

A randomized, open-label study of once-a-day AVINZA[®] (morphine sulfate extended-release capsules) versus twice-a-day OxyContin[®] (oxycodone hydrochloride controlled-release tablets) for chronic low back pain: The extension phase of the ACTION trial

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ABSTRACT

Study design and objective: The ACTION[®] trial, an open-label, randomized, multicenter, two-part study, compared the efficacy and safety of two sustained-release opioids (SROs), AVINZA (A-MQD), morphine sulfate extended-release capsules given once a day, and OxyContin[®] (O-ER), oxycodone modified-release tablets given twice a day, in subjects with chronic, moderate to severe low back pain. The first part of the study, the evaluation phase, was followed by an optional four-month extension phase aimed at evaluating the long-term stability of pain control, SRO dose, and quality of sleep.

Results: Three hundred and ninety-two subjects were enrolled in the study; 220 completed the evaluation phase, and 174 entered the extension phase. During the latter phase, subjects in the A-MQD group ($n = 79$) continued to report lower pain scores, better quality of sleep, lower daily morphine-equivalent doses (means of 86 mg versus 119 mg), and a comparable usage of ibuprofen compared to subjects in the O-ER group ($n = 95$). The incidence and severity of elicited opioid side effects were similar between the two groups.

Conclusions: Both study drugs resulted in significant pain relief and improved sleep in SRO-naïve patients with chronic low back pain, and this outcome was attained with a stable daily SRO dose. In patients who completed opioid dose titration, AVINZA performed significantly better than OxyContin in reducing pain scores and improving sleep—with a lower morphine-equivalent daily dose—during both the evaluation and extension phases.

INTRODUCTION

The ACTION study was a randomized, parallel-group, open-label, multicenter trial comparing the efficacy and safety of once-a-day AVINZA (A-MQD) and twice-a-day OxyContin (O-ER) in patients with chronic, moderate to severe low back pain. The study consisted of a three-to-six-week opioid dose titration period followed by an eight-week in-depth evaluation phase and an optional four-month extension phase. The primary efficacy objective of the study was to compare pain scores, daily sustained-release opioid (SRO) dose, and rescue medication usage between the two groups. The results from the evaluation phase were recently reported in this journal (Volume 2, Number 3) and demonstrated that in patients who completed opioid dose titration, A-MQD was significantly better than O-ER at reducing pain and improving sleep, while requiring a lower morphine-equivalent daily dose.¹ The current report presents the final results of the extension phase of this trial.

METHODS

Detailed information about the ACTION study design was previously reported.¹ In brief, eligible subjects were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER dosed every 12 hours and were instructed to take their study medication at the same time each day, ± 30 minutes. Subjects who enrolled in the extension phase continued on the same study

Table 1. Reasons for treatment discontinuation

	Total	A-MQD	O-ER
Titration and evaluation phases			
Number of discontinuations	172	93	79
Extension phase			
Number of discontinuations	42	24	18
Reason for discontinuation			
Subject withdrew consent	15 (35.7 percent)	10 (41.7 percent)	5 (27.8 percent)
Noncompliance	9 (21.4 percent)	5 (20.8 percent)	4 (22.2 percent)
Subject lost to follow-up	7 (16.7 percent)	4 (16.7 percent)	3 (16.7 percent)
Other	6 (14.3 percent)	3 (12.5 percent)	3 (16.7 percent)
Serious adverse event	3 (7.1 percent)	1 (4.2 percent)	2 (11.1 percent)
Lack of efficacy/persistent pain	1 (2.4 percent)	0 (0.0 percent)	1 (5.6 percent)
Investigator withdrew subject	1 (2.4 percent)	1 (4.2 percent)	0 (0.0 percent)

medication they had been taking, with doses adjusted at the discretion of the treating physician to maintain an optimal balance of pain control and tolerability. Ibuprofen (200 mg tablets, maximum of 2,400 mg/d) was the only rescue medication permitted for breakthrough pain throughout the study.

Objectives of the extension phase

The primary objective was to measure the daily SRO dose over time. Other objectives included comparing the safety and efficacy of A-MQD and O-ER by assessing pain scores, sleep measures, quality of life, and patient satisfaction.

Outcome assessments during the extension phase

Assessments were conducted monthly for four months. Subjects assessed their average pain intensity over the preceding month using a numerical rating scale in which 0 = "no pain" and 10 = "pain as bad as you can imagine." Subjects were also asked to report their highest dose of study medication in the preceding month and the number of instances ibuprofen was used for breakthrough pain during the two days prior to the clinic visit. At the final visit, subjects were asked to report their overall satisfaction with the study drug after being given five choices ranging from "extremely satisfied" to "extremely dissatisfied."

Statistical methods

Baseline demographics were compared between the two groups using the Wilcoxon two-sample test for continuous variables and the Pearson's χ^2 test for categorical variables. Efficacy variables were analyzed for predefined assessment time points and presented as absolute values or as absolute and relative changes from baseline values, where baseline values were those obtained upon enrollment in the study. Categorical efficacy variables were compared using the Cochran-Mantel-Haenszel test. All comparisons between groups were two-sided, and significance was assigned to p values < 0.05. No adjustments were made for multiple comparisons. Standard descriptive statistics were used to describe the incidence and severity of the elicited opioid-related side effects, and in the case of multiple occurrences of the same event for a single subject the event was only counted once, and the highest reported severity grade was used to rate the event. The final results of the extension phase of the ACTION study were previously presented in an abstract form.²

RESULTS

Subject disposition

A total of 392 subjects were randomized, with 203

Table 2. Patient demographics

	All subjects enrolled		Extension phase	
	A-MQD (n = 203)	O-ER (n = 189)	A-MQD (n = 79)	O-ER (n = 95)
Gender				
Male	74 (36.5 percent)	79 (41.8 percent)	27 (34.2 percent)	42 (44.2 percent)
Female	129 (63.5 percent)	110 (58.2 percent)	52 (65.8 percent)	53 (55.8 percent)
Age (years)				
Mean	49.6	50.4	47.7	49.8
Median (range)	50 (28 to 70)	50 (29 to 73)	49 (28 to 63)	50 (30 to 73)
Race				
African American*	47 (23.2 percent)	32 (16.9 percent)	24 (30.4 percent)	14 (14.7 percent)
Caucasian	154 (75.9 percent)	156 (82.5 percent)	54 (68.4 percent)	80 (84.2 percent)
Other	2 (1.0 percent)	1 (0.5 percent)	1 (1.0 percent)	1 (1.1 percent)
Weight (kg)				
Median (range)	87 (47 to 211)	91 (43 to 166)	86 (47 to 159)	91 (47 to 146)
Height (cm)				
Median (range)	168 (147 to 193)	168 (144 to 196)	166 (147 to 192)	169 (145 to 193)
Back pain history				
Median (years)	7	6	9	7
Cause of back pain**				
Mechanical	155 (76.4 percent)	160 (84.7 percent)	61 (77.2 percent)	85 (89.5 percent)
Nonmechanical	48 (23.6 percent)	29 (15.3 percent)	18 (22.8 percent)	10 (10.5 percent)
Nerve involvement**				
Yes	75 (36.9 percent)	51 (27.0 percent)	34 (43.0 percent)	27 (28.4 percent)
No	128 (63.1 percent)	138 (73.0 percent)	45 (57.0 percent)	68 (71.6 percent)

* p < 0.05 for extension phase; ** p < 0.05 for all subjects enrolled.

assigned to the A-MQD group and 198 to the O-ER group. Of those, 220 subjects (56 percent of all subjects enrolled) completed the evaluation phase (110 per group), and 174 continued on to the extension phase, with 79 in the A-MQD group and 95 in the O-ER group. Of the 174 subjects who entered the extension phase, 42 (24 percent) withdrew from the study before completing the four-month therapy protocol (24 in the A-MQD group and 18 in the O-ER group). Thus, 132 of the initial 392 subjects (34 percent) completed the entire seven-month study (55 in the A-MQD group and 77 in the O-ER group). The reasons for discontinuation during the extension phase are shown in Table 1.

Baseline characteristics

Subject demographics and baseline characteristics are shown in Table 2. The demographics of subjects who entered the extension phase were comparable between the two groups, and they did not differ from those of the 392 subjects who enrolled in the study.

Exposure to study drug

There were no differences in the number of days of opioid use between the two treatment groups. The mean total daily opioid dose was 86 mg of morphine in

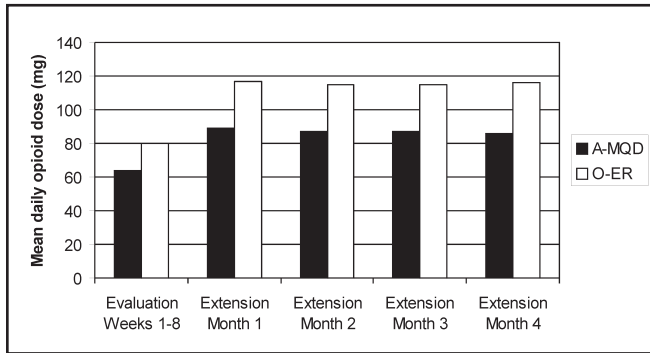


Figure 1. Mean morphine-equivalent daily dose.

the A-MQD group (range: 30 to 480 mg) and 79.5 mg of oxycodone in the O-ER group (range: 20 to 320 mg). After converting the O-ER dose into morphine equivalents using the ratio of 1:1.5 (1 mg oxycodone equivalent to 1.5 mg morphine), the mean daily morphine-equivalent dose in the O-ER group was found to be significantly higher than the mean daily morphine dose in the A-MQD group (119.2 mg versus 86 mg; $p = 0.0004$). The mean daily ibuprofen dose was comparable between the two groups for each month from Month 1 to Month 4 and for the four months combined. Figure 1 shows the mean daily morphine-equivalent doses used on a monthly basis, and Table 3 summarizes study medication and ibuprofen use in the extension phase.

Pain assessments

The mean pain scores at baseline were comparable between the two groups (6.5 in the A-MQD group and 6.6 in the O-ER group). Pain scores had decreased to ≤ 4 in all subjects who entered the evaluation phase as required by study design, and they remained at ≤ 4 throughout the evaluation phase of the study. During the four-month extension phase, the monthly average pain scores remained at ≤ 4 in both groups, with mean monthly scores consistently lower in the A-MQD group than in the O-ER group (Figure 2). The mean absolute change in pain scores from baseline for each of the four monthly evaluations was consistently larger in the A-MQD group (Figure 3), and the differences were significant at Month 2 ($p = 0.029$) and Month 3 ($p = 0.023$).

Sleep and other efficacy assessments

Both treatments resulted in improved Pittsburgh Sleep Quality Index (PSQI) scores compared to baseline. The relative changes in PSQI scores from baseline were consistently better in the A-MQD group at each of the four monthly assessments (Figure 4), with a significant difference noted at Month 1 ($p = 0.004$). At the time of exit from study, subjects were asked, "Please rate your satisfaction with the study medication you have received during your participation in this clinical trial." In the A-MQD group, 68 percent reported being "extremely satisfied"

Table 3. Exposure to study medication

	A-MQD (n = 79)	O-ER (n = 95)
Days on study medication		
Mean	103.9	107.1
Median (range)	114 (11 to 149)	113 (14 to 143)
Total daily opioid dose (mg)		
Mean	86.0	79.5
Median (range)	90 (30 to 480)	80 (20 to 320)
Total daily morphine-equivalent dose (mg)		
Mean	86.0	119.2
Median (range)	90 (30 to 480)	120 (30 to 480)
Total ibuprofen dose in past two days (mg)		
Mean	621.6	626.1
Median (range)	500 (0 to 2,200)	425 (0 to 4,800)

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