ORIGINAL ARTICLE

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-naive 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

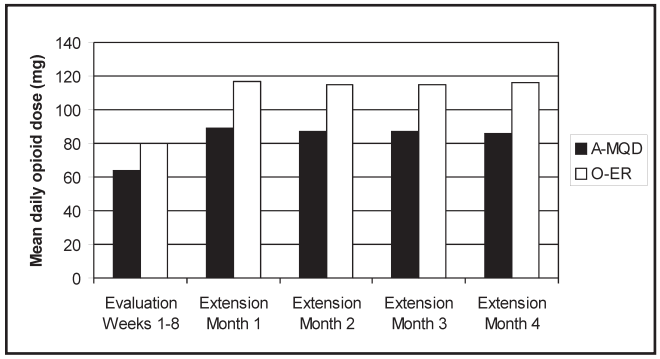

Figure 1. Mean morphine-equivalent daily dose.

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-MDQ 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)

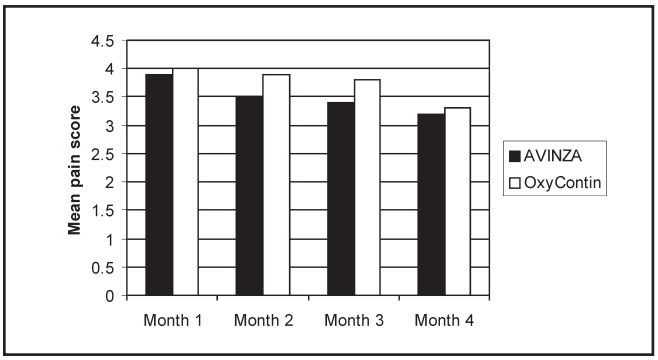

Figure 2. Mean monthly pain scores.

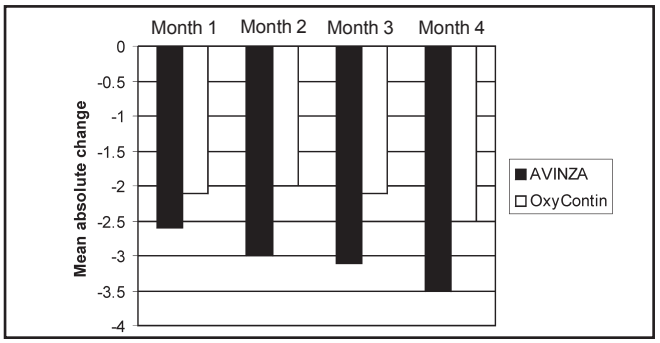

Figure 3. Mean absolute changes from baseline in monthly pain scores.

and 32 percent said they were "satisfied"; in the O-ER group, 57 percent reported being "extremely satisfied," 35 percent reported being "satisfied," and 8 percent said they were "neither satisfied nor dissatisfied."

Safety assessments

The incidence and severity of elicited opioid side effects were comparable between the two groups (Table 4) and were generally lower than those reported during the evaluation phase of the study.[1]

DISCUSSION

The ACTION study was conducted to compare the efficacy, safety, and daily SRO dose over time of A-MQD and O-ER in patients with chronic, moderate to severe low back pain. The evaluation phase of the study showed that in patients who completed opioid dose titration, A-MQD resulted in significantly better changes in pain scores from baseline, better sleep parameters, and a lower daily opioid dose (when converted into morphine equivalents) than O-ER, as well as a comparable safety profile.[1] The extension part of the study shows that A-MQD continued to perform better than O-ER on all these efficacy parameters and that the opioid daily dose remained stable over time in both groups.

In 2003, the American Pain Society issued guidelines indicating a preference for long-acting opioids over

Table 4. Incidence and severity score of elicited opioid side effects during the extension phase

	Incidence (percentage)		Mean severity*	
	A-MQD (n = 46)	O-ER (n = 40)	A-MQD (n = 46)	O-ER (n = 40)
Constipation	65	67	2.4	1.9
Dizziness	33	35	0.7	0.4
Drowsiness	54	60	1.3	1.0
Dry mouth	56	52	1.7	1.1
Itchiness	39	45	0.7	0.9
Nausea	24	22	0.5	0.2
Vomiting	9	12	0.2	0.1

* Using a scale from 0 to 10 where 0 = "not at all" and 10 = "an awful lot."

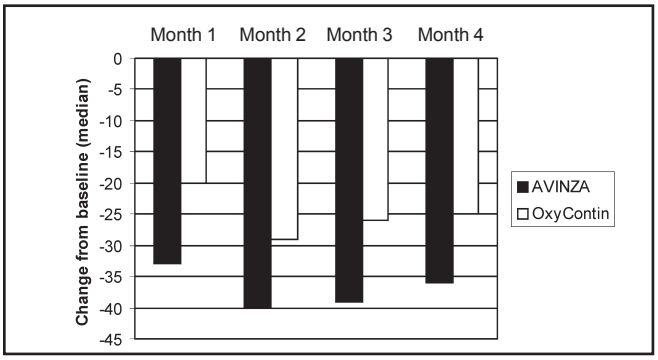

Figure 4. Median relative changes in PSQI scores from baseline.

short-acting opioids based on the belief that they may lessen the incidence and severity of end-of-dose pain.[3] Despite these recommendations, many patients with chronic, moderate to severe low back pain continue to be managed with short-acting opioids over the long term. Until this trial, there have been few reported studies on the long-term use of SROs, and these have been limited to smaller clinical trials which were not evaluated in a randomized setting.[4,5] To our knowledge, the ACTION trial is the first randomized study to evaluate the long-term use of SROs in patients with chronic low back pain. Together, the titration, evaluation, and extension phases correspond to a treatment period of approximately seven to eight months, during which comprehensive data on opioid dose, rescue medication use, pain scores, enhancement of sleep and quality of life, and safety were collected.

About two-thirds of the patients who enrolled in the study did not complete all phases of the trial. This rate of patient withdrawal is not unique to this trial and is comparable with rates reported in other randomized and single-arm studies of various SROs.[6-9] Withdrawal from the study was due to several factors, including intolerance to opioid side effects, persistent pain, and unwillingness to continue participating in a trial. The rate of withdrawal decreased at each phase of the study, with 35 percent of patients withdrawing during the three-to-six-week titration, 17 percent during the eight-week evaluation, and 18 percent during the four-month extension, corresponding to average monthly withdrawal rates of 23 percent, 9 percent, and 5 percent, respectively. The reason for withdrawal changed over time, with adverse reactions cited in 38 percent of the withdrawals during the titration and evaluation phases but in only 7 percent of the withdrawals during the extension phase. In contrast, withdrawal of consent was the most frequent cause during the extension phase, cited in 36 percent of the cases, compared to 22 percent of the cases during the titration and evaluation phases. Lack of efficacy was cited in only 2.4 percent of withdrawals during the extension phase.

In the extension phase of the study, the mean daily opioid dose remained constant at each monthly assessment in both groups. The low incidence of withdrawals due to lack of efficacy or toxicity during the extension phase and the stable opioid dose over time suggest that patients with low back pain whose SRO dose can be properly titrated may achieve pain relief over the long term with limited toxicity. Furthermore, the stable opioid dose observed over a period of four months suggests the slowing down, or maybe the abrogation, of the development of tolerance to opioids in patients whose pain is reliably well controlled. Additional clinical benefits observed in the study were improvement of sleep and limited use of rescue medication for breakthrough pain. These results support the recommendations of the American Pain Society for prescribing sustained-release rather than short-acting opioids when opioids are expected to be needed for the long term.

The ACTION trial showed that for patients who remained in the study, A-MQD was superior to O-ER in terms of improving pain scores from baseline, improving sleep scores, and allowing for lower morphine-equivalent daily doses and use of rescue medications. These differences were statistically significant during the evaluation phase and continued to be seen during the extension phase. Except for the opioid daily dose, which remained significantly lower in the A-MQD group for each of the four months of the extension phase, the other differences were not always statistically significantly different, most likely because the small number of patients continuing in the extension phase didn't offer an opportunity to detect significant differences. As in the evaluation phase, the incidence and severity of elicited opioid side effects during the extension phase were comparable between the two groups.

In conclusion, the two parts of the ACTION study demonstrate that for patients who completed opioid dose titration, once-daily A-MQD allowed for better pain scores and quality of sleep, with a lower daily morphine-equivalent dose and fewer uses of rescue medication than twice-daily O-ER. The study also documented that SROs are useful agents for the symptomatic management of patients with chronic low back pain and that pain was well controlled with stable doses of the SRO over a four-month period of time.

FINANCIAL DISCLOSURE

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REFERENCES

1. Rauck RL, Bookbinder SA, Bunker TR, et al.: The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA®) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin®) for the treatment of chronic, moderate to severe low back pain. *Journal of Opioid Management*. 2006; 2(3): 155-166.
2. Rauck RL, Bookbinder SA, Bunker TR, et al.: Once-daily AVINZA vs. twice-daily OxyContin in an open-label extension (Part II) of the ACTION trial for the treatment of chronic moderate to severe low back pain. *J Pain*. 2006; 7(4 Suppl 1): 6314.
3. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. Glenview, IL: American Pain Society, 2003.
4. Schofferman J: Long-term opioid analgesic therapy for severe refractory lumbar spine pain. *Clin J Pain*. 1999; 15(2): 136-140.
5. Chao J: Retrospective analysis of Kadian (morphine sulfate sustained-release capsules) in patients with chronic, nonmalignant pain. *Pain Med*. 2005; 6(3): 262-265.
6. Hale M, Dvergsten C, Gimbel J: Efficacy and safety of oxymorphone extended release in chronic low back pain: Results of a randomized, double-blind, placebo-controlled and active-controlled Phase III study. *J Pain*. 2005; 6(1): 21-28.
7. Hale MF, Rauck R, Ma T, et al.: Open-label titration of oxymorphone extended release in opioid-experienced patients with chronic low back pain. Poster #138. Presented at the 22nd Annual Meeting of the American Academy of Pain Medicine, San Diego, 2006.
8. Hale ME, Fleischmann R, Salzman R, et al.: Efficacy and safety of controlled-release versus immediate-release oxycodone: Randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999; 15(3): 179-183.
9. Markenson JA, Croft J, Zhang PG, et al.: Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain*. 2005; 21(6): 524-535.