

DUAL-OPIOID TREATMENT OF ACUTE POSTOPERATIVE PAIN: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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ABSTRACT

Preclinical and clinical evidence suggests that the co-administration of two opioids with differing opioid receptor-binding properties, such as morphine and oxycodone, produces enhanced analgesic effects. The current study was a double-blind, placebo-controlled, randomized, ascending-cohort dose-response evaluation of an immediate-release formulation (Q8003) of morphine plus oxycodone administered as 3/2 mg, 6/4 mg, 12/8 mg, and 18/12 mg pm. Flexible dosing was used with a minimum of 1-2 hrs between doses over the 48-hr dosing period in the 256 patients with moderate to severe pain following unilateral bunionectomy surgery who were randomized to treatment. There were ~50 patients in each of the 5 treatment arms. Following IRB approval and obtaining written informed consent, patient eligibility for randomization included the following requirements: a stable medical condition, BMI <32, lack of significant opioid use in the prior year, absence of a history of opioid intolerance, a SpO₂ value of at least 95%, a post-surgical pain score of moderate or severe (Likert scale) and a NPRS pain score of at least 4 (0-10 scale). Post-baseline efficacy measures consisted of pain intensity (PI) and pain relief (PR) ratings starting at 0.25 hr after initiation of dosing with frequently scheduled measures over the ensuing 48 hrs, including measures at the time of each dose of study or rescue medication and 1 hr later. The primary efficacy endpoint was the sum of the 48-hr pain intensity differences (SPID48) from baseline. Other efficacy measures included the patient global impression score, onset to confirmed perceptible pain relief (stop watch method), amount of rescue medication used and various derived scores using the PI and PR outcomes (TOTPAR, PID, SPRID), as well as a percent responder curve using changes from baseline in the SPID48 values. Imputation of missing efficacy scores used the last observation (LOCF) method for all missing values except for patients who dropped out due to an adverse event, in which case the baseline scores were assigned for the missing values (BOCF). The primary method of comparison of a dosing cohort vs placebo was an analysis of covariance. Safety measures included the incidence of spontaneously reported adverse events (AE), AE severity, SpO₂ values, vital signs, clinical labs, physical exams and ECG. In addition, the patient rated Gan et al (2004) scale of bothersomeness of opioid-related AEs and the NCI AE severity scoring for opioid-related events were employed. These measures will provide for a unique within-study comparison of 3 methods of judging opioid-related AEs. This multicenter trial was conducted at 6 sites in the U.S. Dropouts due to AEs were ~5% and due to lack of efficacy were ~16%. Of the AE-related dropouts, the most common reasons were nausea, emesis or hypotension. One patient discontinued due to intermittent hypoxia. There were 3 serious AEs, 2 of which were unrelated to study medication and the other (hypotension) was possibly related to study medication.

INTRODUCTION

- Acute postoperative pain is frequently managed inadequately; if such pain persists, it can lead to a greater risk of developing chronic pain^{1,2}
- Opioids are the most commonly used drugs for acute postoperative pain³
- Opioids, while effective in most patients, are frequently accompanied by adverse events that limit their efficacy or cause early discontinuation
- Q8003 is a dual-opioid formulation that provides a fixed ratio (3:2) of morphine and oxycodone in an oral, immediate-release (IR) capsule for the management of postoperative pain
- The combination of morphine and oxycodone is believed to potentiate analgesia as a result of the interaction of these opioids on a broader spectrum of opioid subreceptors, including but not limited to μ and κ receptors^{4,7}
- Enhanced efficacy can result in the need to administer lower doses, leading to improved patient acceptance and response

OBJECTIVE

To determine the dose-responsive analgesic effects and safety of Q8003 in patients with moderate to severe pain following unilateral bunionectomy surgery

METHODS

Study design

- Randomized, double-blind, placebo-controlled, ascending-cohort, dose-response, 48-hour inpatient study following unilateral bunionectomy surgery
- Q8003 was administered in 4 ascending cohorts: 3/2 mg, 6/4 mg, 12/8 mg, and 18/12 mg vs placebo
 - After completion of each dosing group, enrollment in the next higher dosing group began if not more than 10 Q8003-treated patients in the previous dosing group experienced intolerable opioid-related adverse events (AEs)
 - Q8003 was dosed pm with a required interdose interval of at least 1-2 hours to ensure patient safety (maximum of 5 doses in 12 hours for the 2 higher doses)
 - Rescue medication was allowed during the interdose interval (ibuprofen 600 mg)
- Analysis of covariance (ANCOVA) was used to compare individual dosing cohorts vs placebo
- Time to perceptible analgesia was analyzed using Kaplan-Meier estimates

Patients

- Men and women ≥ 18 years of age with a body mass index (BMI) <32 kg/m² who met the American Society of Anesthesiologists (ASA) Class I or II patient criteria, and who were scheduled for unilateral uncomplicated bunionectomy surgery, were eligible for the study
- To continue in the study following surgery, patients were required to have:
 - Pain score of 2 or 3 on a 4-point Likert scale (moderate or severe intensity)
 - Pain score of ≥ 4 on an 11-point Numerical Pain Rating Scale (NPRS; 0=no pain and 10=worst pain imaginable)
 - Pulse oximetry score (SpO₂) of $\geq 95\%$ oxygen saturation
 - Respiration rate of ≥ 12 breaths/minute
- Patients were excluded if they had significant opioid use in the prior year, a history of opioid intolerance, a history of drug abuse, or evidence of current alcohol abuse

Efficacy measures

- Primary efficacy measure
 - Mean sum of pain intensity differences from baseline during the 48-hour treatment period (SPID48)
- Secondary efficacy measures
 - Global patient satisfaction using a 5-point scale (0=not effective to 4=excellent) recorded 48 hours after the initial dose
 - Onset of analgesia following first dose of study medication using the two stopwatch method
 - Mean morphine and oxycodone doses and mean interdose interval
 - Time to first dose of ibuprofen following first dose of study medication and mean number of ibuprofen doses
 - Number of patient withdrawals for lack of efficacy

Safety assessments

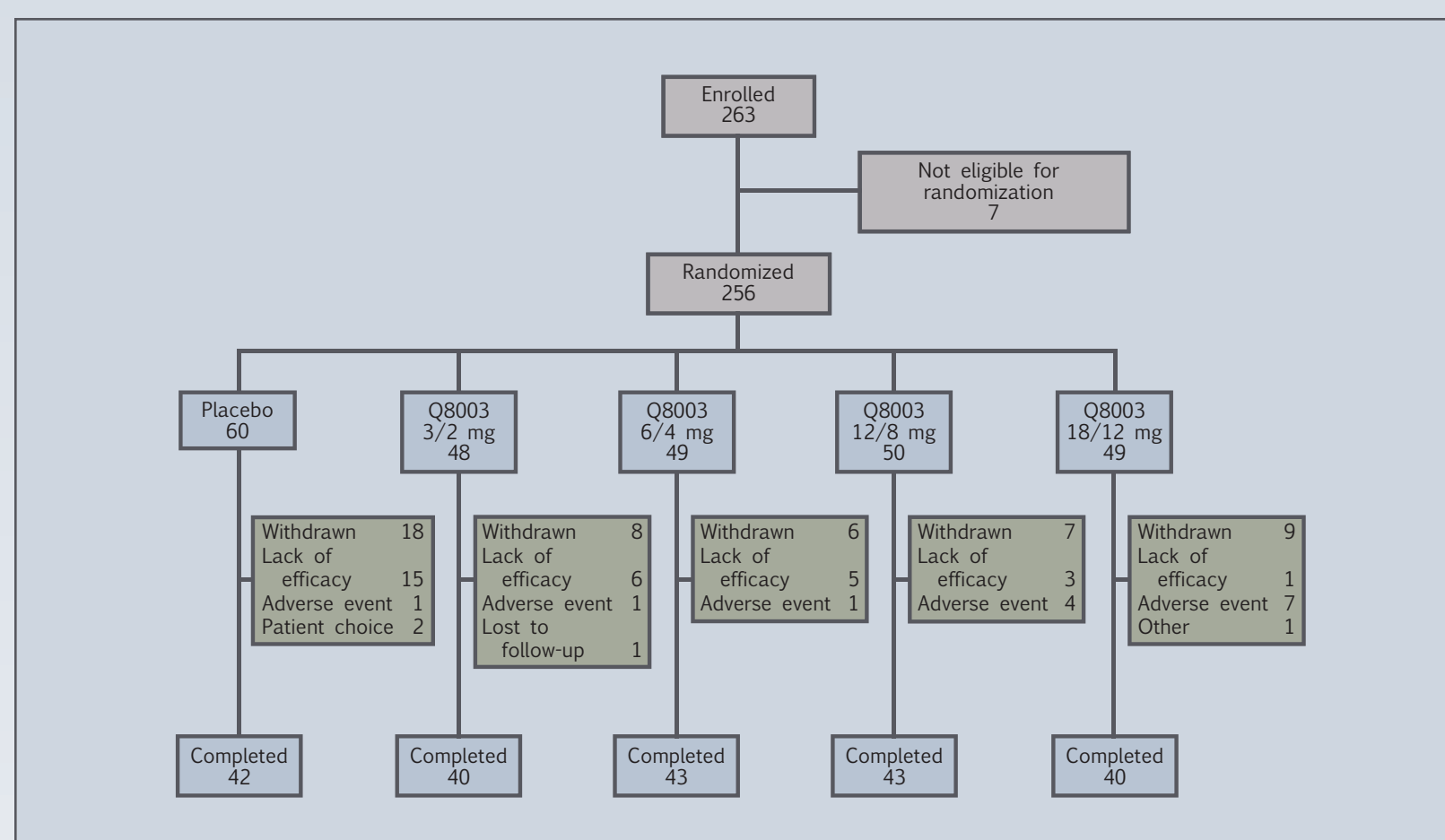
- Spontaneously reported AEs
- SpO₂ and respiration rate
- Opioid-Related Symptom Distress Scale patient checklist⁸
 - Rates occurrence of pre-defined opioid-related AEs
 - Completed 24 and 48 hours after initial dose of study medication

RESULTS

Patients

- Of 263 patients enrolled, 256 were randomly assigned to treatment and received ≥ 1 dose of study medication (Figure 1)

FIGURE 1. PATIENT DISPOSITION



- Patient demographics and baseline pain characteristics are presented in Table 1

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE PAIN CHARACTERISTICS

Characteristic	Placebo (n=60)	3/2 mg (n=48)	6/4 mg (n=49)	12/8 mg (n=50)	18/12 mg (n=49)
Age, y, mean (SD)	46.7 (14.5)	43.9 (14.6)	42.3 (13.6)	44.5 (13.1)	43.5 (12.8)
Gender, n (%)					
Men	14 (23)	13 (27)	5 (10)	8 (16)	9 (18)
Women	46 (77)	35 (73)	44 (90)	42 (84)	40 (82)
Race, n (%)					
White	44 (73)	34 (71)	38 (78)	31 (62)	32 (65)
Black	10 (17)	10 (21)	5 (10)	9 (18)	12 (25)
Asian	4 (7)	1 (2)	1 (2)	4 (8)	3 (6)
Hispanic	1 (2)	3 (6)	4 (8)	6 (12)	2 (4)
Other	1 (2)	0	1 (2)	0	0
BMI, kg/m ² , mean (SD)	26.4 (4.1)	25.6 (3.5)	25.0 (3.7)	25.0 (4.0)	25.4 (3.6)
NPRS, mean	6.6	6.2	6.7	6.6	6.8
Patients with moderate pain ^a , n (%)	46 (77)	39 (81)	39 (80)	40 (80)	34 (69)

^aRemainder of patients had severe pain at baseline.
 BMI=body mass index.
 NPRS=Numerical Pain Rating Scale (0=no pain; 10=worst pain imaginable).

Extent of exposure

- The mean dose of morphine/oxycodone per 6-hour period (mg/6h) and the mean interdose interval over the 48-hour study period are presented in Table 2
- The longest average interdose interval was observed in the 12/8-mg group (6.8 hours)

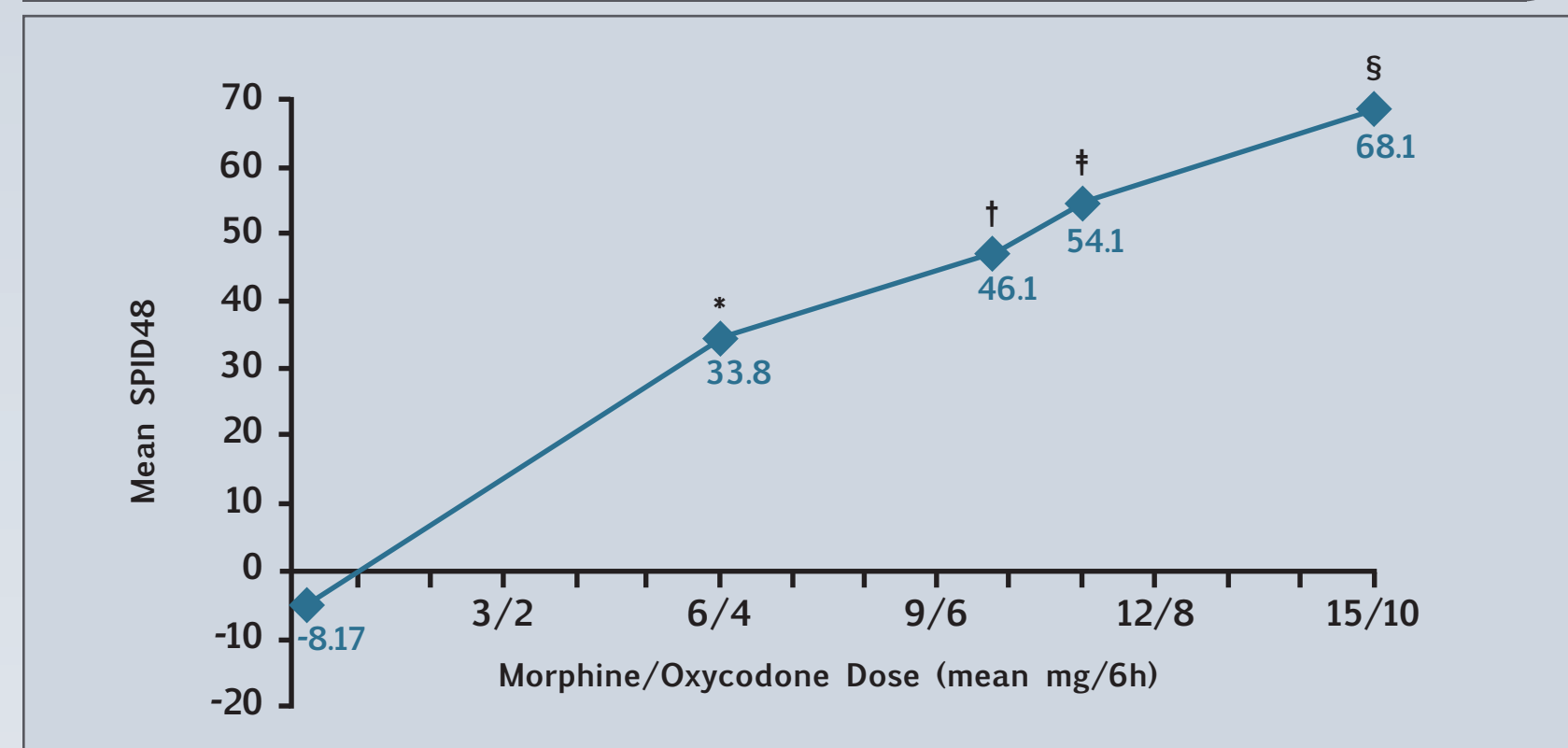
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Mean dose of morphine/oxycodone, mg/6h	0/0	6/4	9.8/6.5	11/7.3	15/10
Mean interdose interval, h	4.2	2.9	4.1	6.8	6.6

Efficacy

- SPID48 was significantly greater with each Q8003 dose compared with placebo (Figure 2)

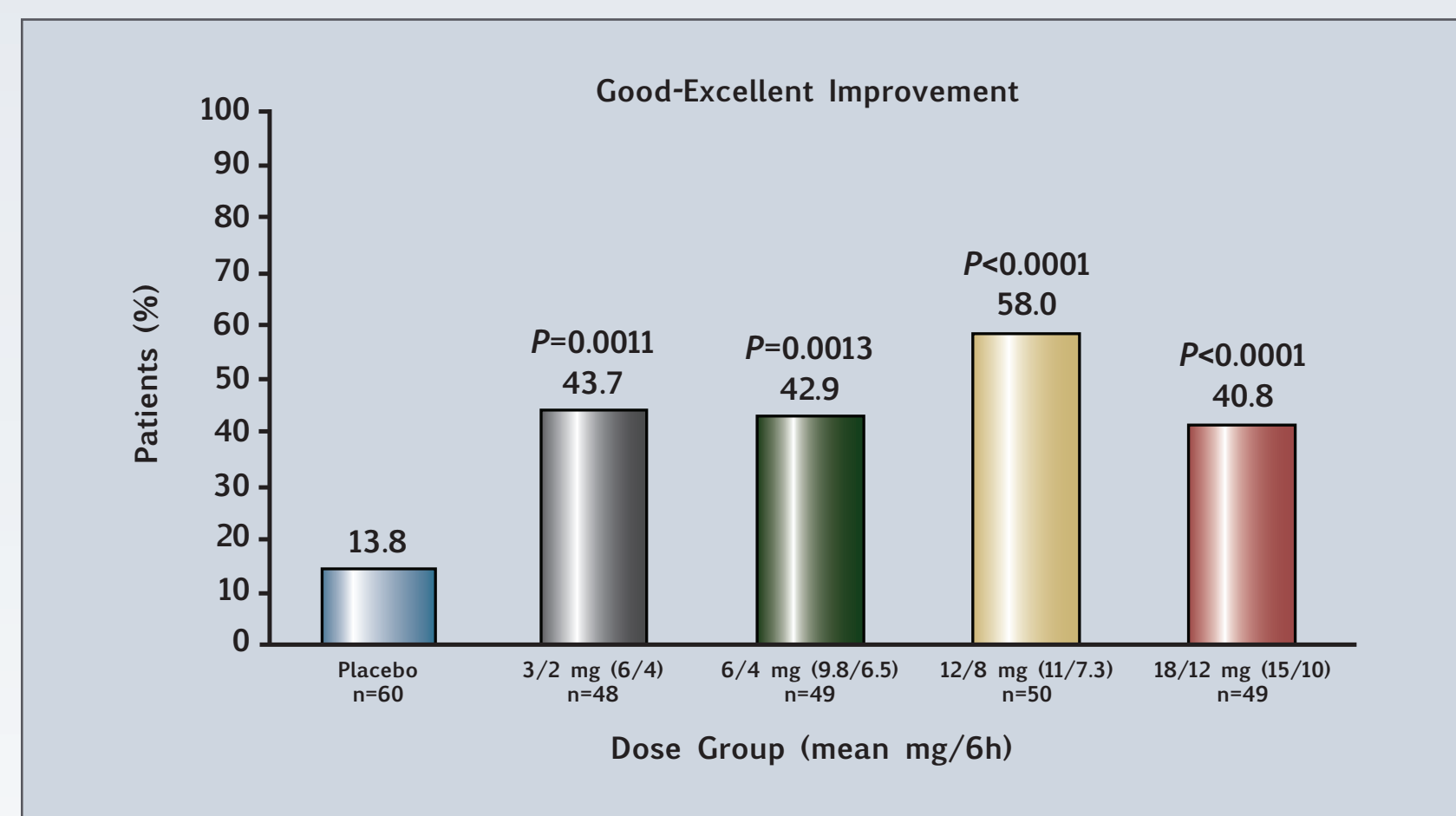
FIGURE 2. MEAN SUM OF PAIN INTENSITY DIFFERENCES DURING THE 48-HOUR TREATMENT PERIOD (SPID48)



*P=0.0015 vs placebo, SD \pm 98; †P=0.0016 vs placebo, SD \pm 111; ‡P=0.0001 vs placebo, SD \pm 75; §P<0.0001 vs placebo, SD \pm 75

- The percentage of patients reporting "good" or "excellent" improvement was significantly greater with each dose of Q8003 compared with placebo (Figure 3)
- Patient satisfaction was greatest with the 12/8-mg dose (58.0% good or excellent, P<0.0001 vs placebo)

FIGURE 3. GLOBAL PATIENT SATISFACTION WITH Q8003 VS PLACEBO



- Following the first dose of study medication, patients who received Q8003 had a shorter time to confirmed perceptible analgesia (range across dose groups, 0.67 to 1.93 hours) compared with patients receiving placebo (4.4 hours)
 - The shortest time to confirmed perceptible analgesia was observed in the 12/8-mg group compared with the 3/2-mg, 6/4-mg, and 18/12-mg groups (0.67 hours vs 1.93, 1.04, and 0.73 hours, respectively)
- Following the first dose of study medication, patients who received Q8003 waited longer before taking ibuprofen (range across dose groups, 3.2 to 7.9 hours) compared with patients receiving placebo (2.9 hours)
- Patients receiving Q8003 required fewer doses of ibuprofen (mean, 1.9 to 2.3 doses/24h, range across dose groups) compared with patients receiving placebo (mean, 3.3 doses/24h)

- Fewer patients receiving Q8003 withdrew from the study for lack of efficacy (range across dose groups, 1 to 6 patients) compared with patients receiving placebo (15 patients)

Safety and tolerability

- The rate of discontinuation due to AEs was low in all treatment groups
 - Placebo, 2% (1 patient, hypotension); 3/2 mg, 2% (1 patient, nausea); 6/4 mg, 2% (1 patient, nausea); 12/8 mg, 8% (1 patient each: nausea, vomiting, decreased SpO₂, and hypotension); and 18/12 mg, 14% (2 patients each: nausea and vomiting; 1 patient each: hypoxia, pruritus, and hypotension)
- The most commonly reported AEs were those associated with opioid use (Table 3)
 - The majority of AEs were mild to moderate in intensity and the incidence decreased over time

TABLE 3. ADVERSE EVENTS OCCURRING IN $\geq 5\%$ OF PATIENTS BY DOSE GROUP AND ACTUAL DOSE (MEAN mg/6h)

Adverse event, n (%)	Placebo (0/0) (n=60)	3/2 mg (6/4) (n=48)	6/4 mg (9.8/6.5) (n=49)	12/8 mg (11/7.3) (n=50)	18/12 mg (15/10) (n=49)
Nausea	5 (8)	18 (38)	28 (57)	28 (56)	32 (65)
Vomiting	1 (2)	11 (23)	18 (37)	16 (32)	25 (51)
Dizziness	4 (7)	4 (8)	12 (25)	10 (20)	12 (25)
Headache	5 (8)	5 (10)	8 (16)	10 (20)	8 (16)
Pruritus/Generalized pruritus	0	3 (6)	10 (20)	9 (18)	9 (18)
SpO ₂ decrease	1 (2)	0	5 (10)	3 (6)	5 (10)
Somnolence	0	1 (2)	2 (4)	1 (2)	4 (8)
Constipation	1 (2)	3 (6)	3 (6)	6 (12)	2 (4)
Dry mouth	2 (3)	3 (6)	2 (4)	3 (6)	2 (4)

- In general, the percentages of patient-reported AEs on the Opioid-Related Symptom Distress Scale were higher than corresponding patient- and investigator-reported AEs; selected AEs for the entire treatment period are presented below:
 - Nausea was reported by 10% of patients receiving placebo and by 52%, 76%, 64%, and 78% of patients in the 3/2-mg, 6/4-mg, 12/8-mg, and 18/12-mg groups, respectively
 - Vomiting was reported by 0% of patients receiving placebo and by 23%, 37%, 40%, and 51% of patients in the 3/2-mg, 6/4-mg, 12/8-mg, and 18/12-mg groups, respectively
- Overall, 3 patients experienced serious AEs
 - 1 patient in the 18/12-mg group had hypotension that resulted in discontinuation of study medication
 - 2 patients in the placebo group had events not related to study medication (1, hand injury; 1, deep vein thrombosis)
- Desaturations were transient, infrequent, responded quickly to supplemental oxygen, and were more frequent in the 18/12-mg dose group than in other groups; none of the patients receiving Q8003 had a respiration rate of <10 breaths/minute
- Sedation was seen in 1 patient in the 18/12-mg group; somnolence ranged from 2% to 8% across the Q8003 groups; euphoria was not observed

CONCLUSIONS

- Q8003 was associated with dose-related reductions in acute postoperative pain; even the lowest dose group (mean 6/4 mg every 6h) showed analgesic efficacy superior to placebo
- Q8003 was well tolerated, with few serious AEs or discontinuations, minimal changes in respiration and blood oxygenation, few occurrences of somnolence, and no occurrences of euphoria
- The low levels of somnolence and respiratory depression warrant further study
- The 12/8-mg dose appeared to provide the optimal combination of efficacy and tolerability; future studies will examine Q8003 with the dosing schedule of every 4 to 6 hours

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METHODS

Study design

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- Primary efficacy measure
 - Mean sum of pain intensity differences from baseline during the 48-hour treatment period (SPID48)
- Secondary efficacy measures
 - Global patient satisfaction using a 5-point scale (0=not effective to 4=excellent) recorded 48 hours after the initial dose
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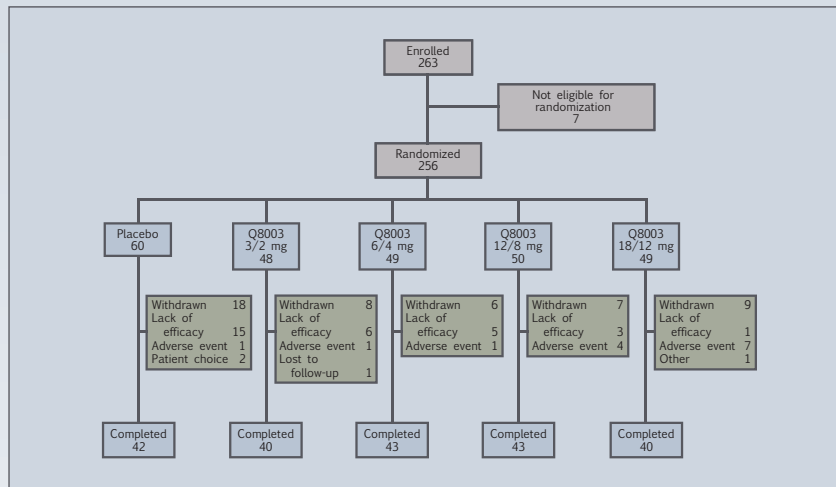
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RESULTS

Patients

- Of 263 patients enrolled, 256 were randomly assigned to treatment and received ≥1 dose of study medication (Figure 1)

FIGURE 1. PATIENT DISPOSITION



- Patient demographics and baseline pain characteristics are presented in Table 1

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE PAIN CHARACTERISTICS

Characteristic	Placebo (n=60)	3/2 mg (n=48)	6/4 mg (n=49)	12/8 mg (n=50)	18/12 mg (n=49)
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Women	46 (77)	35 (73)	44 (90)	42 (84)	40 (82)
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White	44 (73)	34 (71)	38 (78)	31 (62)	32 (65)
Black	10 (17)	10 (21)	5 (10)	9 (18)	12 (25)
Asian	4 (7)	1 (2)	1 (2)	4 (8)	3 (6)
Hispanic	1 (2)	3 (6)	4 (8)	6 (12)	2 (4)
Other	1 (2)	0	1 (2)	0	0
BMI, kg/m ² , mean (SD)	26.4 (4.1)	25.6 (3.5)	25.0 (3.7)	25.0 (4.0)	25.4 (3.6)
NPRS, mean	6.6	6.2	6.7	6.6	6.8
Patients with moderate pain ^a , n (%)	46 (77)	39 (81)	39 (80)	40 (80)	34 (69)

^aRemainder of patients had severe pain at baseline.
 BMI=body mass index.
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Extent of exposure

- The mean dose of morphine/oxycodone per 6-hour period (mg/6h) and the mean interdose interval over the 48-hour study period are presented in **Table 2**
- The longest average interdose interval was observed in the 12/8-mg group (6.8 hours)

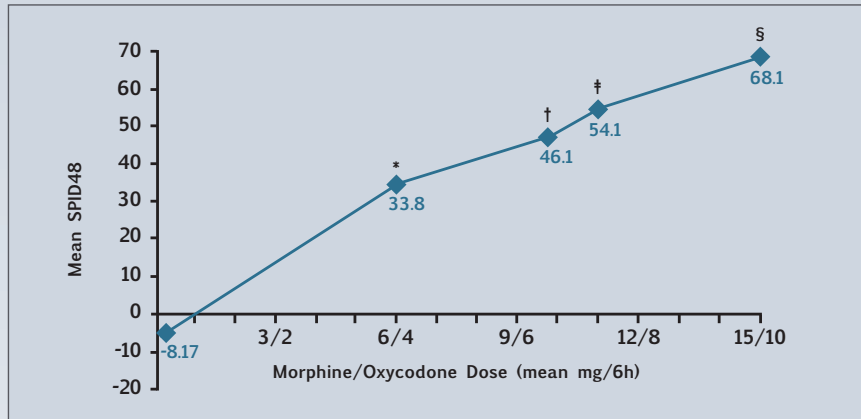
TABLE 2. STUDY MEDICATION DOSING

Dosing	Placebo (n=60)	3/2 mg (n=48)	6/4 mg (n=49)	12/8 mg (n=50)	18/12 mg (n=49)
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Efficacy

- SPID48 was significantly greater with each Q8003 dose compared with placebo (**Figure 2**)

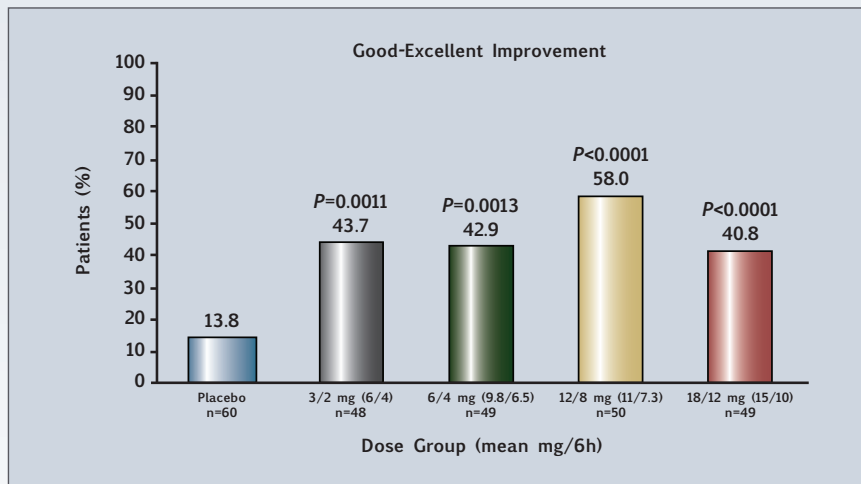
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*P=0.0015 vs placebo, SD ± 98; †P=0.0016 vs placebo, SD ± 111; ‡P=0.0001 vs placebo, SD ± 75; §P<0.0001 vs placebo, SD ± 75

- The percentage of patients reporting “good” or “excellent” improvement was significantly greater with each dose of Q8003 compared with placebo (**Figure 3**)
- Patient satisfaction was greatest with the 12/8-mg dose (58.0% good or excellent, P<0.0001 vs placebo)

FIGURE 3. GLOBAL PATIENT SATISFACTION WITH Q8003 VS PLACEBO



- Following the first dose of study medication, patients who received Q8003 had a shorter time to confirmed perceptible analgesia (range across dose groups, 0.67 to 1.93 hours) compared with patients receiving placebo (4.4 hours)
 - The shortest time to confirmed perceptible analgesia was observed in the 12/8-mg group compared with the 3/2-mg, 6/4-mg, and 18/12-mg groups (0.67 hours vs 1.93, 1.04, and 0.73 hours, respectively)
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- Patients receiving Q8003 required fewer doses of ibuprofen (mean, 1.9 to 2.3 doses/24h, range across dose groups) compared with patients receiving placebo (mean, 3.3 doses/24h)

- Fewer patients receiving Q8003 withdrew from the study for lack of efficacy (range across dose groups, 1 to 6 patients) compared with patients receiving placebo (15 patients)

Safety and tolerability

- The rate of discontinuation due to AEs was low in all treatment groups
 - Placebo, 2% (1 patient, hypotension); 3/2 mg, 2% (1 patient, nausea); 6/4 mg, 2% (1 patient, nausea); 12/8 mg, 8% (1 patient each: nausea, vomiting, decreased SpO₂, and hypotension); and 18/12 mg, 14% (2 patients each: nausea and vomiting; 1 patient each: hypoxia, pruritus, and hypotension)
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TABLE 3. ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS BY DOSE GROUP AND ACTUAL DOSE (MEAN mg/6h)

Adverse event, n (%)	Placebo (0/0) (n=60)	3/2 mg (6/4) (n=48)	6/4 mg (9.8/6.5) (n=49)	12/8 mg (11/7.3) (n=50)	18/12 mg (15/10) (n=49)
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Vomiting	1 (2)	11 (23)	18 (37)	16 (32)	25 (51)
Dizziness	4 (7)	4 (8)	12 (25)	10 (20)	12 (25)
Headache	5 (8)	5 (10)	8 (16)	10 (20)	8 (16)
Pruritus/Generalized pruritus	0	3 (6)	10 (20)	9 (18)	9 (18)
SpO ₂ decrease	1 (2)	0	5 (10)	3 (6)	5 (10)
Somnolence	0	1 (2)	2 (4)	1 (2)	4 (8)
Constipation	1 (2)	3 (6)	3 (6)	6 (12)	2 (4)
Dry mouth	2 (3)	3 (6)	2 (4)	3 (6)	2 (4)

- In general, the percentages of patient-reported AEs on the Opioid-Related Symptom Distress Scale were higher than corresponding patient- and investigator-reported AEs; selected AEs for the entire treatment period are presented below:
 - Nausea was reported by 10% of patients receiving placebo and by 52%, 76%, 64%, and 78% of patients in the 3/2-mg, 6/4-mg, 12/8-mg, and 18/12-mg groups, respectively
 - Vomiting was reported by 0% of patients receiving placebo and by 23%, 37%, 40%, and 51% of patients in the 3/2-mg, 6/4-mg, 12/8-mg, and 18/12-mg groups, respectively
- Overall, 3 patients experienced serious AEs
 - 1 patient in the 18/12-mg group had hypotension that resulted in discontinuation of study medication
 - 2 patients in the placebo group had events not related to study medication (1, hand injury; 1, deep vein thrombosis)
- Desaturations were transient, infrequent, responded quickly to supplemental oxygen, and were more frequent in the 18/12-mg dose group than in other groups; none of the patients receiving Q8003 had a respiration rate of <10 breaths/minute
- Sedation was seen in 1 patient in the 18/12-mg group; somnolence ranged from 2% to 8% across the Q8003 groups; euphoria was not observed

CONCLUSIONS

- Q8003 was associated with dose-related reductions in acute postoperative pain; even the lowest dose group (mean 6/4 mg every 6h) showed analgesic efficacy superior to placebo
- Q8003 was well tolerated, with few serious AEs or discontinuations, minimal changes in respiration and blood oxygenation, few occurrences of somnolence, and no occurrences of euphoria
- The low levels of somnolence and respiratory depression warrant further study
- The 12/8-mg dose appeared to provide the optimal combination of efficacy and tolerability; future studies will examine Q8003 with the dosing schedule of every 4 to 6 hours

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