Dual Opioid Technology & MoxDuo®

A NON-CONFIDENTIAL OVERVIEW OF DUAL OPIOID TECHNOLOGY AND MOXDUO

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QRx Pharma

Contents

MOXDUO®

FOR IMPROVED MANAGEMENT OF MODERATE TO SEVERE PAIN

Opioids have been the mainstay of treatment of moderate to severe pain for decades. About 250 million prescriptions are written annually in the US alone. Despite a large medical need for effective pain relief in the absence of clinically important adverse side effects, few drugs with new mechanisms of action have come to market for use in this segment of the pain market and none have supplanted the use of opioids based on improved efficacy or improved tolerability with comparable efficacy.

The 75 year search for a product having opioid efficacy without the typically associated adverse events has been compared with that for the "Holy Grail."[1] These commonly occurring adverse events, including nausea, vomiting, dizziness, sedation, and constipation, have been estimated to occur in "tens of millions" of Americans every year.[2] Incremental costs to the health care system for GI events alone are estimated to range from $4,880 to $36,152 per patient.[3] Risk of respiratory impairment is the most medically serious opioid related side effect at therapeutic doses and is the main cause of overdose related deaths. In a published letter to the journal *Anesthesiology* in 2010, one expert professed that postoperative respiratory failure is the third most common patient safety-related adverse event affecting the Medicare population in the US hospitals. The incidence was noted as 113 events per 1,000 at-risk patient admissions and 50% of postoperative respiratory failure events involved patients receiving opioid analgesia. Death or anoxic brain injury was the result in a significant proportion of cases.[4]

Across the MoxDuo clinical program, MoxDuo has shown an appreciably lower incidence of experiencing nausea, vomiting, dizziness, somnolence and pruritus compared to patients receiving equi-analgesic doses of morphine or oxycodone. The likelihood of experiencing one of these side effects with morphine or oxycodone is 1.1 to 2.0 times greater than with MoxDuo. Furthermore, patients over the age of 60 years were 7-8 times less likely to have a potentially life threatening oxygen desaturation event when treated with MoxDuo than those treated with morphine or oxycodone. To the best of our knowledge, MoxDuo IR is the first opioid product to demonstrate a lower risk of respiratory depression in a clinical study comparing morphine equivalent (equi-analgesic) doses. These important benefits provide the potential for significant healthcare cost reductions in the treatment of patients receiving opioid therapy and is a significant step toward achieving the Holy Grail of opioid therapy.

Dual Opioid® technology

While combination analgesic products, such as an NSAID plus an opioid (e.g. Vicodin® or Percocet®) are widely used, at present there are no combination products available commercially anywhere in the world containing two opioids. Dual Opioid® technology refers to the use of two opioids that bind to different opioid receptor subtypes, thus providing improved efficacy and/or fewer side effects.

Whilst QRxPharma holds proprietary patent positions on Dual Opioid products, independent researchers have carried out clinical studies co-administering marketed forms of morphine and oxycodone. The results of these studies support the MoxDuo product concept of excellent pain relief with substantially reduced side effects.

Table 1: Non-QRxPharma studies conducted using Dual Opioid technology

Reference	Summary
Blumenthal, S et al (2007) Postoperative intravenous morphine consumption, pain scores, and side effects with perioperative oral controlled-release oxycodone after lumbar discectomy. *Anesth Analg,* 105: 233-237.	Blumenthal et al evaluated the co-administration of PCA morphine plus oral oxycodone (CR) vs. PCA morphine plus oral placebo in 40 lumbar discectomy patients for 2 days post-surgery. They found improved analgesic control ($p<0.05$) and reduced nausea/vomiting, as well as a significant shortening of the time to the first bowel movement ($p<005$) in patients receiving Dual Opioid treatment than occurred in PCA morphine treated patients.
Catala, E et al (2008) Patient affected by cancer pain treated with combined opioids. *Advances in Pain Management,* 2(2): 76-78.	This is a case report of the beneficial effects of combining more than one opioid in the clinical situation where severe chronic pain cannot be managed adequately by conventional opioid monotherapy.
Grach, M et al (2004) Can coadministration of oxycodone and morphine produce analgesic synergy in humans? An experimental cold pain study. *Br J Clin Pharmacol*, 58(3): 235-242.	Grach et al evaluated in a double-blind manner the analgesic effects of single doses of the combination of morphine plus oxycodone vs. its components in a cross over study in normal volunteers who experienced experimental pain induced by immersion of an arm in ice water. The results showed additive but not synergistic analgesic effects in this experimental pain model.
Ladd, L.A et al (2005). Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under hypercapnic and hypoxaemic conditions. *Br J Clin Pharmacol*, 59: 524-35.	Ladd et al evaluated the respiratory safety of various ratios of morphine to oxycodone (all dosed iv) in a sophisticated crossover study using normal volunteers in whom respiratory gasses and respiration rates were monitored. The combination of morphine plus oxycodone had effects on respiratory function comparable to that of morphine.

Lauretti, G.R et al (2003). Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. *Br J Cancer*, 89, 2027-30.	Lauretti et al compared the amount of opioid used and side effect incidence in a double-blind crossover in 22 cancer patients with moderate to severe pain when receiving monotherapy with either CR formulations of morphine or oxycodone. Rescue medication consisted of oral doses of IR morphine. In the oxycodone CR group, the amount of IR morphine rescue was reduced by 30-40% compared to the IR morphine rescue consumed by patients receiving CR morphine, suggesting there was synergy when the Dual Opioid combination was used. Dual Opioid treatment was also accompanied by marked reductions in nausea and vomiting compared to morphine CR plus morphine IR rescue.
Mercadante, S et al (2004) Addition of a second opioid may improve opioid response in cancer pain: Preliminary data. *Supportive Care Cancer,* 12: 762-766.	Mercadante et al conducted a multi-week open label study in 14 cancer patients with poor pain control. They evaluated various combinations of mu agonist opioids in patients receiving monotherapy with fentanyl transdermal or methadone. Results showed that addition of graded amounts of oral morphine markedly diminished pain and reduced the need for further dose increases without any appreciable increase in opioid related adverse events. These results illustrate that the beneficial effects of combining opioids is not restricted to morphine plus oxycodone.
Smith, M.T. et al (2005) Co-administration of oxycodone and morphine analgesic synergy re-examined. *Br J Clin Pharmacol*, 59:4 486-488.	This short article, written in response to the Grach et al paper, highlights methodological and design problems that might account for the failure to observe analgesic synergy in the Grach et al study.
Smith MT (2008) Differences between and combinations of opioids re-visited. *Current Opinion in Anaesthesiology*, 21: pp?	This article reviews recent studies addressing between-opioid differences in clinical trial and animal study outcomes as well as differences in opioid receptor interactions. It provides evidence to support the notion that morphine and oxycodone produce their effects by activating different opioid receptor populations.

The MoxDuo pipeline

The MoxDuo pipeline is based on Dual Opioid® technology - the concurrent use of two opioids that bind to different opioid receptor subtypes and which provide improved efficacy and/or fewer side effects than existing opioid drugs. QRxPharma is developing three proprietary Dual Opioid formulations of fixed ratios of morphine and oxycodone:

- MoxDuo IR – an immediate release oral formulation for moderate to severe acute pain (3:2 morphine to oxycodone by weight)
- MoxDuo IV – an intravenous formulation for moderate to severe acute pain (1:1 ratio)

  [Because orally administered morphine and oxycodone have substantially different levels of bioavailability, whereas IV dosing results in 100% bioavailability for each opioid, it is appropriate to adjust the morphine to oxycodone ratio for IV dosing.]

- MoxDuo CR – a controlled release oral formulation for moderate to severe chronic pain (3:2 ratio). The product contains a proprietary abuse deterrent component that is at least as effective as that of the recently reformulated Oxycontin.

Stage of development:

- MoxDuo IR – NDA filed August 2011, Complete Response Letter received 25 June 2012
- MoxDuo IV – Proof-of-concept clinical trial completed
- MoxDuo CR – Phase 1 clinical trials completed, phase 2 trials are ready to be initiated

The following sections regarding published literature on Dual Opioid therapy mechanism of action, the concept of morphine equivalent doses and intellectual property are relevant to all three presentations of MoxDuo.

MoxDuo mechanism of action

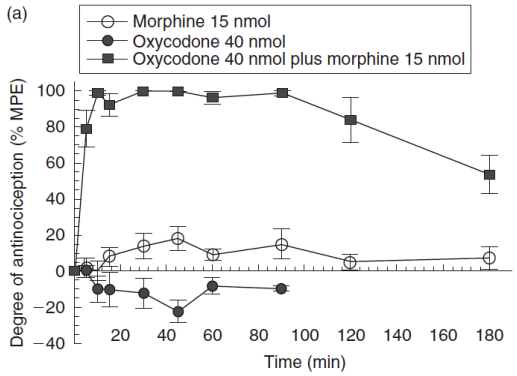
Opioid receptors

It is well recognised that there are at least 3 classes of opioid receptors, mu, kappa and delta, each with receptor sub-types. Most opioid drugs have a unique pattern of binding to specific opioid receptor classes and sub-receptors within each class. For example, morphine and fentanyl are classic mu agonists, while e.g., nalbuphine and pentazocine, are relatively selective kappa agonists. Buprenorphine, a well known drug is a partial mu agonist and a kappa antagonist. Within the mu receptor class, molecular biology studies in humans have shown DNA segments that code for over seven unique receptor subtypes, with different patients showing differential proportions of mu receptor sub-types and with various mu agonists also showing differential potencies at these subtypes. The key point is that the remarkable array of opioid receptor subtypes and the receptor-receptor interactions that occur at a molecular level likely give rise to novel pharmacological profiles (such as decreased adverse events) when different opioid agents are dosed concurrently, affects not achievable by dosing one agent at a time. Examples of the unique pharmacological properties that can occur when more than one opioid is given concurrently are:

Antagonism of opioid side effects: Ross *et al*[5] reported in the rat that co-administration of morphine of morphine plus oxycodone at ED50 doses of each resulted in marked diminution of sedation and an absence of locomotor behavioural inactivity. When a kappa agonist and a mu agonist were given concurrently, Dosaka-Akita *et al*[6] reported antagonism of respiratory depression. Pan[7] has reviewed a large series of preclinical studies in which kappa and mu agonists given concurrently antagonize the pharmacological actions of each agent. The pharmacology studies of the M. Smith group have emphasised the role of the kappa-2 receptor in the antagonism of the CNS side effects of mu agonists[5].

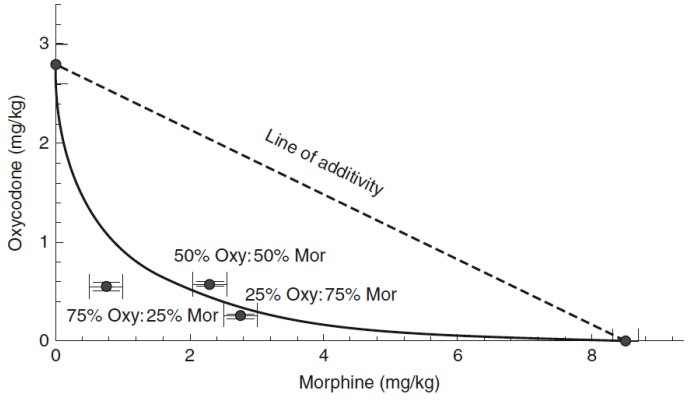
Potentiation of analgesic action: Ross *et al*[5] demonstrated in a series of oral, parenteral and intracerebroventricular isobologram studies in rats that oxycodone and morphine in a dose-responsive manner, resulted in marked potentiation of analgesic response to acute pain. Similar observations were reported by Bolan *et al*[8] with several other opioid combinations given to mice, including methadone plus oxycodone and methadone plus codeine. This suggests that opioid-opioid analgesia potentiation is probably a common occurrence across many opioids. The concept of potentiation of analgesic effects by concurrent dosing of morphine plus oxycodone is further supported by QRxPharma rat data (Fig. 1) and isobologram analyses (Fig. 2) in which it was demonstrated that morphine: oxycodone when dosed in ratios of 3:1, 1:1 or 1:3 produced marked analgesic synergy in response to painful stimuli in rodent models.

Figure 1: Analgesic Synergy by Combined Administration of Morphine and Oxycodone



Degree of antinociception expressed as the % of maximum possible effect versus time following ICV administration of oxycodone 40 nmol, morphine 15 nmol and the coadministration of the two drugs.

Figure 2: Isobolographic Analysis of Opioid Synergy in Rats



The isobologram was generated from the ED_{50} doses determined from the dose response curves. The isobole bows well below the line of additivity, indicating a synergistic interaction between oxycodone and morphine (2).

Incomplete cross tolerance: Opioid tolerance and withdrawal symptoms can be readily induced in rodents by repeated dosing over several days to two weeks. Upon abrupt discontinuation of dosing, withdrawal effects (such as shaking, hyper-reactivity to sound, light avoidance, irritability) are fully reversed when the initial opioid to which tolerance was induced is re-administered. Similarly, in monkeys, doses of morphine or methadone (mu agonists) needed to maintain avoidance of painful stimuli are markedly increased during sub-chronic administration (four weeks) but administration of other opioids to morphine tolerant monkeys, such as kappa agonists (U50,488 or bremacozine) gave a normal analgesic dose-response curve to these kappa acting agents[9].

Pain models: With respect to differing analgesic properties, in certain types of pain, such as diabetic neuropathic pain in rats, oxycodone is effective in producing dose-dependent analgesia, whereas morphine has little effect[10]. These results demonstrate that the receptor binding profiles of drugs such as morphine and oxycodone have important differences and that these differences have pharmacological consequences.

Opioid rotation; clinical relevance: It has been observed clinically that switching from one opioid, which has failed to control pain or caused intolerable side-effects, to an alternative opioid, can result in improved tolerability, or pain control, or both. Opioid rotation, or more accurately opioid switching, is the term given to the clinical practice of substituting one strong opioid with another (e.g. morphine with oxycodone) in an attempt to achieve a better balance between analgesia and side effects. Thus, the widespread clinical use of opioid rotation,[11] in which patients with chronic pain are switched from one opioid to another when the first ceases to provide sufficient analgesia following a period of analgesic efficacy, further reinforces the functional clinical differences among opioids that are likely mediated by different opioid-specific receptor interactions.

Conclusions

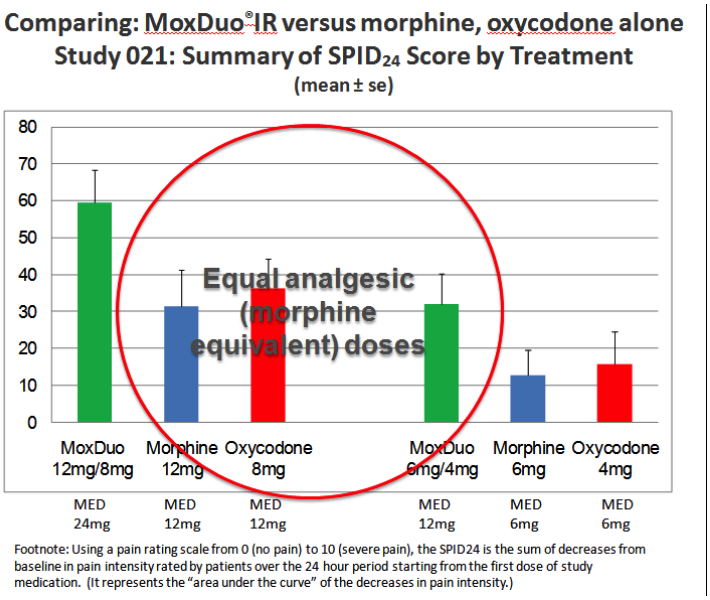
The overall conclusion from these and other studies is that all opioids are not the same, e.g., they often have important biological differences that may be the results of different opioid receptor binding patterns. Thus, it is entirely reasonable that clinical studies of the combination of morphine plus oxycodone could produce clinically important changes in the intensity of side effects, in the development of tolerance and possibly in analgesic action. The data from MoxDuo clinical studies and studies from independent research summarized below report a consistent pattern of diminished intensity of adverse events, especially CNS related events of sedation, dizziness, nausea and emesis. Some studies also report the possibility of increased analgesic action. While at present it is not possible to delineate the precise underlying receptor level changes responsible for these novel clinical properties of the combination, it is clear that the diversity of opioid receptors and the complex allosteric interactions that can occur between different receptor subtypes when agonists of each are given, allows for the emergence of beneficial pharmacological properties from the co-administration of morphine plus oxycodone. In fact, even if morphine alone and oxycodone alone are considered to be pure mu agonists, the large number of mu receptor sub-types makes it likely that co-administration of these two opioids will achieve a broader array of sub-receptor occupancy than either agent given alone.

The concept of "morphine equivalent doses"

The term "morphine equivalent dose" [MED] describes the dose of an opioid other than morphine (e.g. oxycodone, MoxDuo) that will produce equi-analgesic efficacy to a stated dose of morphine.

The literature on opioid conversion is vague and based on clinical observation. For example, Anderson et al (2001)[12] describe a morphine: oxycodone ratio of 2:1 to 1:1. Ten years later, there is no further support in the literature that is not anecdotal. Patanwala et al (2007)[13] attempted a systematic evaluation of opioid conversions in acute care in an analysis that included textbooks, national guidelines and review articles. They concluded that equi-analgesic dose ratios and calculation of dose ratios for opioids based solely on conversion tables is an oversimplification and must take into account patient and institution specific factors.

In calculating the morphine equivalent and oxycodone equivalent doses of MoxDuo we have used a morphine:oxycodone ratio of 1.5:1 – a mid-point based on the various ratios in the literature. QRxPharma Study 021 (described later in this document) compared the dose of MoxDuo 6mg/4mg vs morphine 12 mg and oxycodone 8 mg, which based on the 1.5:1 ratio were expected to be equi-analgesic doses. Similarly, Study 022 that compared 12 mg/8 mg of MoxDuo to 24 mg of morphine and to 16 mg of oxycodone (n~125 per group) also demonstrated comparable analgesic effects in post-surgical patients with moderate to severe pain (see Fig. 10). The results of these clinical studies did in fact support the 1.5:1 conversion ratio for equi-analgesic doses. Because there is no literature based "gold standard ratio", the best data in this case is empiric.



We therefore conclude that our data and the literature support the 1.5:1 conversion ratio of morphine: oxycodone.

This concept is important in understanding MoxDuo clinical data where MoxDuo produces the same level of pain relief as a comparator treatment, such as morphine alone or oxycodone alone, with a substantially improved side effect profile for MoxDuo given at equi-analgesic doses to that of morphine or oxycodone.

Intellectual property

Intellectual property protection covering the MoxDuo portfolio consists of the originally issued patent on Dual Opioid technology – the "Smith patent" and a substantial suite of other US applications and provisional filings that are anticipated to provide patent protection for MoxDuo to 2029.

The title of the Smith patent is "Production of Analgesic Synergy by Co-Administration of Sub-Analgesic Doses of a Mu Opioid Agonist and a Kappa-2 Opioid Agonist". It is granted in many jurisdictions.

Table 2 – The Smith Patent

Application Type	Country	Serial Number	File Date	Publication Number
Issued	US	08/921,187	08/29/1997	6,310,072
Issued	Austria	996933277	10/21/1996	292,982
Issued	Australia	1996-72076	10/21/1996	AU 706,691
Issued	Canada	2,235,375	10/21/1996	2,235,375
Issued	China	96199071	10/21/1996	1,104,910
Issued	Denmark	996933277	10/21/1996	EP 871,488 DK 871,488
Issued	EPO	996933277	10/21/1996	EP 871,488
Issued	Germany	996933277	10/21/1996	EP 871,488 DE 69634609
Issued	Spain	996933277	10/21/1996	EP 871,488 ES 2,241,003
Issued	New Zealand	319,531	10/21/1996	319,531
Issued	South Africa	1996-8808	10/19/1996	9,608,808
Allowed	Japan			

The "dosing algorithm patent" (granted US patent 728, 677) is entitled "Methods of converting a patient's treatment regimen from intravenous administration of an opioid to oral co-administration of morphine and oxycodone using a dosing algorithm to provide analgesia". The patent provides a dosing algorithm for converting patients from IV morphine to oral MoxDuo, thus identifying an optimal starting dose of MoxDuo following varying amounts of IV morphine given after surgery. This evidence based dosing algorithm has been included in the MoxDuo IR proposed label, providing important safety information that will guide doctors away from starting patients on doses of MoxDuo IR that are lower or higher than what is likely to be needed. Listing of the patent in the Orange Book (US) will provide exclusivity to 2029.

The "3:2 ratio patent" (granted US patent 8,182,837) is entitled "Method comprising administering sub-analgesic dose of morphine salt and oxycodone salt in a 1:0.66 ratio" and specifically covers the ratio of morphine to oxycodone in the oral MoxDuo formulations. This patent is granted in the US and is under prosecution in Europe, has an expiry date of 2023.

The MoxDuo portfolio is expected to benefit from 10 years data exclusivity in Europe.

MoxDuo CR incorporates proprietary controlled release and ADF (abuse deterrent formulation) features that are the subject of additional patent applications. Further information is available under a non-disclosure agreement.

MOXDUO®IR

AN IMMEDIATE RELEASE ORAL FORMULATION FOR THE MANAGEMENT OF MODERATE TO SEVERE ACUTE PAIN

Product profile

Dual Opioid technology delivers greater tolerability than conventional opioid analgesics, increasing the therapeutic window and enabling physicians to better titrate the dose required for effectiveness in moderate-severe pain. MoxDuo IR has been developed as first line opioid therapy for patients with moderate to severe acute pain. The MoxDuo IR clinical program supports the following product profile:

- Label indication for the relief of moderate to severe acute pain
- Immediate release formulation of morphine and oxycodone in a fixed 3:2 ratio in capsules of the following strengths: 3 mg/2 mg, 6 mg/4 mg, 9 mg/ 6 mg and 12 mg/8 mg. These strengths provide for careful dose titration and the 3 mg/2mg strength is often much less than the lowest available strength of morphine (country specific differences).
- Four to six hourly dosing with adequate pain control throughout each dosing period
- A substantial reduction in the likelihood of experiencing severe oxygen desaturation events compared to morphine or oxycodone*
- Substantial reduction in risk (often by greater than 50%) in the occurrence of clinically significant opioid-related side effects such as nausea, emesis, dizziness, somnolence, pruritus and respiratory depression compared to equivalent pain-relieving doses of the standards of care - morphine and oxycodone*

*The degree to which these findings from the MoxDuo clinical program can be shown in the product label is a matter for negotiation with the regulatory authority in each territory.

Under the following sections we overview the preclinical and clinical studies that have been completed or are planned in support of the above target profile.

Pre-clinical

At a 2008 End of Phase 2 Meeting and the 2011 preNDA Meeting with the US FDA, the Agency agreed that in view of the safety pharmacology and short term toxicology studies of morphine plus oxycodone performed by QRxPharma and prior single entity toxicology studies conducted by others, all animal safety testing needed for the MoxDuo IR NDA purposes had been completed. The GLP studies conducted by QRxPharma included single dose CNS, GI and respiratory safety pharmacology studies in rodents, a CV safety pharmacology study in dogs and 2 week and 13 week repeat dose toxicology studies in rodents. Each of these studies contained high dose morphine and oxycodone control groups. Results showed the toxicity profile of MoxDuo IR to be highly similar to that of the individual opioid control groups.

Pharmacokinetics

Studies in rodents and humans show that concurrent dosing of morphine sulfate and oxycodone HCl in a ratio of 3:2 had no effect on the kinetics of either opioid. The half-lives of each opioid in humans are similar, thus supporting the co-administration of each at the same dosing interval.

Four Phase 1 pharmacokinetic (PK) studies in normal volunteers were performed: studies 005, 006, 013 and 017. Studies 005 and 006 used a formulation that is slightly different from the final formulation employed in all subsequent studies and the to be marketed MoxDuo IR product. At the End of Phase 2 Meeting with the FDA, the Agency accepted the relevance for the NDA of the food effects study (Study 005) and did not ask for it to be repeated. However, QRxPharma elected to repeat the original dose proportionality study (Study 006) using the lowest and highest final dosage strengths of 3 mg/2 mg and 12 mg/8 mg (Study 013). These normal volunteer studies also co-administered oral naltrexone, an opioid receptor blocker, to enable therapeutically relevant doses of MoxDuo to be given. Thus, the low side effect profile seen in these studies is not indicative of what would be observed in patients who do not receive an opioid blocker. Additionally, a population PK statistical model was created and plasma level drug analyses were conducted using sparse sampling (3 time points per patient) in the Phase 3 bunionectomy pain study 007 in order to evaluate potential pharmacokinetic/pharmacodynamic (PK/PD) relationships to analgesic efficacy.

The results of these four phase 1 studies showed the following:

- the kinetics of morphine and oxycodone from the MoxDuo IR formulation were well behaved
- dose proportionately of AUC and Cmax over the lowest to highest capsule strengths (3 mg/2 mg vs. 12 mg/8 mg)
- repeat dose kinetics are predicted from single dose data
- a food effect in which about 15% higher AUC and a 20% diminished Cmax occurs when MoxDuo is ingested following a high fat meal. This food effect is well

established for single entity opioids and is of a sufficiently modest magnitude so as to not appear in product labeling

- when compared to the reference standards (NDA approved IR formulations of morphine and of oxycodone), plasma levels of oxycodone and of the morphine metabolites, M3G, M6G) were bioequivalent to MoxDuo. However, morphine Cmax values after MoxDuo were slightly above the limits for bioequivalence to marketed morphine. This finding is acceptable for a NDA filing since there is no requirement that MoxDuo be bioequivalent to its component doses.

The population PK/PD relationships seen in Study 007 indicate that patients with a plasma ratio of morphine to oxycodone that is less than 0.33 have an appreciably superior ($p<0.001$) analgesic response than patients with higher ratios (proportionally higher levels of morphine to oxycodone) in a bunionectomy pain model. Also, not surprisingly, higher plasma drug levels were significantly associated with an improved therapeutic effect.

Clinical

Four Phase 2 studies and four Phase 3 double-blind studies have been conducted either with MoxDuo IR or with co-administered marketed oral solutions of morphine and of oxycodone. The first two Phase 2 trials were crossover studies conducted in Australia in which co-administration of ratios of 3:2 and 1:2 morphine: oxycodone were given for up to 1 week per arm to ~45 patients with chronic pain with oral morphine as an active comparator. There was a 34-40% decrease in the amount of combination morphine plus oxycodone needed to achieve an equi-analgesic dose (measured using morphine equivalents) compared to morphine. This was accompanied by decreased rates of drowsiness, dizziness, constipation and nausea in the combination treatment group relative to morphine therapy.

Combination Rule Pilot Study (Phase 2) – Study 021

The purpose of Study 021, performed in bunionectomy patients, was to prepare for the successful conduct of the Phase 3 Combination Rule trial in which QRxPharma is required by the FDA to show that MoxDuo IR at a given dose is superior to its mg components. This study had 3 objectives:

- to provide an estimate of the analgesic effect size and treatment variance, providing a basis for the sample size determination for the Phase 3 Combination Rule study

- to determine which dose level of MoxDuo (6 mg/4 mg or 12 mg/8 mg) should be used in the Combination Rule study

- to provide the first fixed morphine equivalent dose (MED) comparisons of the efficacy and tolerability MoxDuo vs. its equi-analgesic components—MoxDuo 6 mg/4 mg vs. morphine (12 mg) and vs oxycodone (8 mg).

This was a double-blind, randomized, multicenter, 48 hr treatment duration, bunionectomy study using the same procedures and endpoints described below for study 007. However, $SPID_{24}$ was defined as the primary endpoint and $SPID_{48}$ was a secondary endpoint. Also, in this trial ibuprofen rescue medication was 400 mg and was limited to a total dose of 3200 mg per 24 hours. The fixed dose treatment arms (q6h) were MoxDuo IR 12mg/8mg, MoxDuo IR 6mg/4mg, morphine 12mg, morphine 6mg, oxycodone 8mg and oxycodone 4mg. A total of 197 (approximately 30-35 per group) patients were enrolled in this trial that was conducted at 6 centers in the U.S.

Although this study was not powered to detect significant efficacy differences between treatments, MoxDuo IR at the 12mg/8mg dose was statistically superior to its components (12 mg morphine and 8 mg oxycodone) on the primary endpoint of $SPID_{24}$ (area under the curve of the changes in pain from baseline for the 24 hr period following the first dose of study medication). The MoxDuo IR 6mg/4mg group showed strong trends in favor of MoxDuo IR vs. its components. In respect to safety, there were two serious adverse events (SAEs) in the study (infection, worsening of pain leading to hospitalization)—both occurred in the low dose morphine and low dose oxycodone monotherapy arms.

When comparing equi-analgesic doses, the 6mg/4mg MoxDuo IR treatment group (which is the **morphine equivalent** dose of 12 mg morphine and of 8 mg oxycodone) had 50-75% decreases in rates of clinically significant (i.e. moderate-severe) nausea, vomiting and dizziness in the MoxDuo IR patients compared to the monotherapy patients. Fig. 3 below shows the efficacy results from Study 021 while Fig. 4 shows the safety results.

Figure 3: Summary of $SPID_{24}$ Score by Treatment (mean ± se)

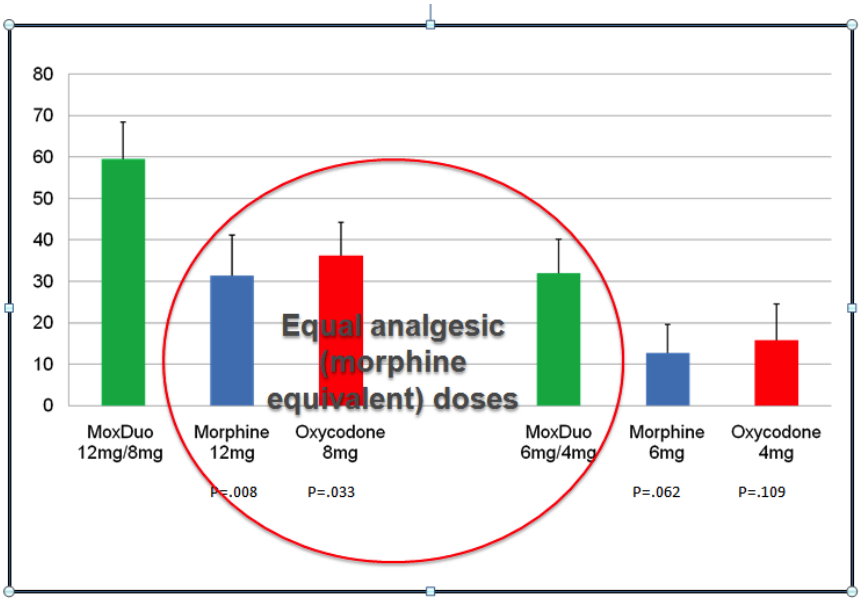
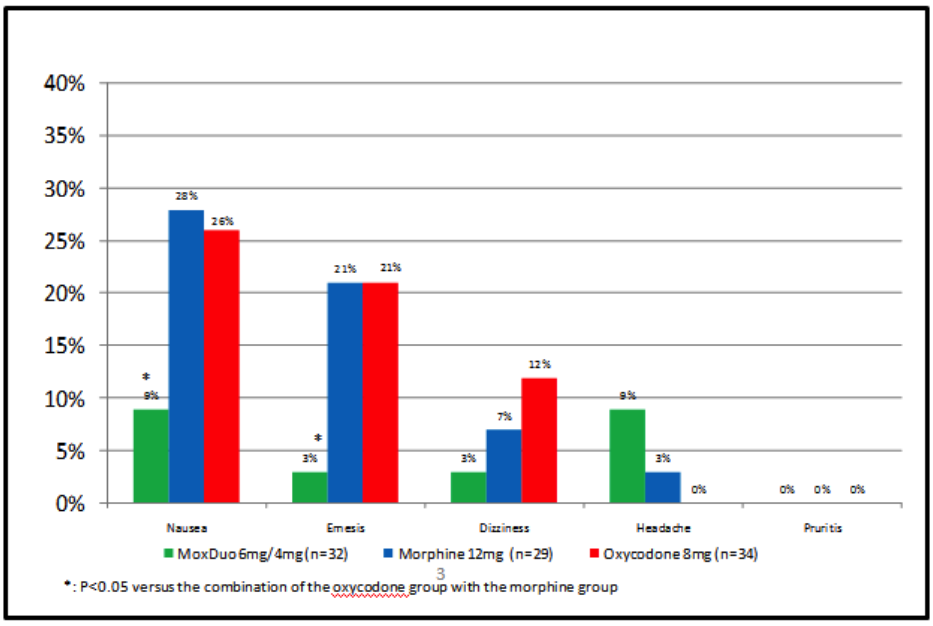


Figure 4: Moderate to Severe Adverse Events Commonly Associated with Opioids Observed in Study 021 (% patients)



The observation that MoxDuo IR treatment appreciably lowered the rates of occurrence of the most common types of opioid AEs relative to an equi-analgesic morphine equivalent dose is consistent with the reduced dropout rate for MoxDuo. MoxDuo IR 6mg/4mg had a 3% dropout rate (all causes) from the study compared to 7% and 12% for the 12 mg morphine and 8 mg oxycodone groups, respectively. Thus, from the perspective of a therapeutic ratio, MoxDuo IR 6mg/4mg is superior to its morphine equivalent/equi-analgesic doses of morphine 12mg and oxycodone 8mg.

Total Knee Replacement Pilot / Comparison to Percocet® – Study 020

Based on the End of Phase 2 meeting with the FDA, it was agreed that one of the pivotal Phase 3 trials would be a double-blind comparison of MoxDuo flexible dosing to an active control group in patients with moderate-severe pain following total knee replacement surgery. A placebo control was deemed to be inappropriate by QRxPharma since the drop-out rate would be too high, even with ibuprofen or acetaminophen rescue medication. Study 020, a Phase 2 total knee replacement study was performed to evaluate two alternative control groups for the MoxDuo flexible regimen: either a fixed low dose MoxDuo IR (3 mg/2 mg per dose) or Percocet® (1-2 tablets of 325 mg acetaminophen/5 mg oxycodone). Since there is a wide variety in patient requirement for opioids, the standard dose regimen for MoxDuo was planned as a flexible dose regimen of MoxDuo IR in which doses of ranging from 6 mg/4 mg to 24 mg/18 mg per dose, depending on patient need, would be administered q4-6h. Additionally, the study evaluated a proprietary dosing algorithm for converting the dose of IV PCA morphine given immediately after surgery (prior to randomization to a dose of MoxDuo IR) to an oral dose of MoxDuo.

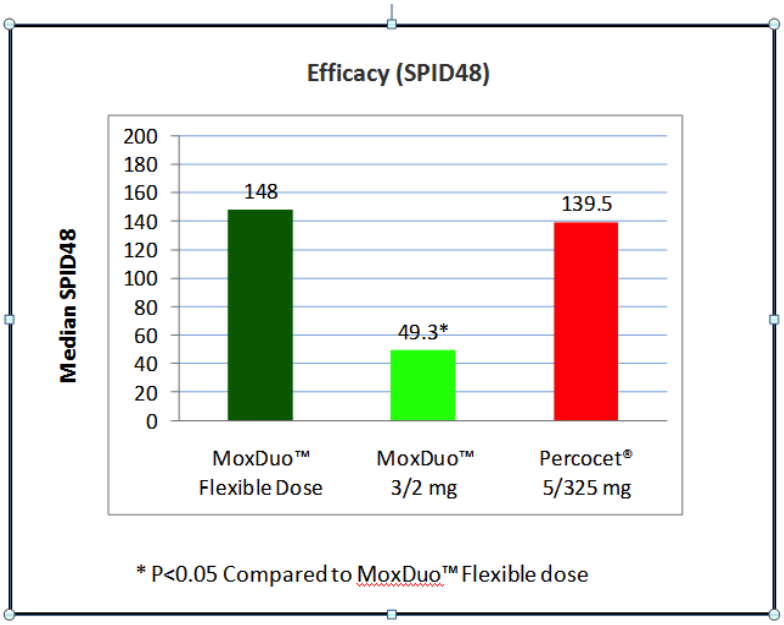
This was a randomized, parallel treatment, open label comparison of flexible dose MoxDuo IR vs

fixed low dose of MoxDuo IR and vs a flexible dose of Percocet in 5 US sites.

Following knee replacement surgery, patients received PCA morphine for 12-24 hrs. PCA dosing was discontinued and when the pain became moderate to severe (NPRS of at least 4), patients were randomized to the three open label treatment arms (n=14-15 per group). The three treatment groups were dosed for up to 48 hrs, during which pain intensity ($SPID_{48}$ is the primary endpoint) and pain relief measures, as well as the Brief Pain Inventory, safety parameters (AEs, SpO_2, etc) and exploratory efficacy measures were taken.

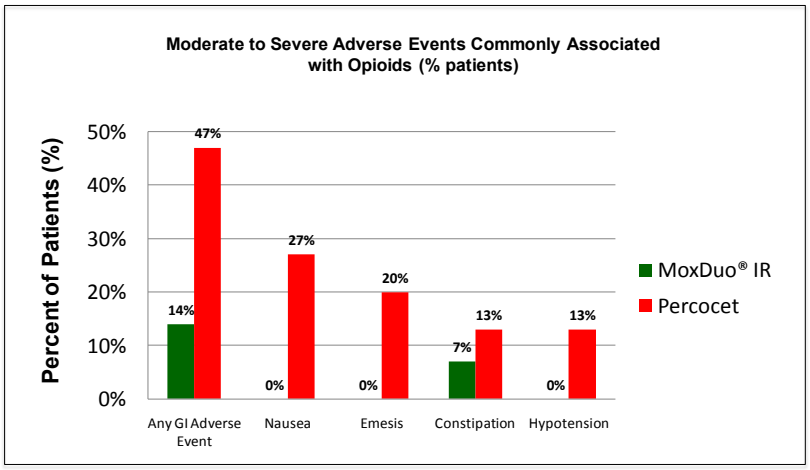
The histogram of median $SPID_{48}$ scores for each treatment arm is given in Fig. 5. It shows that MoxDuo IR flexible dose and Percocet (flexible dose, 1-2 tablets of 5 m5/325 mg) were comparable in analgesic efficacy for the level of pain present in this study. (As an aside, due to safety concerns the 2 tablets of Percocet received by many subjects in the Percocet group will be withdrawn from product labeling according to a 2011 announcement by the FDA.) MoxDuo IR fixed low dose was significantly inferior to MoxDuo IR flexible suggesting that the MoxDuo 3 mg/2 mg would be a good comparator dose for the pivotal efficacy study. About two thirds of the low dose control group was able to complete the 48 hr dosing period, making it a valid control treatment for Phase 3.

Figure 5: $SPID_{48}$ scores for MoxDuo® IR Flexible and Fixed Low Doses vs Percocet



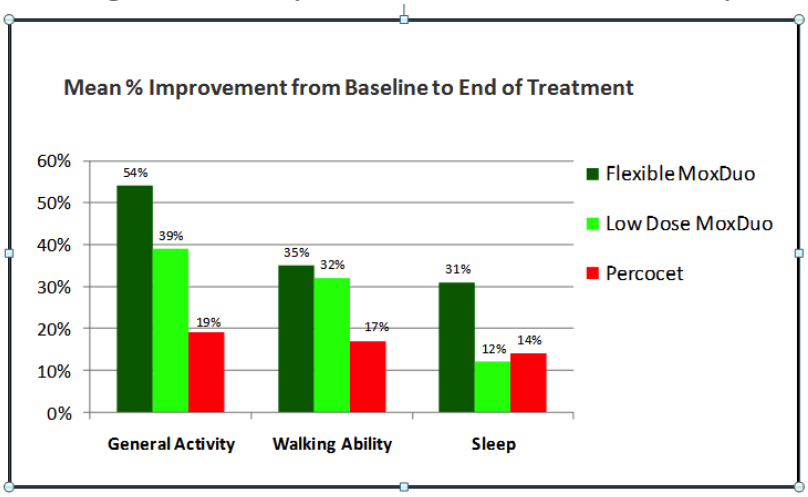
When the equi-analgesic doses of MoxDuo IR and Percocet were compared, interesting differences emerged in side effects and patient self-ratings. Moderate to severe nausea and emesis was appreciably less frequent (0%) in the MoxDuo IR flexible arm relative to the 20-27% incidence in the Percocet arm. Almost 50% of Percocet treated patients reported a moderate to severe gastrointestinal AE compared to 14% in the MoxDuo IR flexible dose patients (Fig. 6).

Figure 6: Comparison of Adverse Events with Equi-analgesic doses of MoxDuo and Percocet®



Relevant measures from the Brief Pain Inventory are shown in Fig. 7. The MoxDuo IR flexible dose group and in some instances the MoxDuo IR low dose group showed greater improvements from baseline (just prior to the start of oral dosing) to the end of dosing than the Percocet treated patients in respect to patient self-ratings of general activity, walking ability and sleep. The improved sleep ratings were not the result of an overall increase in drowsiness since daytime adverse reactions of drowsiness were quite low and were comparable to that of the Percocet group. It is likely that these improvements relative to those receiving Percocet are related to enhanced analgesic action in the MoxDuo IR treated patients.

Figure 7: Study 020 – Brief Pain Inventory



Phase 3 Dose-Response Acute Pain Study – Study 007

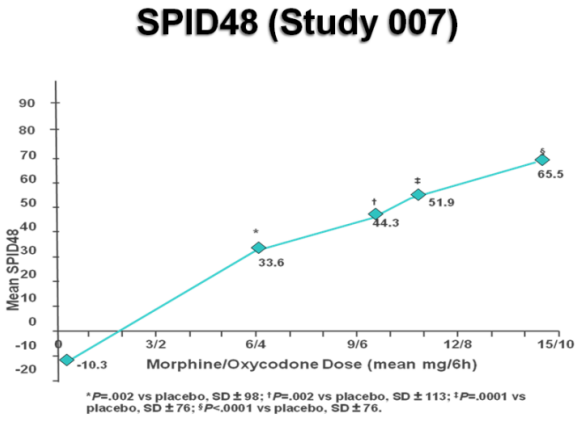
The purpose of Study 007, a double-blind randomized, placebo-controlled ascending dose post-bunionectomy study was to demonstrate in patients with moderate to severe post-surgical pain, the

dose-dependent analgesic effects and safety profile of MoxDuo IR and to determine the preferred dosing frequency for four dose strengths for use in subsequent trials. This study was the first trial conducted under the US IND.

The individual ascending cohorts (approximately 50 active drug patients and 13 placebo per cohort) (n=256) received MoxDuo IR doses of 3 mg/2 mg, 6 mg/4 mg, 12 mg/8 mg and 18 mg/12 mg, respectively. Dosing intervals were flexible, but could not be less than 1-2 hrs, depending on dose. Rescue medication of 600 mg ibuprofen was provided. The withdrawal rate due to lack of efficacy was 25% of placebo patients vs. 4-13% for MoxDuo IR ($p<05$). Dropout rates in MoxDuo IR groups due to adverse events ranged from 2-14% vs. 2% for placebo. The average dose received per 6 hrs for the four cohorts of MoxDuo IR ranged from 6 mg/4 mg to 15 mg/10 mg. Ibuprofen rescue medication use was significantly higher in the placebo group than in the MoxDuo IR treated patients.

The primary efficacy endpoint was the $SPID_{48}$ (sum of pain intensity differences from baseline over 48 hrs). There was a highly significant linear dose-response curve, with all treatment groups being statistically (ANCOVA) superior to placebo.

Figure 8: Dose-Response Curve in Acute Post-Surgical Pain

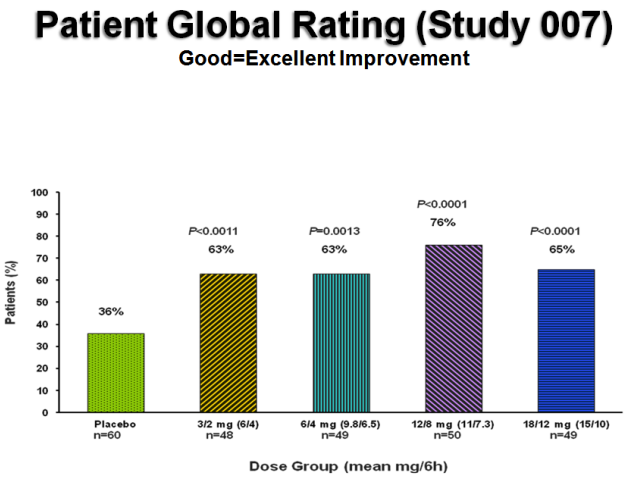


From a safety perspective, one placebo treated patient had an SAE, as did one patient in the MoxDuo high dose group due to dehydration. In respect to spontaneously reported AEs, for most events there was a dose-dependent relationship, with the majority of events being mild. Most of the opioid related adverse events in were not clinically significant since they were usually not reported by the patient to be "bothersome" and since very few patients (4%) in the 3 mg/2 mg to 12 mg/8 mg MoxDuo IR groups discontinued dosing due to one of these side effects. The most likely doses of MoxDuo IR to be administered to patients with moderate to severe pain following surgery will be 6 mg/4 mg or 12 mg/8 mg once every 4-6 hrs. These doses give the optimal combination of efficacy and tolerability. However, even unit doses of 3mg/2mg resulted in significant efficacy with benign AE profile. Interestingly, due to the flexible dosing regimen, some patients received up to 144 mg/96 mg over certain 6 hr periods—such doses were not associated with major adverse reactions, indicating the safety of MoxDuo even at very high doses.

MoxDuo IR was superior to placebo on all secondary efficacy endpoints, including pain relief, time to onset of analgesia and patient global satisfaction. MoxDuo IR treatment was superior to placebo

in respect to the percentage of patients who rated their treatment effects as good to excellent (Fig. 9).

Figure 9: Patient Global Rating (Study 007)



It is clear that while nausea and vomiting were the most common spontaneously reported AEs, they were usually not (about 80% of the time) of an intensity to be considered bothersome by the patient. This is consistent with the low dropout rate due to adverse events. Interestingly, the incidence of drowsiness/somnolence was very low (0-2%) in all of the active arms and there were no reports of euphoria. In respect to other safety measures, MoxDuo IR did not produce any unusual results.

Table 3: Most Common Opioid Adverse Events (Study 007)

Adverse Events Commonly Associated with Opioid Use (% Patients)

Mean Dose per 6 h (mg/mg)	Placeb0 (0/0)	3/2 (6/4)	6/4 mg (9.8/6.5)	12/8 mg 11/7.3)	18/12 mg (14.8/10)
N	60	48	49	50	49
Nausea	8.3	37.5	57.1	56.0	63.3
Vomiting	1.7	22.9	36.7	32.0	49.0
Dizziness	5.0	8.3	24.5	20.0	24.5
Headache	8.3	10.4	16.3	20.0	14.3
Pruritus	0.0	6.3	14.3	14.0	12.2
Generalized pruritus	0.0	2.1	8.2	4.0	4.1
Constipation	1.7	6.3	6.1	12.0	4.1
Dry mouth	3.3	6.3	4.1	6.0	4.1
Somnolence	0.0	2.1	4.1	2.0	8.2
Euphoria	0.0	0.0	0.0	0.0	0.0
O_2 decrease	1.7	0.0	4.1	0.0	12.2

Table 4: Percentage of Patients with Bothersome Adverse Events in the Optimal Dose Group (12mg/8mg)

Specific Adverse Event	Placebo (%) N=60	Q8003 12 mg/8 mg (%) N=50
CNS Adverse Events		
Difficulty concentrating	6.7	2.0
Drowsiness	0.0	0.0
Feeling confused	0.0	2.0
Feeling of fatigue/weakness	3.3	2.0
Feeling dizzy*	1.7	4.0
Headache	10.0	12.0
Gastrointestinal and Other Adverse Events		
Nausea	6.7	22.0
Vomiting	0.0	22.0
Constipation	3.4	8.0
Itchiness	0.0	18.0
Dry mouth	1.7	10.0
Difficulty passing urine	0.0	0.0

*Could also be related to hypotension.

Phase 3 Pivotal Combination Rule Study – Study 008

Study 008 was undertaken to satisfy the "Combination Rule" required by the FDA for approval of combination products. The rule requires that the combination be demonstrated to have greater efficacy than its mg components. The 48 hour study compared the efficacy of 12 mg/8 mg of MoxDuo vs. 12 mg morphine and vs. 8 mg oxycodone given q 6 hours in 522 patients who had undergone bunionectomy surgery.

The primary efficacy endpoint was the mean Sum of Pain Intensity Difference scores during the 48-hour treatment period ($SPID_{48}$) for each treatment group. Study 008 showed superior efficacy ($p<0.05$) for MoxDuo IR 12 mg/8 mg vs. morphine 12 mg and vs. oxycodone 8 mg on the primary endpoint and on secondary endpoints, such as $SPID_{24}$, $SPRID_{48}$ and $SPRID_{24}$ and likelihood of use of analgesic rescue medication). Interestingly, patients in the two control arms used on average 25-50% more ibuprofen rescue medication than the MoxDuo treated patients, thus biasing the analgesic effects in favor of the controls.

The morphine and oxycodone comparators in this trial were administered at half the morphine equivalent dose of MoxDuo IR, therefore it is not appropriate to directly compare the AE rates because the comparator drugs are at much lower doses and the doses are not equi-analgesic to that of MoxDuo IR. Adverse events associated with opioid drugs are dose related – the incidence and severity of adverse events appreciably increases with dose.

Phase 3 Pivotal Total Knee Replacement Study – Study 009

Study 009, a pivotal Phase 3 study, was designed to evaluate the analgesic efficacy and safety of

MoxDuo IR comparing a flexible dose against a fixed low-dose regimen for managing moderate to severe pain following total knee replacement surgery (TKR). The study was conducted at 10 U.S. sites in 142 patients who developed moderate-severe pain following discontinuation of IV PCA morphine on the day after surgery.

This double-blind, two-arm study compared a flexible dose regimen (range: 6 mg/4 mg to 24 mg/16 mg) versus a fixed low dose (3 mg/2 mg after an initial 6 mg/4 mg loading dose) of MoxDuo. Following TKR surgery, all patients received morphine IV for up to 24 hours. Patients were then randomised into one of two MoxDuo treatment regimens, with doses given once every 4-6 hours for up to 48 hours. After the initial treatment period, patients were eligible to continue dosing as an outpatient with study medication for up to 10 days.

The primary efficacy endpoint was the SPID48. Patients in the flexible dose treatment group achieved statistically superior pain reduction ($p<0.001$) compared to those receiving the lower dose, thus demonstrating a dose-response effect. Superior efficacy ($p<0.05$) for the higher dose group was also demonstrated for secondary efficacy endpoints, including SPID24, less pain during the final 24 hours (Brief Pain Inventory) and less use of acetaminophen rescue medication. Side effects were similar to those observed in earlier MoxDuo studies.

Phase 3 Bunionectomy Study – Study 022

Study 022 was a double-blind, randomized, fixed dose trial that enrolled 375 patients with moderate to severe post-operative pain following bunionectomy surgery at four U.S. clinical research sites. Patients received equi-analgesic doses of opioid once every 6 hours – MoxDuo IR 12 mg/8 mg, morphine 24 mg or oxycodone 16 mg. The main objective of Study 022 was to explore, as a primary safety endpoint, the performance of MoxDuo IR relative to morphine and oxycodone comparators with respect to oxygen desaturation, a direct measure of respiratory function. The main objective of the study was met, with valuable information gained that will allow the design of future studies aimed at securing a comparative label claim for the respiratory advantages of MoxDuo IR. Additionally, Study 022 will support the European Marketing Authorization Application (MAA) and the re-filing of the NDA to the FDA since it demonstrates an important respiratory safety advantage for MoxDuo.

Respiratory depression is the leading cause of death from high doses of opioids and is the most serious of opioid-related adverse events. At therapeutic doses, opioid induced respiratory impairment, either as a result of a slow respiration rate or shallow breathing, places patients at higher risk of experiencing a stroke, myocardial infarction or cognitive impairment due to periods of low blood oxygen (hypoxia). While severe respiratory impairment with opioids is not as common as other opioid-related adverse events, the risk of this serious and potentially lethal side effect is among the most important considerations in the risk: benefit evaluation of opioid analgesics. In a study of 1,524 patients receiving IV or neuraxial morphine in a university-affiliated 700 bed tertiary hospital, approximately 1.2% of patients were noted to have post-operative opioid-induced respiratory depression.[4] In a published letter to the journal *Anesthesiology* in 2010, one expert professed that postoperative respiratory failure is the third most common patient safety-related adverse event affecting the Medicare population in the US hospitals. The incidence was noted as 113 events per 1,000 at-risk patient admissions and 50% of postoperative respiratory failure events

involved patients receiving opioid analgesia. Death or anoxic brain injury was the result in a significant proportion of cases.[4]

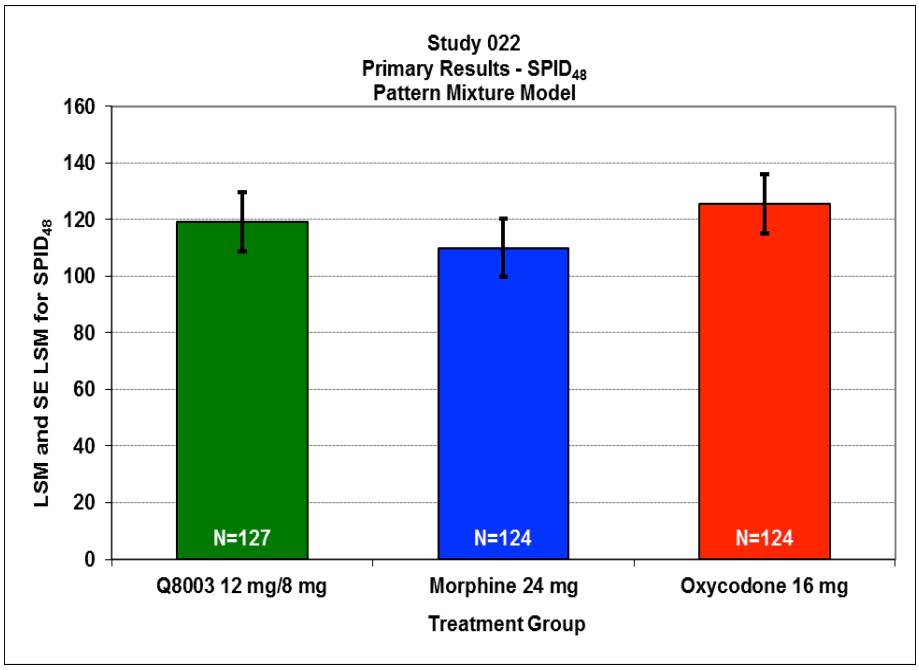
In Study 022, the extent of respiratory impairment was measured by decreases in blood oxygen levels from the healthy normal range of 96-100% seen at baseline before dosing. Values below 90% (a "desaturation") are usually considered clinically meaningful. It is also widely accepted that the greater the decline in blood oxygen saturation levels and the longer the desaturation lasts, the more severe the clinical outcome if no therapeutic intervention occurs to end the desaturation. Duration of desaturation event was not a useful measure in the Study 022 clinical trial setting as the study protocol provided for an intervention after 16 seconds of desaturation for patient safety. Therefore, the level of oxygen desaturation reached, before intervention, was the key informative measure in evaluating the respiratory related performance of MoxDuo IR compared to equi-analgesic doses of morphine and oxycodone.

Study 022 employed a sophisticated electronic methodology for recording the occurrences of desaturations. A Masimo pulse oximeter using a finger-tip sensor was used to continuously electronically record the blood oxygen concentration (oxygen saturation level, measured as a percentage of hemoglobin containing oxygen, ie, SpO2%) every two seconds for each patient over the 48 hour study treatment period, allowing for precise detection and quantifiable assessments of the extent and severity of any desaturations.

SPID48 (Analgesic Response)

Patients were enrolled in the study following their bunionectomy surgery, a process involving manipulation of the portion of the foot bone responsible for the bunion. Once the surgical anaesthetic had sufficiently worn off and pain intensity scores were at least 5 on a 10 point NPRS scale (0= no pain, 10= worst imaginable pain), patients were randomized to study medication. Analgesic effects were based on reductions in pain intensity from the post-surgical baseline, summed over the 48 hr opioid dosing period during which MoxDuo, morphine or oxycodone were given at 24 mg MED (morphine equivalent dose) once every 6 hours. These summed changes in pain scores is the Sum of the Pain Intensity Differences over 48 hrs ($SPID_{48}$). The MoxDuo and control group doses employed in the study were selected to achieve comparable analgesic effects in order to enable a valid comparison to be made of potential differences in respiratory function and in the occurrence of vomiting.

Fig 10: $SPID_{48}$ Scores – Primary Efficacy End Point



The $SPID_{48}$ scores did in fact show comparable analgesic effects among the treatment groups. No statistically significant differences were found among any of the treatment groups. The MoxDuo group score was 14% better than that of morphine and 4% less than that of oxycodone. These differences are likely due to chance and thus demonstrate that comparable analgesic effects were achieved for the three treatment regimens that used morphine equivalent doses of these three opioids.

Primary Safety End Point – Lowest Blood Oxygen Desaturation Value

A key safety end point of Study 022 was a comparison between the treatment groups of the percentage of patients with lowest blood oxygen desaturation values of less than or equal to 90%, 85%, 80%, 75%, 70%, 65% and 60%.

Table 5: Patients in Each Treatment Arm with a Desaturation Episode as a Function of Depth of the Desaturation

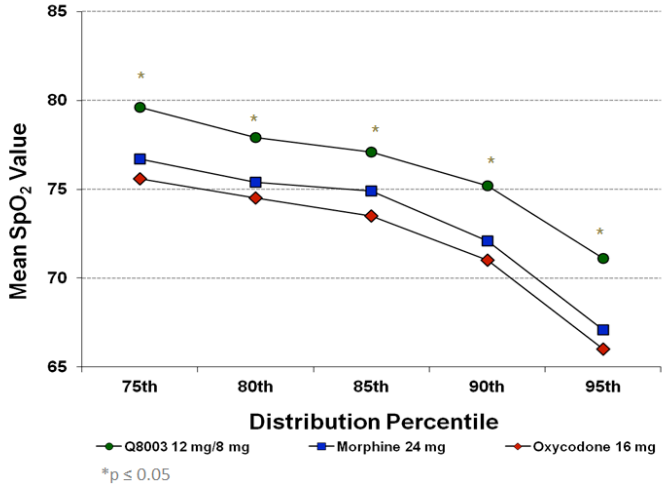
	Q8003 12 mg/8 mg N=127 N (%)	Morphine 24 mg N=124 N (%)	Oxycodone 16 mg N=124 N (%)
Number of Subjects with continuous SpO_2 data	126	123	122
Subjects with desaturation episodes[a] with minimum SpO_2%:			
<90%	98 (77.8%)	99 (80.5%)	107 (87.7%)
≤85%	88 (69.8%)	88 (71.5%)	99 (81.1%)
≤80%	55 (43.7%)	57 (46.3%)	66 (54.1%)
≤75%	25 (19.8%)	33 (26.8%)	49 (40.2%)
≤70%	9 (7.1%)	15 (12.2%)	26 (21.3%)
≤65%	7 (5.6%)	12 (9.8%)	14 (11.5%)
≤60%	7 (5.6%)	9 (7.3%)	9 (7.4%)

[a] Desaturation episodes are defined as SpO_2 <90% that is sustained for a period of ≥16 seconds in the Masimo electronic record. Episodes are categorized by the minimum SpO_2 within the event.

The percentage of MoxDuo IR patients who had a desaturation event at each cut-point was lower than patients treated with morphine or oxycodone. The differences were more pronounced at the lower desaturation values. For example, the risk of having a desaturation at or below 70% is approximately 200% higher with oxycodone and 70% higher with morphine than with MoxDuo.

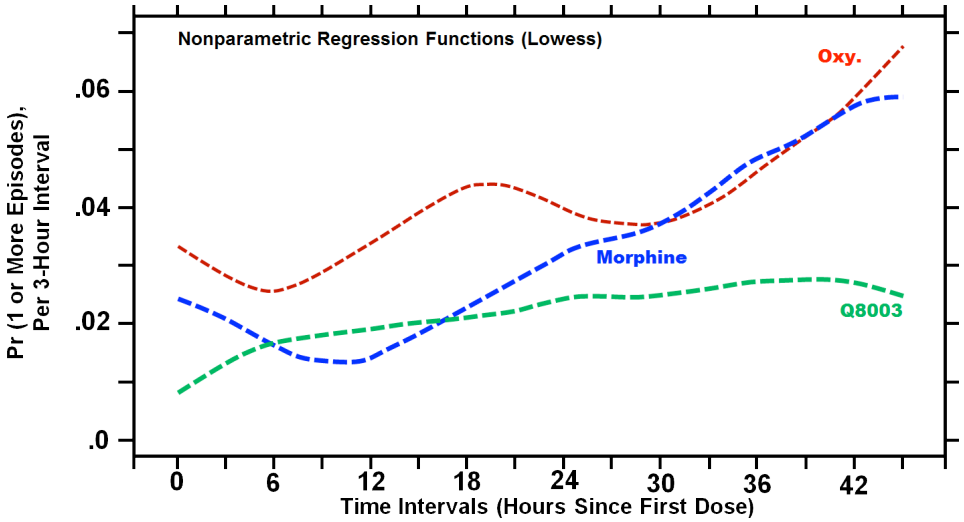
An alternative analysis of desaturation levels across the groups looked at mean SpO2 level for the 25 worst percentiles of desaturations in each group. Figure 11 shows that in general, the average SpO2 level for MoxDuo was about 5 SpO2 units higher (closer to normal values) than morphine and oxycodone. These findings were statistically significant for each point from the 75th percentile through to the 95th percentile.

Figure 11: Mean SpO2 for Most Severe Desaturation Events



An analysis of the time-dependent probability of having a desaturation event per three hour period from the inception of dosing through to 48 hours showed that the risk of a desaturation event was approximately the same in the first 18 hours for patients on morphine and MoxDuo, and higher for patients on oxycodone (Figure 12). However, beyond 18 hours, the risk of a desaturation even rose significantly in the morphine and oxycodone arms and only slightly in the MoxDuo arm. Patients on morphine or oxycodone may be at their greatest risk of oxygen desaturation at the time that they are being discharged from hospital or moved out from an intensive care (carefully monitored) environment to the general ward.

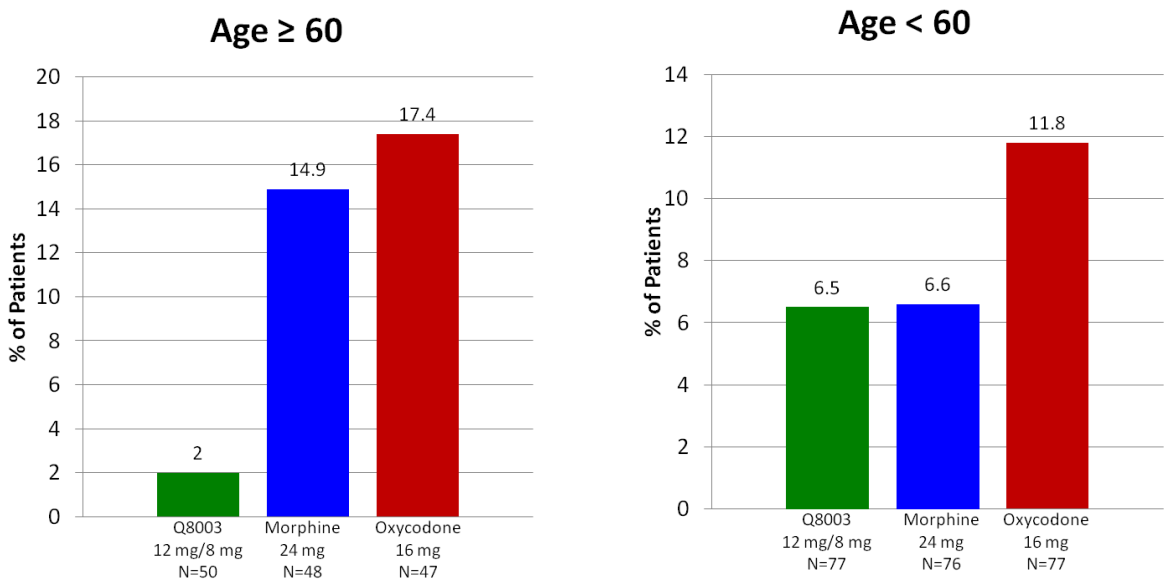
Figure 12: Lowess Curves at 80% SpO2 Severity Cut Point



Secondary Safety End Point – Comparison of desaturation risks between treatment groups

About 40% of patients in each treatment group were age 60 years or older, an age group that is at enhanced risk of opioid induced respiratory impairment. Figure 14 shows that patients receiving treatment with morphine or oxycodone were approximately seven and nine times more likely to have a sustained severe oxygen desaturation event compared to patients receiving treatment with MoxDuo.

Figure 13: Percent of Subjects with Sustained (30+ sec.) SpO_2 Desaturations by Age at 70% Cut Point



Study 022 Summary

At equi-analgesic doses, episodes of oxygen desaturation were less severe in patients receiving MoxDuo IR compared to those receiving either morphine or oxycodone alone. These differences were most marked in respect to the intensity of severe desaturations, with the duration of desaturations being truncated due to clinical actions of the study site staff. The incidence of desaturations (percentage of patients) were also higher in the oxycodone ($p<0.05$) and morphine groups. To the best of our knowledge, MoxDuo IR is the first opioid product to demonstrate a lower risk of respiratory depression in a clinical study comparing morphine equivalent (equi-analgesic) doses. Further, this study included a substantial number (40% of the total enrolment) of subjects age 60 years or older, a demographic group that is at enhanced risk of opioid induced respiratory impairment. The reduced occurrence of blood oxygen desaturations was most pronounced in MoxDuo treated subjects who were greater than 60 years. Thus, the respiratory benefits of MoxDuo were demonstrated in a study of substantial size (about 125 patients per group) and at equi-analgesic doses relative to morphine alone or oxycodone alone given for 48 hours in

patients needing opioids for the management of moderate to severe acute pain. This is an important safety advantage, one we expect will differentiate MoxDuo IR in the acute pain market place.

Pooled Analysis Across the MoxDuo IR Clinical Program

A pooled analysis was performed of the common opioid adverse events reported by patients throughout the full IND based phase 2 and 3 program (n=6 studies, total patient exposure >1500 patients) for patients receiving MoxDuo, morphine or oxycodone. All studies were 48 hours in duration and used a consistent method of recording adverse events. Since different studies used various dosage regimens, and not all studies contained every treatment group, the pooled analysis of AEs incorporate the morphine equivalent dose values administered to a given patient. The odds ratios derived from this analysis of every patient in every study showed that relative to MoxDuo treatment, patients receiving morphine or oxycodone had a 1.1 to 2.0 times higher likelihood of reporting nausea, emesis, dizziness, headache, pruritis, somnolence/sedation or decreased oxygen desaturation. In contrast, constipation was reported to occur more frequently in the MoxDuo patients, a difference that is likely due to the use of IV PCA morphine for up to 24 hrs prior to randomizing patients to MoxDuo in the total knee replacement study (Study 009) which did not have morphine or oxycodone comparator arms. Thus, of the eight opioid-associated adverse events that occurred in at least 5% of patients in the full development program, seven were more likely to occur when MEDs of morphine or oxycodone were given relative to the adverse event incidence seen in patients receiving MoxDuo (Figures 14 and 15).

Figure 14 : Pooled Analysis of Opioid Related Adverse Events in All Studies using Odds Ratios [95% CI] – Oxycodone vs MoxDuo

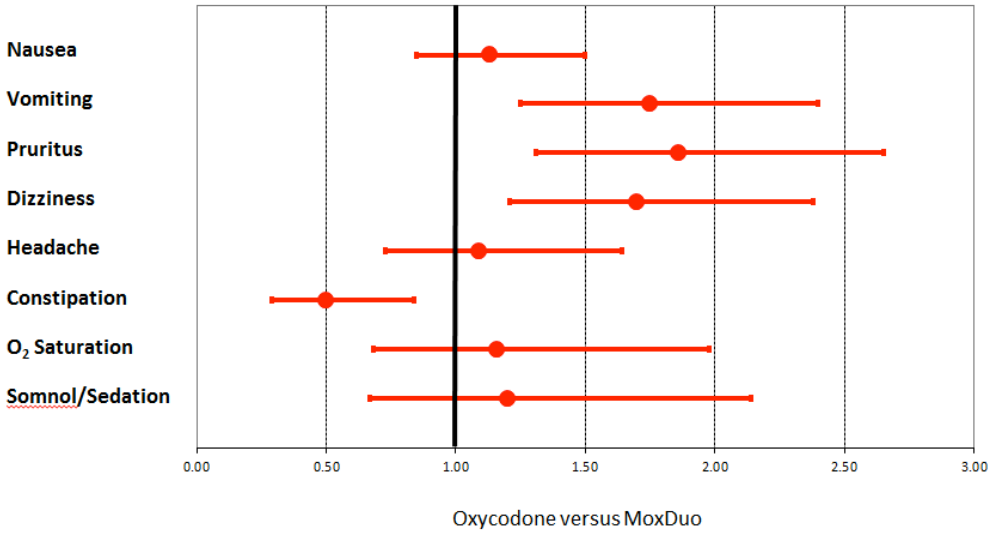
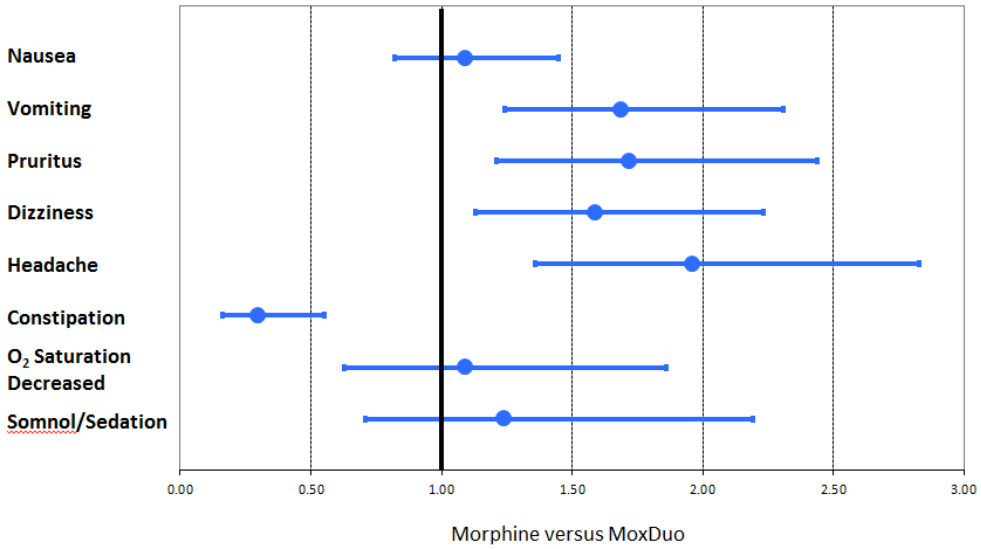


Figure 15: Pooled Analysis of Opioid Related Adverse Events in All Studies using Odds Ratios [95% CI] – Morphine vs MoxDuo



MoxDuo IR regulatory status

An NDA for MoxDuo IR was filed with the US FDA in August 2011. On June 25th 2012 QRxPharma received a Complete Response Letter (CRL). In a subsequent post submission review meeting the FDA requested further information regarding data filed as part of the MoxDuo NDA and additional analysis of trials completed to date, including Study 022 which evaluated oxygen desaturation levels in patients receiving MoxDuo compared to those administered morphine or oxycodone alone at equi-analgesic doses. Analysis of Study 022 was completed after the MoxDuo NDA filing, although early safety data were included in the 120-day update filed December, 2011. Accordingly, additional efficacy and safety information from this study was of significant interest to the FDA. QRxPharma is presently preparing an additional data package for review and believes that subsequent refiling of the NDA could result in a positive decision from the FDA by mid-2013.

Regulatory filings in Canada, Europe and Australia are scheduled for the first half of 2013.

MoxDuo IR labeling and market analysis

MoxDuo IR will be indicated for the acute treatment of moderate to severe pain. Further information on the labeling and market positioning of MoxDuo IR is available under a confidentiality agreement.

The US immediate release opioid market for managing acute pain is primarily driven by two products: oxycodone/acetaminophen (e.g., Percocet®) and hydrocodone/acetaminophen (e.g.,Vicodin®). Combined, these two products represent 75% of all prescriptions for immediate release opioid drugs – 132million prescriptions per year[14] for hydrocodone/acetaminophen and 44 million prescriptions per year for oxycodone/acetaminophen. Indeed, Vicodin (or generic substitutes) has been the number one prescribed pharmaceutical product in the US for the last seven years. One of the main reasons for the large volume of prescriptions for hydrocodone/acetaminophen products compared to other immediate release opioids is the Drug Enforcement Association's (DEA) regulation of these products as Schedule III, which places fewer restrictions on the prescriber than the more stringent Schedule II that is mandated for most other opioid drugs. Largely because of its ease of prescription, Vicodin is the most abused prescription drug in America[15]. Accordingly, there is a growing momentum for the rescheduling of hydrocodone/acetaminophen combination products from Schedule III to Schedule II, including a bill that is presently before Congress.

In January 2011 the FDA announced that combination opioid/acetaminophen products containing greater than 325mg acetaminophen must be withdrawn from the market within three years. The most frequently prescribed formulation of Vicodin contains 500mg acetaminophen, and typical dosing (up to 8 tablets/day) can result in the ingestion of 4grams of acetaminophen, resulting in potentially fatal consequences. The hepatotoxic effects of acetaminophen are the leading cause of acute liver failure in the US[16]. The American Geriatrics Society affirms that because of this significant risk, "No one should take more than a total of 4 grams of acetaminophen within any 24-hour period". Thus, daily dosing with Vicodin is known to result in acute liver failure and poses a significant risk for all patients, particularly the elderly.

MoxDuo IR is expected to launch in the US into a dynamically changing acute pain marketplace in 2013 as a Schedule II opioid. The anticipated rescheduling of Vicodin and its generics to Schedule II, as well as the recent restrictions imposed by the FDA on acetaminophen-containing opioids, creates a significant void in the acute pain marketplace and thus provides significant upside for the sales potential of MoxDuo IR. A modest market share will translate into substantial sales of MoxDuo IR.

The European market for immediate release opioids is dominated by morphine, oxycodone, codeine and codeine combination products (usually in combination with paracetamol). The immediate release oxycodone and morphine markets total approximately US$110 million per annum, whereas the codeine/codeine combo markets total approximately $440 million.[14] Key markets are Germany, UK, France and Italy.

MoxDuo IR Competitive Landscape

Unlike other therapeutic categories, since the introduction of morphine almost two centuries ago and oxycodone in the early 1900s, there has not been an advantaged opioid compound launched for the treatment of moderate to severe pain. As noted in the section above, in the immediate release segment of the market, the main competitors to MoxDuo IR are Vicodin and Percocet (and their generic equivalents) in the US. Both compounds are similar in that while they provide

efficacy for moderate to severe acute pain, their use is limited by their adverse event profile. In Europe the main competitors are morphine and oxycodone, although the codeine and codeine combination products may be targeted providing a significant upside to the market opportunity for MoxDuo IR. Nausea, vomiting, dizziness, and sedation, are the dose limiting adverse events having the greatest impact from a pharmacoeconomic standpoint, and respiratory depression from a morbidity and mortality standpoint.

The most recent market entrant, Oxecta, from Pfizer via Acura/King, is an abuse deterrent formulation of oxycodone. From market research conducted around this product, both payors and prescribers have said they would only utilize Oxetca in patients who have been identified as abusers as they would not want to cost burden the patient who is not abusing. Therefore, its potential in the market is already limited. Nucynta from J&J, while gaining some traction amongst tramadol prescribers (more for mild to moderate pain) is not seen as a strong enough drug to treat patients who have more moderate to severe pain.

Similarly, the products listed below in development do not bring the same kind of advantages to the market as MoxDuo IR. They are characterized as either different formulations of opioids with the same adverse event profile, or they are products like ketamine that bring their own adverse event issues and/or have been in development for extended periods and have a high risk of non-approval. In the case of burprenorphine, pain specialists believe its partial agonist properties will not demonstrate the same amount of pain relief that older opioids provide and will be a niche player in this space.

Innovation in the acute pain opioid category has been based around different formulations of essentially the same compounds. With an appreciably lower rate of clinically significant opioid induced adverse events such as respiratory depression, nausea, vomiting, dizziness, sedation, and pruritus, MoxDuo has the potential to create a paradigm shift in the IR opioid market.

Immediate Release					
Company	Molecule/Product	Phase	MOA	Formulation	Indication
Javelin/Archimedes	Morphine/Rylomine	III	Mu agonist	Nasal Spray	Acute pain
Javelin	Ketamine/Ereska	III	NMDA Receptor Antagonist	Nasal Spray	Acute Pain
Adolor	ADL5859	II	Delta receptor Agonist	Oral	Acute pain
Array BioPharma	ARRY797	II	P38 MAP Kinase Inhibitor	Unknown	Dental pain
Ikano Therapeutics	Hydromorphone	II	Mu agonist	Nasal Spray	Acute pain
BioDelivery Sciences	Buprenorphine/BEMA Buprenorphine	II	Kappa receptor	Oral (Buccal Film)	Acute/Chronic pain

			antagonist partial mu agonist		

Risk evaluation and mitigation strategy (REMS)

In response to pre-NDA meeting questions posed by QRxPharma, the FDA advised that a REMS program is not required for MoxDuo IR.

MOXDUO®CR

A CONTROLLED RELEASE ORAL FORMULATION FOR THE MANAGEMENT OF MODERATE TO SEVERE CHRONIC PAIN

Target product profile

MoxDuo CR is being developed as first line opioid therapy for patients with chronic non-cancer and cancer pain. Phase 1 studies on MoxDuo CR, together with later stage clinical data from other MoxDuo studies and independent clinical research, support the following key features of the MoxDuo CR target profile:

- Controlled release formulation of morphine plus oxycodone in a fixed 3:2 ratio in a compressed tablet
- Extended opioid plasma concentrations due to the CR component for at least 12 hours after administration
- Twice daily dosing frequency with adequate pain control throughout each 12 hour period; specifically - higher plasma levels than OxyContin® in the last half of the dosing interval
- Substantial reduction in the occurrence, intensity and duration of clinically significant opioid-related side effects such as nausea, emesis, dizziness, somnolence and constipation compared to standards of care such as OxyContin® and Avinza®
- Tamper and abuse resistant features that derive from physiochemical properties of the formulation (no noxious agents added)
- Patent protection to 2029
- No patent infringement concerning the release profiles of marketed drugs such as sustained release formulations of oxycodone (OxyContin®) or morphine (Avinza®)

Under the following sections we briefly overview clinical studies that have been completed in support of the above target profile.

Pre-clinical / IND

No preclinical studies have been conducted with MoxDuo CR. The IND application became effective in early 2010 without restrictions.

Clinical

Three Phase 1 pharmacokinetic (PK) studies in normal volunteers have been performed: studies 001, 002, and 003. Study 001 was a pharmacokinetic crossover study in 12 normal volunteers in which two novel experimental components, sustained release oxycodone beadlets with differing dissolution rates, were compared with pharmacokinetic parameters to OxyContin®. The final tablet formulation will contain the CR beadlets of morphine and oxycodone along with abuse deterrent properties in 3 different MoxDuo strengths.

The pharmacokinetic results from a cross over comparison of plasma oxycodone levels using the QRxPharma novel sustained release technology demonstrated a PK profile that matched the pre-specified target and was superior to that of OxyContin.

Study 002 compared MoxDuo CR with CR beadlets and the prototype tablet (30mg morphine /20mg oxycodone) to the pharmacokinetic profiles of the same doses of MS Contin® (30mg morphine) and OxyContin® (20 mg oxycodone) in 10 healthy adult human subjects using a three-way crossover design. Pharmacokinetic results from the measurement of opioid blood levels over time revealed a MoxDuo CR profile consistent with expectations for a once to twice-daily formulation.

Study 003 compared the pharmacokinetic profiles of morphine and oxycodone from the MoxDuo CR (30 mg/20 mg) final tablets using a two-way crossover design of single vs. multi-dose with 17 healthy volunteers. An evaluation of the food effect on MoxDuo CR was also incorporated into the study and demonstrated that food consumption does not alter the pharmacokinetic profiles of morphine and oxycodone from MoxDuo CR. To demonstrate the effects of chronic use on steady-state blood levels, this study also measured the repetitive-dose pharmacokinetic profiles of morphine and its metabolites as well as oxycodone during repetitive (twice daily) administration of MoxDuo CR tablets for 5 days.

With the successful completion of these three Phase 1 studies for MoxDuo CR, QRxPharma intends to initiate Phase 2 Proof-of-Concept clinical studies in 2013.

Clinical development plan

Available under a confidentiality agreement.

MoxDuo CR market analysis

The sustained release opioid market is currently valued at $5.2 billion in the US alone and approximately $7.5 billion with the EU major markets included. In modeling the impact of MoxDuo CR on this market segment, a few newer entrants to this space were analyzed. The launch of sustained release oxymorphone (Opana®, Endo Pharmaceuticals) shows an undifferentiated opioid reaching approximately $300 mm in annual sales within 3-4 years from launch. Similarly, the launch of a sustained release hydromorphone (Exalgo®, Covidien) is expected to show a comparable growth rate. In addition, the new formulation of OxyContin launched by Purdue with some abuse resistant measures is expected to prevent this market from becoming generic anytime in the near future. In the EU, Targinact® (oxycodone/naloxone Mundipharma), which claims a somewhat reduced rate of constipation, outpaced OxyContin® in the first 18 months following launch.

MoxDuo CR Competitive Landscape

The current market leader in the oral chronic pain opioid segment is OxyContin from Purdue. Its success, beyond Purdue's marketing efforts to increase the use of opioids, is tied to the perception that it has effective pain relief and may be somewhat more tolerable than morphine. However, its adverse event profile is relatively the same. Innovation in this category has only been limited to differentiated formulations of essentially the same compounds. Until recently, the chronic pain segment of the opioid market consisted of morphine, oxycodone, fentanyl, and methadone as the only opioid molecules available for the treatment of moderate to severe pain. With the introduction of oxymorphone (Endo's Opana) and hydromorphone (Covidien's Exalgo) there are now a few more choices which helps in regard to opioid tolerance, but in essence the issues in the opioid market remain the same - gold standard efficacy, but dose limiting, costly adverse events.

The products listed below (still in development) are mostly characterized as new formulations of existing opioid molecules with or without abuse deterrence, having the same adverse event profile, or products like Nucynta that bring their own adverse event issues.

MoxDuo CR has a favourable pharmacokinetic profile that is expected to provide superior analgesic coverage compared to the market leader based on twice or once daily dosing. With significant decreases in clinically significant adverse events, and superior abuse deterrent features, MoxDuo CR is forecast to achieve blockbuster status in this market.

Sustained Release					
Company	Molecule/Product	Phase	MOA	Formulation	Indication
J&J/Grunenthal	Tapentadol	III	Mu Agonist NE Reuptake Inhibitor	Oral	Chronic Pain
Pfizer	Oxycodone/Remoxy	III	Mu and	Oral	Chronic

			Kappa Agonist		Pain
Zogenix	Hydrocodone/ZX002	III	Mu Agonist	Oral	Chronic Pain
Egalet	Morphine/EG-PO66	IIB	Mu Agonist	Oral	Chronic Pain
Elite Pharmaceuticals	Oxycodone/ELI154	II	Mu and Kappa Agonist	Oral	Chronic Pain
Elite Pharmaceuticals	Oxycodone-naltrexone/ELI216	II	Mu and Kappa Agonist Opioid Antagonist	Oral	Chronic Pain
Endo/Pennwest	Nalbuphine/PW4142	IIa	Kappa Agonist Mu Antagonist	Oral	Chronic Pain

MOXDUO®IV

AN INTRAVENOUS FORMULATION FOR THE MANAGEMENT OF MODERATE TO SEVERE ACUTE PAIN

Target product profile

MoxDuo IV is being developed as first line opioid therapy for patients with acute moderate to severe pain in a hospital setting such as that associated with surgery, injury or other acute pain disorders. Results from a phase 2 proof of concept study entailing co-administered intravenous morphine and intravenous oxycodone, together with later stage clinical data from other MoxDuo studies and independent clinical research, support the following key features of the MoxDuo IV target profile:

- Increased efficacy for the MoxDuo IV vs. morphine (based on results of proof of concept study)
- An intravenous formulation of morphine and oxycodone in a fixed 1:1 ratio whose presentation will be both in an injectable syringe vial and a pre-filled syringe.
- The pharmacokinetic profile will be the same as if IV morphine or IV oxycodone were administered singly.
- Substantial reduction in the occurrence, intensity and duration of clinically significant opioid-related side effects such as moderate-severe nausea, emesis, dizziness, and somnolence compared to standards of care, such as intravenous morphine
- Substantial reduction in the intensity and duration of oxygen desaturation events compared to intravenous morphine or oxycodone

Clinical

One phase 1 study and three exploratory phase 2 studies have been conducted in Australia and recently in Germany using co-administration of morphine IV and oxycodone IV. Future studies will be conducted using MoxDuo IV containing both morphine and oxycodone at a ratio of 1:1.

Proof of concept early Phase 2 study

A double-blind, randomized trial was recently completed in Germany comparing a 1:1 ratio of morphine: oxycodone IV vs morphine IV in 40 inpatients with moderate-severe pain following hip replacement surgery.

The study had two phases. The first phase involved a fixed dose titration in which study drug was administered once every 5 minutes for up to 60 minutes or until pain scores declined to 2 or less on the 0-10 point Numerical Pain Rating Scale (NPRS). Individual doses were either morphine 1.5 mg or 0.75mg morphine plus 0.75 mg oxycodone. The second phase involved patient controlled analgesia (PCA) which was self-administered for the following 47 hours. Patients received their assigned drug (0.25 mg morphine plus 0.25 mg oxycodone; or 0.5 mg morphine) up to 3 doses per hr, but not more than once every 6 minutes.

Results showed that during the dose titration period, the mean SPID65 minutes (change from baseline pain) was 50% greater for the morphine plus oxycodone regimen than morphine alone (see fig. 16). Over the entire 48 hr study period, 98% of which was PCA period, a time at which patients could adjust their dosage level to the optimal combination of pain relief and tolerability, the SPID48 for the combination group was 10% greater than the PCA morphine control (see fig. 17).

Consistent with the results from the phase 2 comparative adverse event evaluations using oral MoxDuo IR and the published literature comparing oral morphine plus oxycodone to morphine alone, a similar pattern of substantially reduced moderate to severe nausea and emesis occurred in the morphine plus oxycodone group vs the morphine alone treatment for the 48 hr study period (see fig. 18). Also of potential importance was the difference in the rate of desaturation of blood oxygen levels (<90%) for the morphine plus oxycodone combination (5% of patients) vs 19% in the initial dose titration period for the morphine group. Both groups received a comparable number of IV doses during the titration period.

Figure 16: IV Study Results from Titration Period

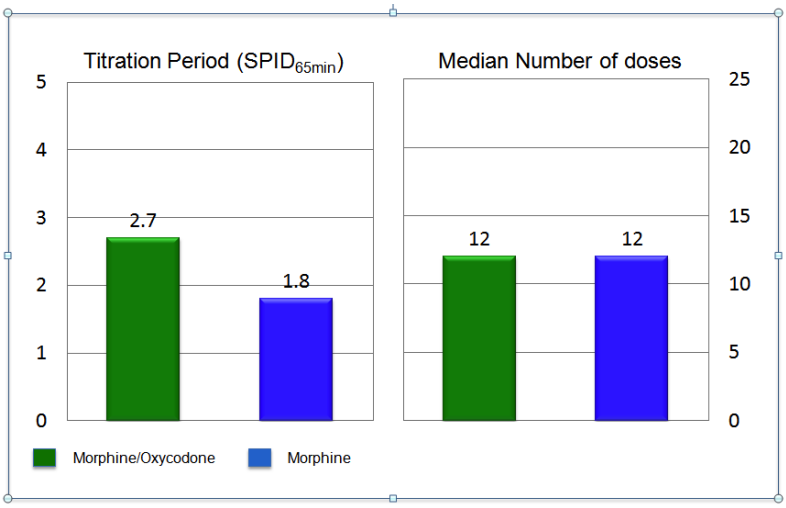


Figure 17: IV Study Results from PCA Period

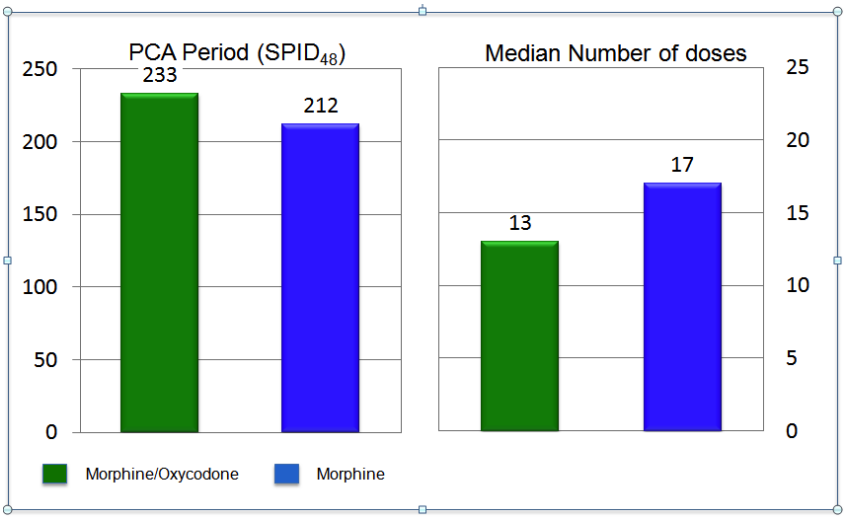
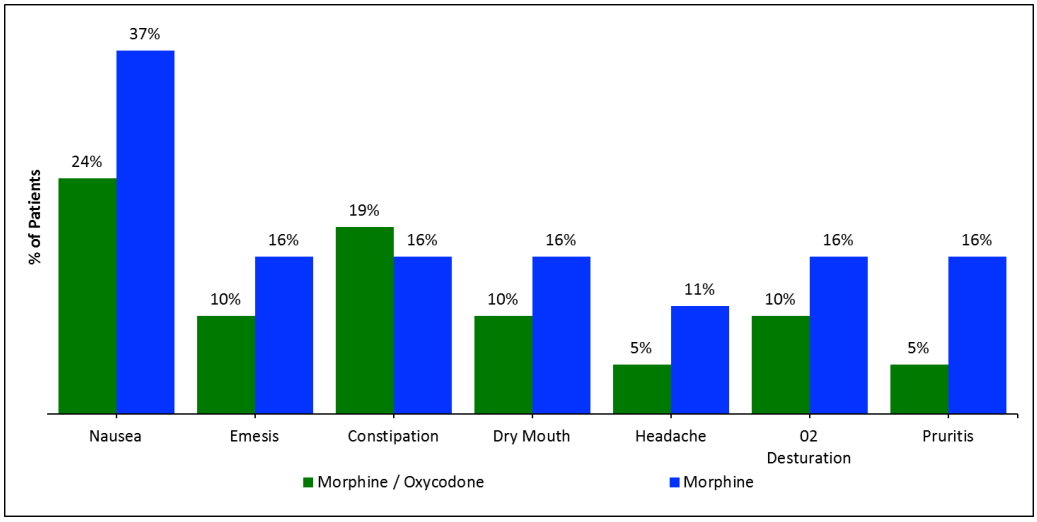


Figure 18: IV Study Opioid Related Adverse Events



Remaining clinical development plan

Available under a confidentiality agreement.

MoxDuo IV market analysis

Similar to the immediate release segment, the IV market is characterized by a huge volume of use, generic players, and a low dollar volume. In 2010 this translated into approximately 230 million vials used with an annual sales value of $275 million in the US. The annual sales value in major EU

markets in 2011 was $135 million. The key unmet needs in this market center around a drug that will produce the same degree of efficacy as the opioids but with less adverse events, particularly dizziness/sedation, nausea, vomiting and respiratory depression. A key priority in post-operative care is to move patients as quickly as possible from the PACU (post anesthesia care unit), one of the most expensive places for patients to reside in the hospital, to the nursing floors so they can begin their rehabilitation and be discharged. MoxDuo IV with its demonstrated reduction in adverse events will have a dramatic impact on pharmacoeconomic factors by reducing the time the patient spends in the PACU thereby decreasing payor costs by a multiple of the drug cost.

MoxDuo IV Competitive Landscape

As noted in the section above, in the intravenous segment of the market, the main competitors to MoxDuo IR are IV morphine and hydromorphone. Both compounds are similar in that while they provide efficacy for moderate to severe acute pain, they are limited by their adverse event profile. Nausea, vomiting, dizziness, and sedation, are the dose limiting adverse events having the greatest impact from a pharmacoeconomic standpoint, and respiratory depression from a morbidity and mortality standpoint. The most recent entrant peripherally into this arena is Cadence's Ofirmev, an intravenous acetaminophen that is touted as morphine sparing and thus able to reduce the adverse events associated with opioids that would be used in conjunction with this compound to control post-operative pain. From early indications, both payors and prescribers are not responding to this product as the cost of adding Ofirmev to generic IV opioids will not provide either a pharmacoeconomic or clinical effect great enough to offset the economics.

Similarly, the products listed below, that are in development, will not bring advantages to the market that will parallel MoxDuo IV. M6G has been in development for several years and has yet to demonstrate equal efficacy and less adverse events. The efficacy of bupivacaine for moderate to severe nociceptive pain has been questioned by pain specialists, and the NCEs have yet to demonstrate whether they will be able to make it through full development process, with Pfizer's tanezumab as the prime example of the challenge faced (clinical trials are currently on hold due to results noted in their phase III trials).

With marked reductions in clinically significant opioid induced adverse events such as respiratory depression, nausea, vomiting, dizziness, and sedation, MoxDuo IV has the potential to create a paradigm shift in the IV opioid market.

Intravenous					
Company	Molecule/Product	Phase	MOA	Formulation	Indication
Pacira	Bupivacaine/Exparel	III	Na Channel blocker	IV	Post-op Pain
PAION	M6G	III	Mu Agonist	IV	Post-op Pain
Nycomed/Durect	Posidur/Bupivacaine	III	Na Channel blocker	IV	Post-op Pain

Pfizer	Tanezumab/PF-4383119	III	Anti-NGF antibody	IV	Pain
Cara Therapeutics	CR845	IIa	Kappa Agonist	IV	Post-op Pain
Xenome	Xen2174	II	NE Transporter Inhibitor	IV	Post-op Pain
Innocoli	Bupivacaine/CollRx	II	Na Channel blocker	IV	Post-op Pain

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