally, a footnote will be added stating that when the adjudicated cases of drug withdrawal syndrome are added to the reported events in the table, the resulting percentages in the double-blind period are 4% for TARGINIC ER and 2% for placebo.

The Gastrointestinal Disorder SOC adverse events appears to be dose dependent, however, when the individual AEs within the SOC are assessed, the dose dependence is not consistent. The lack of dose dependence for individual GI disorders is likely due to the development of tolerance as the dose of OXN is titrated higher.

The common adverse events for the pooled studies were reviewed by Dr. Kilgore and are similar to those in the above table.

There were no findings of significance in review of vital signs, ECGs, or laboratory data.

Adverse Events of Special Interest

*Opioid Withdrawal*

Study ONU3701 was prospectively designed to assess the occurrence of opioid withdrawal symptoms in subjects treated with OXN compared to placebo. Although the presence of naloxone in TARGINIC ER is for the purpose of conveying abuse-deterrent properties, there is the possibility that patients treated with this product may be at risk for adverse events due to

the naloxone, specifically opioid withdrawal (OW). The occurrence of OW was assessed in several ways in Study ONU3071:

- Investigator identified OW adverse events of drug withdrawal or withdrawal syndrome (Investigators were required to evaluate all subjects who reported COWS scores  $\geq 5$  or SOWS scores  $\geq 10$  to determine if an AE of opioid withdrawal occurred)
- Prospective, blinded, independent adjudication committee review based on a) COWS score  $\geq 13$ ; b) AE of opioid withdrawal recorded by the investigator in the CRF; c) three 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.
- Plasma concentrations of oxycodone, naloxone, and naloxone-3 $\beta$  gluronide collected at prerandomization (Visit 3), midtreatment (Visit 6), end of treatment (visit 8), and while in opioid withdrawal

Dr. Kilgore extensively reviewed the Applicant's analyses, and arrived at the following 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:

Forty-three OW events (Investigator identified plus Adjudication Committee identified)

- Open-label treatment (OLT)
  - 56% occurred during the OLT period
  - 62% of those in the OLT period occurred when morphine equivalents were being decreased during a transition
- Double-blind (DB)
  - 44% occurred during the DB period
  - 63% of those in the DB period were in TARGINIC ER-treated subjects
    - 58% occurred when dose was being decreased (7 events); 42% when dose was unchanged (5 events)
  - Most (58%) occurred in patients taking OXN 80/40 mg

Dr. Kilgore stated that it is not unexpected that when a subject is transitioned to a dose of OXN that is lower in morphine equivalents than their previous opioid, that symptoms of opioid withdrawal could occur. Therefore the events of interest are the five withdrawal events that occurred in the double-blind period where morphine equivalent doses were unchanged. This is a relatively small number of events, however, it does support the concept that opioid withdrawal symptoms may occur in patients treated with TARGINIQ ER. The product label

will include appropriate language regarding the possibility of occurrence of withdrawal in patients.

Regarding the analysis of plasma concentrations of oxycodone, naloxone, and naloxone-3 $\beta$  glucuronide collected at prerandomization (Visit 3), midtreatment (Visit 6), end of treatment (visit 8), and while in opioid withdrawal, Dr. Kilgore writes

- **In an analysis conducted in pivotal study ONU3701, there were no clear differences in the distribution of naloxone concentrations between subjects with or without opioid withdrawal symptoms, regardless of OXN dose.**

#### *Cardiovascular Safety*

Prior to NDA submission, the Division requested that the Applicant conduct an analysis of OXN safety data in order to determine whether there is a cardiac safety signal for TARGINIC ER. A peripheral opioid antagonist drug intended for the treatment of opioid-induced constipation, Alvimopan, was noted to have an excess of cardiovascular events in its clinical trial database, and an AC was held in 2008 to discuss the issue. Since then, other peripheral opioid antagonists have been developed for the treatment of OIC, and the question has arisen as to whether there is a class effect in terms of a cardiac signal. There is also a question as to whether opioid withdrawal may be associated with the occurrence of cardiac events. Therefore, the Applicant for TARGINIC ER was asked to conduct these analyses. The Division of Cardiovascular and Renal Products (DCaRP) and the Division of Biometrics VII (DB VII) were consulted by DAAAP to review the Applicant's analyses. The acronym MACE stands for Major Adverse Cardiac Events which, in general, include MI, stroke, and cardiac death. The cardiac events were collected as part of routine safety monitoring in the clinical trials, and not from trials prospectively designed to assess CV safety.

Dr. Preston Dunmon (DCRP) provided the following conclusions, however noted several limitations to the analysis in his review. These included the distinct patient populations that were integrated for the assessment, differences in study design, different dosing regimens, the and the relatively high baseline risk of cardiac events in the study populations. Please refer to Dr. Dunmon's review for additional details of his analyses.

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 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.

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).

Language reflecting the above recommendation will be included in the TARGINIC ER label.

Janelle Charles, Ph.D. of DB VII provided a statistical review of results from the Applicant’s analyses of the clinical trial database and results from assessments from other data sources, such as European postmarketing databases. She states in her review that a definitive conclusion that there is no CV safety concern with OXN cannot be made from the data sources evaluated in her review. Therefore, if there is need to further characterize the CV risk of OXN, further assessment may be conducted postmarketing, if it is approved. Please refer to Dr. Charles review for additional details.

Based on the reviews conducted by DCaRP and DB VII, there does not appear to be evidence of a cardiac signal in the clinical trial or postmarketing analyses submitted by the Applicant. In all double-blind trials combined, there were two SMQ-based MACE events (0.2%) in subjects treated with OXN, and seven (0.6%) in comparator-treated subjects. None of the MACE events in OXN-treated subjects occurred in Study ONU3701. However, there are

several limitations of the analyses. Findings from the analysis of CV events will not be included in the TARGINIC ER label, as recommended by Dr. Charles.

#### *Standard and Custom MedDRA Queries*

The Applicant identified Opioid Bowel Dysfunction (MedDRA preferred terms nausea, vomiting, constipation, abdominal pain, abdominal distension, decreased appetite, flatulence) and Diarrhea-Related adverse events (MedDRA preferred terms diarrhea, frequent bowel movements, antidiarrheal supportive care, defecation urgency) as CMQs (Custom MedDRA Queries) 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, (b) (4)

They compared the incidence of these groups of AEs in OXN-treated subjects to OxyCR (controlled-release oxycodone), in studies where OxyCR was a comparator (not the case for ONU3701). They noted that the incidence of opioid bowel dysfunction was slightly less in OXN subjects (11%) compared to Oxy CR subjects (15%). However results were variable, and no labeling claim is either sought by the Applicant nor recommended by the Division.

#### Other SMQ Analyses

- Hepatic safety: This yielded no significant findings that would change the expected safety profile for OXN.
- Respiratory safety: Fourteen subjects were identified who experienced respiratory SAEs across all treatment periods in the controlled studies. Most occurred in open-label extension phases and were due to underlying disease. No unusual or unexpected safety information was noted for this SMQ.
- Gallbladder-related disorders: In the double-blind studies (Group A1, n = 968 OXN, 460 placebo, 554 OxyCR), the rate of gallbladder-related disorders was 0.4% in the OXY CR and OXN groups, and 0.2% in placebo-treated subjects. Three subjects treated with OXN reported an SAE of cholecystitis compared to one in the comparator groups. The MedGuide states, “*Before taking TARGINIC ER, tell your healthcare provide if you have a history of pancreas or gallbladder problems.*” It does not appear that these reports would rise to the level of a warning in the TARGINIC ER label, given the small numbers of cases.
- Drug abuse: The overall incidence of reports related to abuse in Study ONU3701 was 7.5%, with the majority of the abuse involving illicit drug abuse and non-prescribed opioid medication abuse identified by urine drug testing. Abuse of study drug (OXN, OXY IR, or both) occurred in 1% of the safety population of Study ONU3701. Refer to the CSS review for more details regarding abuse in the clinical trial. It is common to observe some degree of opioid abuse during clinical trials of opioid analgesics, as they are Schedule II drugs.
- Drug withdrawal: Refer to previous section on opioid withdrawal.
- Accidents and injuries: There were no unusual findings in this analysis
- Adverse pregnancy outcome/reproductive toxicity: Two pregnancies were reported in completed clinical trials of OXN. One resulted in a healthy newborn and the other was lost to follow up prior to delivery.

#### Safety Conclusions

I agree with Dr. Kilgore's conclusions regarding the safety of TARGINIC ER, which are:

- The overall safety profile for TARGINIC ER is consistent with the ERLA opioid class
- No new or unexpected safety signals were detected
- Opioid withdrawal may occur in patients treated with TARGINIC ER even when they are on a stable dose, and the label should include relevant language
- There does not appear to be a signal for MACE events in the OXN database, however there were limitations to these analyses
- There does not appear to be an association between opioid withdrawal syndrome and MACE events

## 6. Advisory Committee Meeting

An Advisory Committee meeting was not convened specifically for this application. However, on June 11-12, 2014, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss the potential cardiovascular risk associated with products in the class of peripherally-acting mu opioid receptor antagonists (PAMORAs) and the necessity, timing, design, and size of cardiovascular outcome trials to support approval of products in this class (b)(4) in patients taking opioids for chronic pain. The occurrence of opioid withdrawal and its potential contribution to a cardiac signal was also discussed. The impetus for this meeting, conducted by DGIEP, was an imbalance in cardiac events that occurred during development of alvimopan (Entereg), for which an Advisory Committee meeting was held in 2008. The resulting indication for alvimopan was short-term use to accelerate time to upper and lower GI recovery following surgeries. (b)(4).

AADPAC generally agreed that controlled cardiac outcome trials are not needed for this class of drugs (b)(4), due to lack of a clear cardiac signal during development programs. Some members of the panel thought that it may be reassuring to collect post marketing data on cardiac safety via observational studies in order to rule out a large increase in MACE risk.

Although TARGINIC ER is not being approved for the treatment of OIC, and the naloxone component does not act entirely peripherally (the Applicant states there is local action in the GI tract as well as <2% absolute BA largely due to extensive first-pass metabolism, enters the CNS), the effects of this product on cardiovascular safety would be expected to be the same as the PAMORA class of drugs intended for the treatment of OIC, and the intended population of patients with chronic pain requiring around-the-clock treatment with an extended-release opioid is essentially the same as the OIC population. Both oxycodone and naloxone are approved drugs and have a long history of use. The Applicant has provided a large amount of safety data for oxycodone/naloxone in the target population, marketed as Targin outside the U.S. The long history of use and the large safety database provide reassurance regarding the absence of a strong cardiac signal for TARGINIQ ER. Therefore, as per the recommendation of the AADPAC, and to maintain consistency within this class of opioid antagonists, a post marketing requirement will be imposed on the Applicant such that they must conduct an observational study or studies to further assess the risk of major cardiac adverse events in patients treated with TARGINIC ER. The observational study may provide information on whether there is a large excess risk of cardiac events with this drug.

## 7. Pediatrics

As a new combination product that triggers PREA, pediatric studies are required for TARGINIC ER. For extended-release opioid analgesics intended for the treatment of chronic pain, pharmacokinetic and safety studies are required for the age group 7 to 17 years. Efficacy findings from adults can be extrapolated to this age group as the underlying conditions are similar in children and adults, and the exposure response to opioids is expected to be similar in the two groups.

The following pediatric plan was reviewed by the Pediatric Research Committee (PeRC) on May 28, 2014, and agreed upon with the Applicant to be performed as a post-marketing commitment:

Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Final Protocol Submission: December 31, 2014  
Study Completion: December 31, 2018  
Final Report Submission: June 30, 2019

## 8. Other Relevant Regulatory Issues

### 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.

### Office of Scientific Investigation Audits (OSI)

OSI audited three domestic study sites. There was also an attempt to inspect a fourth site whose data was excluded from all analyses by the Applicant. Their conclusions are the following:

Two of the clinical sites inspected, Dr. Almaguer and Dr. Arslanian, were each issued a Form FDA 483 citing inspectional observations and classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for both sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Data from these sites is acceptable for use in support of the indication for this application.

Dr. Potts was not issued a Form FDA 483; the classification of the inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.

Although an audit of Dr. Lassiter's site was not possible, information obtained by the FDA field investigator confirmed the communications from the Sponsor. Data from this site are not considered reliable.

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 Sponsor under this NDA.

### **Pediatric and Maternal Health Staff (PMHS)**

PMHS was consulted to provide input on whether specific language should be added to the label regarding the effect of naloxone on the fetus or nursing infant. They note in their consult response that there are no data pertaining to pregnancy and lactation with the combination of oxycodone and naloxone at the 2:1 ratio seen with TARGINIC ER, however, literature was reviewed for the individual components. Please refer to the consult response for details. The following conclusions and recommendations were put forth:

### **CONCLUSIONS**

A pregnancy category C is the appropriate classification for Targiniq ER labeling due lack of adequate studies in pregnant women, the potential for fetal withdrawal, and findings from available animal reproduction data<sup>26</sup> (see 21 CFR 201.57 (c)(9)(i)(A)(3)). The pregnancy subsection of Targiniq ER labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of Targiniq ER labeling was revised to comply with current labeling recommendations, as well as incorporating the breast feeding benefit/risk statement from the proposed PLLR.

### **LABELING RECOMMENDATIONS**

PMHS-MHT reviewed existing labeling for oxycodone and naloxone to make labeling consistent across products. In addition, PMHS-MHT collaborated with the Pharmacology/Toxicology reviewer in structuring 8.1 Pregnancy and recommends the following revision to the Pregnancy and Nursing Mothers subsections of Targiniq ER labeling. Final labeling will be negotiated with DAAAP and may not fully reflect changes suggested here. See Appendix A for the applicant's proposed Targiniq ER labeling.

The following is the recommendation for the label highlights:

-----**USE IN SPECIFIC POPULATIONS**-----

- **Pregnancy:** Based on animal data, may cause fetal harm; may precipitate fetal withdrawal. (8.1)
- **Nursing Mothers:** Discontinue nursing or discontinue drug depending on importance of drug to mother. (8.3)

Please refer to the final label for the language in the Full Prescribing Information.

**CSS Consult**

The CSS review was conducted by James Tolliver, Ph.D., with secondary concurrence by Silvia Calderon, Ph. D., and Michael Klein, Ph.D. Nine in vitro and four in vivo studies related to abuse potential were reviewed, and the following conclusions and recommendations were taken verbatim from the CSS consult response.

**Conclusions:**

1. Overall, the data provided from in vitro physical and chemical manipulation studies and human abuse potential studies indicate that TARGINIC ER tablets display resistance to abuse by intravenous and intranasal administration, but to a lesser extent to oral administration, depending upon the abusing population.
2. For the population of non-dependent, non-tolerant recreational opioid users manipulation (crushing or extraction from whole tablets in hot water) of TARGINIC ER tablets with the intention of intravenous or intranasal administration will most likely result in little or no drug liking due to the presence of naloxone (study ONU1003) in a 2:1 ratio of oxycodone HCl/naloxone HCl that suppresses the mu-opioid agonist effects of oxycodone. However, such individuals may be expected to experience substantial levels of drug liking as well as possible overdose when TARGINIC ER tablets are crushed followed by ingestion or when chewed followed by swallowing (see Study ONU1007). This may be attributed to the very low ( $\leq 2\%$ ) absolute oral bioavailability of naloxone as well as to the extensive compromise of the controlled release mechanism for oxycodone HCl and naloxone HCl upon crushing (including crushing by chewing) of TARGINIC ER tablets.
3. For the population that is physically dependent and tolerant to opioids, manipulation of TARGINIC ER tablets (crushing or extraction from whole tablets in hot water) following by intravenous or intranasal administration will likely elicit a prominent withdrawal syndrome, depending upon the level of physical dependence. With oral administration of crushed TARGINIC ER tablets or with chewing of TARGINIC ER tablets followed by swallowing, individuals physically dependent and tolerant to opioids will likely experience limited, if any, drug liking. (See Study ONU1008). This may be attributed to the reduced sensitivity of this population to opioid subjective effects as a result of tolerance and to the emergence of at least some levels (mild) of withdrawal.
4. The results of vitro studies indicate that “opioid-naïve or opioid non-tolerant patients” who are initiated with TARGINIC ER tablets, may be at risk of potential

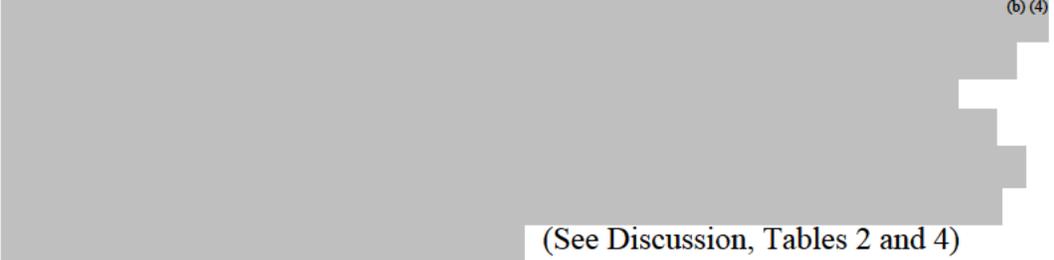
overdose should they administer orally crushed TARGINIC ER tablets or chew TARGINIC ER tablets. Likewise, patients who are physically dependent to opioids (TARGINIC ER or other opioid medications) and orally administer crushed TARGINIC ER tablets or chew TARGINIC ER tablets will likely experience a withdrawal syndrome, the severity of which will depend upon the level of physical dependence.

5. The principal mechanisms underlying the abuse deterrent properties of TARGINIC ER tablets are a) the difficulty involved in separating the naloxone HCl from the oxycodone HCl as evidenced in various in vitro studies and b) the effectiveness of the 2:1 ratio of oxycodone HCl to naloxone HCl in blocking the subjective reinforcing effects of oxycodone and potentially precipitating withdrawal.

6.  (b) (4)

7.  (b) (4)  
(See Discussion, Tables 1, 2, and 3)

8.  (b) (4)  
(See Discussion, Tables 1, 2, and 3)

9.  (b) (4)  
(See Discussion, Tables 2 and 4)

10. Dissolution studies demonstrated that whole TARGINIC ER tablets do not dose dump oxycodone HCl and naloxone HCl in simulated gastric fluid containing 40% ethanol. (See Discussion, Table 5)

11.  (b) (4)

12.  (b) (4)

13. Results of simulated smoking studies indicate that TARGINIC ER tablets most likely cannot be abused by smoking.  (b) (4)

14.  (b) (4)

15. [REDACTED] (b) (4)  
(See  
Table 7)

16. [REDACTED] (b) (4)

17. [REDACTED] (b) (4)

18. Human abuse potential study ONU1003, using non-dependent opioid experienced subjects, demonstrated that the intravenous injection of 0.035 mg/kg naloxone HCl followed within 1 minute by intravenous injection of 0.07 mg/kg oxycodone HCl solution (simulated 2:1 ratio of oxycodone HCl to naloxone HCl as found in TARGINIC ER tablets) produced maximum levels of Drug Liking and High that were similar to that produced by placebo (0.9% NaCl), but well below that produced by oxycodone HCl 0.07 mg/kg solution. In the absence of significant differences in oxycodone HCl plasma levels obtained for the two active treatments, the differences in subjective effects observed, indicate that the 0.035 mg/kg naloxone HCl was effective in reducing the subjective effects of the 0.07 mg/mg oxycodone HCl. The efficacy of the abuse deterrent effect by intravenous administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intravenous injection of the oxycodone HCl and naloxone HCl combination, as compared to injection of just oxycodone HCl. (See Discussion, Tables 9 and 11)

19. Human abuse potential study ONU1003, using non-dependent, opioid-experienced subjects, demonstrated that insufflation of finely crushed TARGINIC ER 40/20 mg resulted in maximum Drug Liking and High that were substantially lower than that produced by insufflation of oxycodone HCl 40 mg powder but similar to that of placebo for Drug Liking and higher than placebo for High. As evidenced by scores on the Take Drug Again VAS, the willingness of subjects to insufflate oxycodone HCl 40 mg powder again was much higher than the willingness to take either crushed TARGINIC ER 40/20 mg or placebo. The maximum oxycodone plasma concentration ( $C_{max}$ ) tended to be higher following crushed TARGINIC ER than with oxycodone HCl powder alone, with both having similar short time to  $C_{max}$  of about 1 hour. The efficacy of the abuse deterrent effect to intranasal administration is also demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following intranasal administration of TARGINIC ER compared to the positive

- comparator. Again, these data suggest the effectiveness of the naloxone HCl in the TARGINIC ER formulation in mitigating the subjective reinforcing effects of oxycodone HCl. (See Discussion, Tables 9 and 10)
20. Human abuse potential study ONU1007, using non-dependent, opioid-experienced subjects, demonstrated that in comparison to oxycodone 40 mg oral solution (active comparator), chewed TARGINIC ER 40/20 mg produced similar maximum levels of Drug Liking, High and Take Drug Again. Ingestion of intact TARGINIC ER 40/20 mg produced significantly lower levels of Drug Liking, High, and Take Drug Again that were, however, significantly above placebo. The maximum oxycodone plasma level ( $C_{max}$ ) tended to be similar between chewed TARGINIC ER 40/20 mg and oxycodone 40 mg oral solution with a similar median time of  $C_{max}$  of 1.05 hours. With ingestion of intact TARGINIC ER 40/20 mg, the oxycodone plasma level was a little less than half that of chewed TARGINIC ER 40/20 mg. Treatment with intact or chewed Tradename resulted in only low maximum plasma levels of naloxone, reflecting the very low oral bioavailability ( $\leq 2\%$ ) of naloxone. The high levels of subjective reinforcing effects with chewed TARGINIC ER may be attributed to the low levels of naloxone available to antagonize the effects of oxycodone following oral. The lower but still significant levels of subjective effects following ingestion of intact TARGINIC ER is most likely due to the controlled release properties of the intact formulation for oxycodone HCl. (See Discussion, Tables 12 and 13)
21. Sponsor conducted human abuse potential study ONU1004 to evaluate the subjective effects of chewed TARGINIC ER 30/15 mg and chewed TARGINIC ER 60/30 mg in opioid dependent (methadone maintained) subjects. However, a review conducted by the Office of Biostatistics found that with respect to Drug Liking VAS there were no significant differences between 30 mg or 60 mg oxycodone HCl solution (active comparator) and placebo. As such, the Office of Biostatistics concluded that differences between chewed TARGINIC ER (either dose) and oxycodone HCl oral solution were not meaningful. A statistical analysis was completed regarding withdrawal scores using the "Subjective Opioid Withdrawal Scale" (SOWS). Subjects treated with TARGINIC ER 60/30 mg had a similar maximum SOWS score compared to placebo but significantly high maximum SOWS score compared to oxycodone HCl 60 mg active solution. Only two subjects had a mean maximum SOWS above 10 with the highest being 14, indicating moderate withdrawal.
22. Human abuse potential study ONU1008 demonstrated that opioid dependent, methadone-maintained subjects may be less susceptible to oral abuse, including chewing, of TARGINIC ER tablets. This may be due to the presence of tolerance to subjective effects (less sensitivity) and to experiencing the adverse effects of withdrawal. Intact and chewed TARGINIC ER 60/30 mg tablets produce similar low levels of Drug Liking and High that were similar to placebo, but significantly lower than that produced by the active comparator oxycodone 60 mg oral solution. The Take Drug Again VAS demonstrated a limited willingness of

- subjects to take again oxycodone 60 mg oral solution but a desire not to take again either placebo, intact TARGINIC ER or chewed TARGINIC ER. Data provided by Sponsor showed that chewed TARGINIC ER 60/30 mg and oxycodone 60 mg oral solution produced similar maximum oxycodone plasma levels reached at a median of 1.08 and 2.07 hours, respectively. With intact TARGINIC ER 60/30 mg maximum oxycodone plasma level was a little less than half that of chewed TARGINIC ER and positive comparator with a median time of 3.05 hours. Chewed and intact TARGINIC ER treatments resulted in low levels of naloxone in plasma reflecting the poor bioavailability of naloxone following oral administration. The efficacy of the abuse deterrent effect by oral administration on opioid dependent subjects is further demonstrated by the high percentage of subjects demonstrating a large percentage reduction in Drug Liking following treatment with either intact TARGINIC ER tablet or chewed TARGINIC ER tablet compared to treatment with the positive comparator. (See Discussion, Tables 14 and 15)
23. In human abuse potential study ONU1008, the use of the “Subjective Opioid Withdrawal Scale” (SOWS) (64 point scale) revealed that for all treatments there were opioid dependent (methadone-maintained) subjects who displayed withdrawal, most often mild withdrawal. Treatment with chewed TARGINIC ER produced the maximum SOWS scores that, according to Sponsor, were significantly greater than those observed following treatment with placebo, intact TARGINIC ER, or oxycodone HCl 60 mg oral solution. Individual subject data revealed that of 29 total subjects, 20, 22, 23, and 19 subjects displayed “mild withdrawal” (SOWS scores 1-10) following treatment with intact and chewed TARGINIC ER, oxycodone HCl 60 mg oral solution, and placebo, respectively. Two and 6 subjects displayed severe withdrawal (SOWS score of > 20) following intact and chewed TARGINIC ER, respectively. Three and 2 subjects, following placebo displayed moderate (SOWS score 11-20) and severe withdrawal, respectively.
24. As part of the safety assessment Sponsor provided eight case narrative reports obtained from an international drug safety database (manufacturer’s adverse effects reporting database: ARGUS) documenting severe withdrawal with hospitalization in subjects who attempted to manipulate (crush) and abuse (intravenous or snorting) oxycodone/naloxone (2:1 ratio) product (i.e., Targin) currently marketed in other countries. (See Discussion, Integrated Assessment)

Dr. Tolliver provided the following summary of the findings regarding drug-liking and withdrawal in different abuse populations, at the NDA wrap-up meeting:

**Non-Dependent, Non-Tolerant Recreational Opioid Users Who Attempt to Manipulate TARGINIC ER for Purposes of Abuse (Example: Teenagers from medicine cabinet or from friends)**

- I.V. Crushed or Intact TARGINIC ER – Little or No Drug Liking
- I.N. Crushed TARGINIC ER – Little or No Drug Liking
- Crushed Oral TARGINIC ER – SUBSTANTIAL Drug Liking + Possible Overdose
- Chewed (Crushed) Oral TARGINIC ER – SUBSTANTIAL Drug Liking + Possible Overdose

**Opioid Dependent, Opioid Tolerant Users Who Attempt to Manipulate TARGINIC ER for Purposes of Abuse**

- I.V. Crushed or Intact TARGINIC ER – Likely WITHDRAWAL
- I.N. Crushed TARGINIC ER – Likely WITHDRAWAL
- Crushed Oral TARGINIC ER – Limited if Any Drug Liking, Possible Withdrawal
- Chewed (Crushed) Oral TARGINIC ER – Limited if Any Drug Liking, Possible Withdrawal

In vitro studies indicate potential overdose effects in “opioid-naïve and opioid non-tolerant patients”, who initiated with Tradename, administer orally crushed tablet(s) or tablets by chewing.

Recommendations:

1. Sponsor should be required to carefully monitor for the oral abuse and potential concomitant overdose of crushed TARGINIQ ER tablets particularly among recreational opioid users who may manifest a lack of or low level of physical dependence and opioid tolerance. Due to the very low bioavailability of naloxone and to the compromise of the controlled release mechanism of oxycodone HCl and naloxone HCl upon crushing, crushed (including chewed) TARGINIC ER tablets are expected to produce high levels of subjective reinforcing effects, analogous to immediate release oxycodone formulation, following ingestion. This outcome is supported by the results of human abuse potential study ONU1007 in which non-dependent subjects chewed TARGINIC ER tablets resulting in high levels of Drug Liking.
2. The label should contain clear warnings of possible precipitated withdrawal occurring in individuals who are opioid dependent and purposely attempt to intravenously or intranasally abuse TARGINIC ER tablets after crushing. Withdrawal may also be observed in opioid-dependent subjects who attempt to chew TARGINIC ER tablets.
3. The language proposed by the Sponsor in Section 9.2 of the label regarding “In Vitro Testing” is appropriate and should be included in the label. This language

affirms the results of in vitro testing, namely that although with crushing the controlled release mechanisms are compromised for both oxycodone HCl and naloxone HCl, it is very difficult to use physical and chemical manipulations to separate the naloxone from the oxycodone.

4. The proposed inclusion of language describing human abuse potential studies ONU1003 and ONU1008 should be granted.

I agree with the CSS recommendations that the label should include a description of the drug liking studies for IV and IN abuse, and the drug-liking study for oral chewing/crushing in methadone maintained subjects. However, the summary statement regarding the abuse potential of TARGINIQ ER should not include wording that implies abuse deterrence by the oral route in all situations. I recommend the following language:

The data from the clinical abuse potential studies indicate that TARGINIQ ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration. In the limited setting of opioid-dependent subjects with a history of opioid addiction maintained on methadone, chewed or crushed oral TARGINIQ ER was found to have less drug liking than an oxycodone comparator. However, abuse of TARGINIQ ER by these routes is still possible.

## 9. Labeling

### Division of Medication Error Prevention and Analysis

- DMEPA conducted a proprietary name review, and determined that the proposed name, TARGINIQ ER, is acceptable from a promotional perspective.
- DMEPA also conducted a review of the labels, insert labeling and Medication Guide (MG) for risk of medication errors, and recommendations were conveyed to the Applicant. Please refer to the DMEPA review as well as final labeling for details.

### Office of Prescription Drug Promotion (OPDP)

- OPDP reviewed the TARGINIC ER prescribing information including the PI and the Medication Guide and provided input to ensure that the MG is consistent with the PI, the language and formatting is consistent with ERLA class MGs, and the MG is free of promotional language. Please refer to OPDP reviews and the final labeling for details.

### ERLA language

The TARGINIC ER label must be consistent with ERLA class labeling, and the safety-related changes to the ERLA labels approved April, 2014, that include a revision of indication for this class of drugs to, “the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate,” and the addition of language related to the risk of Neonatal Opioid Withdrawal Syndrome (NOWS) in the Box Warning.

### **Neonatal Opioid Withdrawal Syndrome**

**Prolonged use of TARGINIC ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].**

### **Opioid withdrawal/Maximum daily dose**

The maximum daily recommended dose for TARGINIC ER will be 80/40 mg, based on the pharmacokinetic modeling performed by the clinical pharmacology team, which shows there is a possibility of withdrawal symptoms occurring in patients when TARGINIC ER is used in doses greater than that.

As recommended by CSS, information will be included in Section 9 (DRUG ABUSE AND DEPENDENCE ) of the label regarding the risk of opioid precipitated withdrawal occurring in individuals who are opioid dependent and purposely attempt to intravenously or intranasally abuse TARGINIC ER tablets after crushing. Withdrawal may also be observed in opioid-dependent subjects who attempt to chew TARGINIC ER tablets.

### **Medication Guide**

A Medication Guide is required for all ERLA opioid analgesics, including TARGINIC ER.

## **10. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

I recommend approval of TARGINIC ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

- Risk Benefit Assessment

The Applicant has provided adequate evidence of efficacy and safety of TARGINIC ER for the proposed indication, based on one adequate and well-controlled clinical trial in patients with chronic low back pain, and a safety database that included more than 3,000 exposures. A single efficacy trial was deemed sufficient by the Division based on the Applicant's reliance, in part, on previous findings of efficacy and safety for OxyContin in this 505(b)(2) application. The majority of the safety data were obtained in studies conducted outside the US in support of approval of Targin in the EU for analgesia and opioid induced constipation. However the key Phase 3 study provided for more than 1,000 subjects who received open-label treatment with TARGINIC ER during the initial titration phase, and 299 who received treatment during the double-blind phase of the study.

The maximum total daily dose for TARGINIC ER has been determined as 80/40 mg (40/20 mg every 12 hours), based on pharmacokinetic modeling that showed that daily doses above

this (160/40 mg fed only, and 320/80 mg fed and fasted) result in plasma naloxone levels that may potentially result in opioid withdrawal. Total daily doses above 80/40 mg are not contraindicated, however prescribers must be aware that higher doses, particularly in opioid-tolerant patients, may be associated with the development of opioid withdrawal symptoms.

TARGINIC ER has a safety profile similar to that of the other ERLA opioid analgesics, with the most common adverse reactions occurring in the central nervous system and gastrointestinal tract. The safety data was also reviewed to determine whether the naloxone component results in additional safety concerns for patients with chronic pain who will take product as labeled. Opioid withdrawal syndrome, possibly caused by naloxone, occurred in 4% of subjects treated with TARGINIC ER in the key efficacy study compared to 2% treated with placebo. There was no evidence, however, that the addition of naloxone compromised the analgesic efficacy of TARGINIC ER, nor does there appear to be a cardiac safety signal (assessed because of concerns in DGIEP regarding the cardiac safety of PAMORAs). While it appears that opioid withdrawal symptoms may occur in some patients taking TARGINIC ER as directed, the product can be labeled to recommend monitoring of patients for withdrawal symptoms, and based on the clinical trial experience, this should not preclude approval.

Based on review of the in vitro and in vivo abuse liability studies submitted by the Applicant, TARGINIC ER appears to have abuse deterrent properties that may mitigate abuse by the IV and IN routes, due to the limited ability of several different manipulations of TARGINIC ER to differentially extract and separate naloxone from the oxycodone, and the resultant lack of drug liking when the product is abused by the IN or IV routes. Dr. Tolliver summarized the findings regarding abuse deterrence as follows.

In non-dependent, non-tolerant recreational opioid users who attempt to manipulate TARGINIC ER for purposes of abuse (i.e., teenagers from medicine cabinet or from friends)

- IV Crushed or Intact TARGINIC ER – Little or No Drug Liking
- IN Crushed TARGINIC ER – Little or No Drug Liking
- Crushed or chewed Oral TARGINIC ER – SUBSTANTIAL Drug Liking + Possible Overdose

In opioid-dependent or opioid-tolerant users who attempt to manipulate TARGINIC ER for purposes of abuse

- IV Crushed or Intact TARGINIC ER – likely withdrawal
- IN Crushed TARGINIC ER – likely withdrawal
- Crushed or chewed Oral TARGINIC ER – Limited if Any Drug Liking, Possible Withdrawal

The label will include appropriate language regarding the abuse-deterrent properties of TARGINIC ER including a discussion of the human abuse potential studies that demonstrated the AD effects.

With approval of TARGINIC ER, there will be two extended-release formulations of oxycodone on the market, both with abuse-deterrent properties. OxyContin's properties stem from physicochemical characteristics that make it resistant to crushing, breaking, and dissolution using a variety of tools and solvents. In contrast, TARGINIC ER's abuse-deterrent

properties are due to the addition of naloxone, an opioid antagonist, that is difficult to differentially extract from the drug product, and results in less drug-liking when abused. Abuse liability studies for both products demonstrate a decrease in abusability by the IN and IV routes. It would have been informative had the Applicant conducted studies that compared the abuse liability of the two products, but they did not. However, there is a place for both products on the market. There is no recommended ceiling dose for OxyContin as there is for TARGINIC ER, so that patients who require more than 80 mg of extended-release oxycodone per day will have a treatment option. Also, even when TARGINIC ER is taken as directed, there is some systemic exposure to naloxone. If a prescriber determines that a patient would be better served by a treatment that did not result in naloxone exposure, they may choose OxyContin rather than TARGINIC ER.

Despite TARGINIC ER's abuse-deterrent properties, the ERLA REMS is required for approval, as no abuse-deterrent ERLA opioid, including TARGINIC ER, is without risk of abuse.

In summary, the overall benefits of TARGINIC ER appear to outweigh the risks for use in the intended population, with incorporation of the TARGINIC ER into the ERLA REMS.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

As a member of the ERLA class of opioid analgesics, a REMS is required for this product.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, FDA has determined that a REMS is necessary for TARGINIC ER to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that TARGINIC ER poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of TARGINIC ER. FDA has determined that TARGINIC ER is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use TARGINIC ER. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed TARGINIC ER.

Pursuant to 505-1(f)(1), we have also determined that TARGINIC ER can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate

prescribing, abuse, and misuse that are listed in the labeling. The elements to assure safe use will inform and train healthcare providers about the potential risks and the safe use of TARGINIC ER.

- Recommendation for other Postmarketing Requirements and Commitments

Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of oxycodone hydrochloride/naloxone hydrochloride extended-release tablets in patients from ages 7 to less than 17 years pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

- Final Protocol Submission: December 31, 2014
- Study Completion: December 31, 2018
- Final Report Submission: June 30, 2019

---

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which TARGINIC ER is a member. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

- 2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.
- b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic

pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014  
Study Completion: 01/2018  
Final Report Submission: 06/2018

- 2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014  
Study Completion: 08/2015  
Final Report Submission: 11/2015

- 2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014  
Study Completion: 08/2015  
Final Report Submission: 11/2015

- 2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014  
Study Completion: 08/2015  
Final Report Submission: 11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids, of which TARGINIC ER is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission: 08/2014  
Trial Completion: 08/2016  
Final Report Submission: 02/2017

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial to provide the best information possible.

FDA has determined that, in addition to participation in the PMR studies required of all ER/LA opioid analgesic application holders listed above, you are required to conduct the following individual post-marketing studies of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets.

XXXX-1: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Targiniq ER (Oxycodone hydrochloride and naloxone hydrochloride) extended release tablets actually result in a significant and meaningful decrease in misuse and abuse, and their consequences addiction, overdose, and death in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Targiniq ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013)<sup>[1]</sup>, and proposed study populations and drug comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 7/2015  
Study Completion: 7/2019  
Final Report Submission: 1/2020

---

The following is a nonclinical PMR:

Conduct a combination in vivo micronucleus and comet assay for (b) (4) (b) (4). The comet assay portion of the study should include assessment of both stomach and liver tissue and include doses of the drug substance that would be obtained at the maximum recommended daily dose of the drug product and result in adequate toxicity to ensure assay validity. (b) (4)

---

The following PMR wording is tentative, and under internal discussion at this writing. The goal dates are pending.

In order to obtain additional information regarding cardiovascular safety for TARGINIC ER, you must conduct one or more post-marketing observational cohort studies designed to assess

---

[1]

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>

the relative incidence of serious cardiovascular events among chronic pain patients taking  
TARGINIQ ER

- Recommended Comments to Applicant

These agreements may be conveyed as Postmarketing Commitments (still under discussion):

CMC

1. We remind you of the agreement provided in NDA amendment dated April 30, 2014, to work with drug substance supplier(s) to tighten the proposed acceptance criteria for individual impurities (e.g., (b)(4)) to the ICH Q3A–recommended levels. Submit revised acceptance specifications for drug substances and provide a table listing maximum daily intake for each impurity and total impurities, based on the proposed acceptance criteria and documented maximum daily dose. Include references to the nonclinical qualification studies as needed.
2. We remind you of the agreement provided in NDA amendment dated April 30, 2014, to submit statistical evaluation of the stability data for drug product supporting the proposed acceptance criteria and the requested expiry period. Discuss observed instability trends and provide graphic comparison of impurity profiles for drug product batches manufactured with naloxone HCl obtained from (b)(4) (old process), (b)(4) (new process) and from (b)(4). Clearly identify which batches are the most representative of the to-be-marketed product (the same formulation, manufacturing, container closure and tablet count) and focus your analysis and proposed acceptance criteria on these batches.

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

/s/  
-----

ELLEN W FIELDS  
07/14/2014