ORIGINAL ARTICLE

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

Richard L. Rauck, MD
Stephen A. Bookbinder, MD
Timothy R. Bunker, MD
Christopher D. Alftine, MD
Richard Ghalie, MD
Andres Negro-Vilar, MD, PhD
Egbert de Jong, MD
Steven Gershon, MD

ABSTRACT

This large, open-label, randomized, parallel-group, multicenter study compared two oral 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 SRO-naive subjects ages 30 to 70 with chronic, moderate to severe low back pain. Of the 392 subjects enrolled and randomized, 266 (132 in the A-MQD group and 134 in the O-ER group) completed the opioid dose titration phase and entered an eight-week evaluation phase. During the evaluation phase, A-MQD achieved significantly better pain control than O-ER, as demonstrated by a greater decrease from baseline in pain scores obtained four times daily during weeks one, four, and eight ($p = 0.002$). The number of breakthrough-pain rescue medication doses adjusted for the number of patient days was significantly lower in the A-MQD group ($p < 0.0001$). Better pain control with A-MQD was achieved with a significantly lower daily opioid dose than with O-ER (mean 69.9 mg and 91 mg morphine equivalents, respectively; $p = 0.0125$). Quality of sleep was significantly better with A-MQD for the entire evaluation phase ($p = 0.0026$). The incidence and severity of elicited opioid side effects were similar in the two groups. This trial demonstrated that once-daily A-MQD provides consistent around-the-clock pain relief in patients with low back pain. In patients who completed opioid dose titration, A-MQD was significantly better than O-ER for reducing pain and improving sleep, while requiring a lower daily opioid dose.

Key words: AVINZA, OxyContin, chronic low back pain

INTRODUCTION

Chronic pain is defined as pain lasting at least six months and/or pain duration longer than the expected time for normal tissue healing.[1] It is estimated that approximately 50 million Americans live with chronic pain caused by disease or accident.[2] One of the most prevalent types of chronic pain is low back pain. Andersson[3] estimated that the annual prevalence of low back pain in the United States ranges from 12 percent to 30.2 percent, and the lifetime incidence ranges from 48.8 percent to 69.9 percent. The socioeconomic impact of chronic low back pain is considerable. It was estimated that total healthcare expenditures incurred in 1998 by individuals with low back pain in the United States were $90.7 billion, and total incremental expenditures attributable to back pain reached approximately $26.3 billion.[4] Treatment of low back pain consists of pharmacological and nonpharmacological approaches, including nonsteroidal anti-inflammatory drugs, muscle relaxants, single-entity opioids, and combinations of nonopioid and opioid analgesics.

Recent clinical studies have demonstrated that opioid pharmacotherapy is effective for the management of

chronic low back pain.[1,5-9] In a recent position paper, the American Pain Society (APS) stated that oral sustained-release opioids (SROs) are one of the most important innovations in the management of moderate to severe cancer-related pain and that they are usually preferred over short-acting opioids because their longer duration of action may lessen the frequency and severity of end-of-dose pain.[1] Over the last several years, SROs have emerged as the most commonly prescribed pharmacological therapy for chronic, moderate to severe pain, and their usage has been steadily increasing.[5]

Several oral SROs are available, characterized by type of opioid and modified-release technology. Because opioids are rapidly absorbed in the gastrointestinal tract, the pharmacokinetic and analgesic properties of an SRO are highly dependent on the technology employed to release the opioid from its carrier. Thus, two different modified-release formulations of the same opioid may result in different analgesic profiles, even if dosed at the same frequency. Among the opioids, morphine has the longest history in the treatment of pain, has a well-defined safety and efficacy profile,[5-9] and is available in several modified-release formulations. The first modified-release morphine formulation to be available for oral administration, MS Contin® (MSC, Purdue Pharma LP, Stamford, CT), was approved for dosing every 12 hours. More recently, AVINZA® (A-MQD, Ligand Pharmaceuticals Inc., San Diego, CA), a morphine-containing SRO with a novel modified-release technology, was approved for once-daily dosing. The technology employed in A-MQD capsules was developed specifically for once-daily use. The capsules are made of hard gelatin shells containing small beads 1 to 2 mm in diameter; 10 percent of the beads release their morphine content rapidly upon ingestion, and the other 90 percent are composed of an inert core surrounded by a morphine layer enclosed in a matrix of soluble and insoluble polymers and release their morphine content over 24 hours. This dual-release formulation allows targeted plasma morphine concentrations to be attained rapidly after ingestion and to be sustained throughout the 24-hour dosing interval.

Caldwell et al.[10] conducted a double-blind, double-dummy, four-arm, Phase III study comparing A-MQD given once in the morning, A-MQD given once in the evening, MSC given every 12 hours, and placebo in opioid-naïve patients with chronic, moderate to severe pain due to osteoarthritis. Designed for regulatory registration, this study was powered as a noninferiority trial to demonstrate that A-MQD is at least as effective as MSC. Results from weekly efficacy assessments confirmed the noninferiority hypothesis and showed that both A-MQD and MSC were significantly better than placebo for improving pain. This trial, however, did not include multiple pain assessments throughout the day to document that the A-MQD formulation provides constant pain relief over 24 hours with a single daily dose. A comparison of the pharmacokinetics of A-MQD given every 24 hours and MSC given every 12 hours showed that both SROs provided similar total systemic exposures, but A-MQD had less fluctuation of morphine concentrations during a 24-hour period.[11]

The formulation used for OxyContin® tablets (O-ER, Purdue Pharma LP, Stamford, CT) delivers approximately 38 percent of its content rapidly upon ingestion and the remaining content over a more extended period.[12] In a randomized double-blind study conducted in patients with chronic, moderate to severe low back pain, O-ER given every 12 hours was shown to have comparable safety and efficacy to short-acting oxycodone given four times daily.[13]

A trial comparing the pharmacokinetics of A-MQD and O-ER has shown fewer and narrower peak-to-trough fluctuations with A-MQD.[14] Prior to the present trial, no trial had been conducted to compare the efficacies of A-MQD and O-ER. In addition, no randomized trials have been published comparing the long-term use of different SROs in patients with chronic low back pain. Therefore, we conducted this randomized, multicenter study with multiple pain assessments throughout the day to demonstrate that A-MQD given once daily provides continuous pain relief over 24 hours and to compare the efficacy and safety of once-daily A-MQD to that of twice-daily O-ER in patients with chronic, moderate to severe low back pain.

METHODS

Study design

The ACTION (AVINZA Comparator Trials in Opioid Naive) study was an open-label, randomized, parallel-group, multicenter trial designed to evaluate and compare the efficacy and safety of A-MQD and O-ER for the treatment of chronic, moderate to severe low back pain. The study protocol was reviewed and approved by a central institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. Informed consent was obtained from each patient before enrollment in the study. The study was cofunded by Ligand Pharmaceuticals Inc. (San Diego, CA) and Organon Pharmaceuticals USA Inc. (Roseland, NJ).

Participants

Subjects between the ages of 30 and 70 were candidates for the study if they had persistent, moderate to severe, chronic low back pain that was judged by the investigator as appropriate for chronic opioid therapy. To be eligible for the study, subjects had to have had suboptimal analgesic response to nonsteroidal anti-inflammatory

drugs, acetaminophen, and/or immediate-release opioids. Subjects were required to have a pain score > 4 on an 11-point numerical scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine." Subjects with neuropathic back pain were allowed in the trial provided that no surgical or pharmacological intervention was anticipated to be required in the next three months. To be eligible for enrollment, subjects had to be willing to be treated with the study drug to which they were randomized, be able to read and understand English, and be willing and capable to input study-specific assessments using a hand-held patient electronic diary (PED).

Subjects were excluded from the study if they were treated with an SRO, had used an SRO within the previous six months, or were previously unresponsive or intolerant to opioids. Other exclusion criteria included a serious diagnosed medical condition that would interfere with the ability to complete the study, back surgery in the past six months, more than two surgeries for back pain, or an expected need for back surgery or steroid injection during the first 12 to 14 weeks of the trial.

Interventions

Eligible patients were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER dosed every 12 hours. Subjects were instructed to take their study medication at the same time of the day ± 30 minutes. The branded formulations of both SROs and ibuprofen were provided free of charge throughout the study. Ibuprofen (200-mg tablets) was the only rescue medication permitted for breakthrough pain and could be used in doses up to 2,400 mg a day. Subjects were instructed not to take an additional dose of their SRO for breakthrough pain. The study protocol provided detailed guidelines for opioid dose escalation. Measures to prevent opioid-induced constipation were recommended but not mandatory.

Titration phase. The subjects underwent opioid dose titration for three to six weeks to establish a patient-specific daily dose that provided an optimal balance between efficacy and safety. The study protocol specified that the opioid dose was considered stabilized when all the following criteria were met: 1) same dose of study medication for seven consecutive days, 2) pain scores consistently = 4 for all scheduled assessments on three consecutive days, and 3) an average of two or fewer ibuprofen doses per day during these three days.

Evaluation phase. Upon completion of the titration phase, subjects entered an eight-week evaluation phase divided in two four-week periods. In the first period, the SRO daily dose attained at the end of the titration phase was to remain fixed for four weeks, and in the event of worsening pain ibuprofen rescue could be used as needed. In the second period, the SRO daily dose could be modified as needed to optimize pain control.

Extension phase. Following completion of the eight-week evaluation phase, the subjects were given the option to continue the study for an additional four months (extension phase). The aim of this extension was to objectively evaluate the long-term efficacy and pattern of SRO use.

Objectives

The objectives of the eight-week evaluation phase of the trial were: 1) to compare the efficacy and safety of A-MQD and O-ER in SRO-naive patients with chronic, moderate to severe low back pain; 2) to evaluate the efficacy of A-MQD in this patient population; and 3) to demonstrate that the modified-release formulation used in A-MQD delivers continuous 24-hour pain relief with a single daily dose.

Patient evaluation

Subjects were requested to assess their pain levels and rescue medications daily. Self-reported scores of the "pain right now" component of the Brief Pain Inventory[15] (BPI), a validated 11-point visual analog scale, were collected every morning prior to the morning dose for the duration of the study. The number of ibuprofen rescue doses used in the preceding 24 hours was also collected daily for the duration of the study. In addition, to provide a detailed evaluation of the extent and duration of pain relief achieved with each SRO, subjects were requested to document their pain scores and rescue medication usage during weeks one, four, and eight of the evaluation phase at four specific times during the day: immediately before taking the morning dose, and then six, nine, and 12 hours after taking the morning dose. In the O-ER group, the 12-hour time point had to be assessed before taking the evening dose. Except for on day one, the pain scores obtained immediately before taking the morning opioid dose correspond to the trough opioid plasma concentration for both drugs and thus represent the end-of-dose pain score. The pain scores obtained 12 hours after taking the morning dose correspond to another trough opioid plasma concentration in the O-ER group only.

Sleep parameters were evaluated monthly using the Pittsburgh Sleep Quality Index (PSQI), a validated multidimensional sleep scale developed for use in clinical trials.[16] Other efficacy assessments consisted of the Short-Form 12 (SF-12) Questionnaire, a validated multipurpose quality-of-life instrument consisting of a 15-item ordinal scale, and the Work Limitations Questionnaire, a validated instrument that measures the physical and mental impact of pain on work-related activities.

Daily for the duration of the study, subjects were asked to answer the Elicited Opioid Side Effect

Table 1. Patient disposition			
	Total (percent)	**A-MQD (percent)**	**O-ER (percent)**
Number of subjects randomized (AST)	392 (100)	203 (100)	189 (100)
Titration phase			
Subject withdrawals during titration	126 (32.1)	71 (35.0)	55 (29.1)
Subjects completing titration	266 (67.9)	132 (65.0)	134 (70.9)
Eight-week evaluation phase			
Subjects entering the evaluation phase (ITT)	266 (100)	132 (100)	134 (100)
Subject withdrawals during evaluation phase	46 (17)	22 (17)	24 (18)
Subjects completing evaluation phase	220 (83)	110 (83)	110 (82)
Discontinuations			
Number of discontinuations	172 (43)	93 (45.8)	79 (41.8)
Reason for discontinuation			
Adverse reactions	65 (37.8)	38 (40.9)	27 (31.2)
Adverse event	60	36	24
Serious adverse event	5	2	3
Subject withdrew consent	37 (21.5)	18 (19.4)	19 (24.1)
Subject lost to follow-up	19 (11.0)	12 (12.9)	7 (7.5)
Lack of efficacy/persistent pain	16 (9.3)	10 (10.8)	6 (7.6)
Noncompliance	11 (6.4)	6 (6.4)	5 (6.3)
Opioid dose not stabilized	9 (5.2)	5 (5.4)	4 (5.1)
Investigator withdrew patient	6 (3.5)	1 (1.1)	5 (6.3)
Protocol violation	5 (2.9)	1 (1.1)	4 (5.1)
Other	4 (2.3)	2 (2.1)	2 (2.5)

Questionnaire, which captures the occurrence of seven adverse reactions commonly reported with opioid use (constipation, nausea, vomiting, dizziness, drowsiness, dry mouth, and itchiness) and their severity using a scale from 0 to 10, where 0 = "no event" and 10 = "an awful lot." Serious adverse events (SAEs), which included any documented or suspected episode of opioid misuse or abuse, were recorded by the investigators and reported to the clinical research organization (CRO) that managed the trial.

As nearly all efficacy, safety, and dosing information was derived from data entered by subjects into their PEDs (PHT Corp., Charlestown, MA), one researcher at each study site was given thorough training in the proper use of the PED and served as trainer for other site personnel and for subjects treated at that site. To enhance compliance with treatment and schedule of assessments, each PED was programmed to sound an alarm at the anticipated times of study medication dosing and data input. Subjects were instructed to submit the data they had entered in their PED daily, by phone, and were contacted by the study-site personnel if they neglected to do so.

Sample size, randomization, and statistical analyses

The number of patients to enroll in the study was determined prospectively, with the intent of having

Table 2. Patient demographics in the all-subjects-treated (AST) and intent-to-treat (ITT) populations

		AST population		ITT population	
		A-MQD (n = 203) (percent)	O-ER (n = 189) (percent)	A-MQD (n = 132) (percent)	O-ER (n = 134) (percent)
Gender	Male	74 (36.5)	79 (41.8)	48 (36.4)	61 (45.5)
	Female	129 (63.5)	110 (58.2)	84 (63.6)	73 (54.5)
Age (years)	Median	50	50	49	51
	Range	28 – 70	29 – 73	28 – 68	30 – 73
Race*	Black/African American	47 (23.2)	32 (16.9)	41 (31.1)	21 (15.7)
	Caucasian	154 (75.9)	156 (82.5)	90 (68.2)	112 (83.6)
	Other	2 (1)	1 (0.5)	1 (0.8)	1 (0.7)
Weight	Median	87 kg	91 kg	87 kg	93 kg
Height	Median	168 cm	168 cm	167 cm	169 cm
Back pain history	Median	7 years	6 years	8 years	7 years
Cause of back pain**	Mechanical	155 (76.4)	160 (84.7)	102 (77.3)	115 (85.8)
	Nonmechanical	48 (23.6)	29 (15.3)	30 (22.7)	19 (14.2)
Nerve involvement***	Yes	75 (36.9)	51 (27)	54 (40.9)	38 (28.4)
	No	128 (63.1)	138 (73.0)	78 (59.1)	96 (71.6)

* p not significant (NS) for AST and $p < 0.02$ for ITT; ** $p < 0.04$ for AST and NS for ITT; *** $p < 0.04$ for AST and $p = 0.03$ for ITT.

approximately 120 subjects enter the extension phase of the study, a cohort size deemed adequate to provide useful information on the long-term use of SROs. We empirically assumed drop-out rates of 30 percent during the titration phase, 10 percent/month during the eight-week evaluation phase, and 10 percent during the transition from the evaluation to the extension phase. With these assumptions, we determined that 400 subjects had to be enrolled in the study, 280 of whom would enter the eight-week evaluation phase; of those, 120 would continue into the extension phase. We also verified that a sample size of 140 subjects/arm entering the evaluation phase would provide an 80 percent power to detect an increase in the proportion of patients achieving pain relief, from 70 percent in the O-ER arm to 85 percent in the A-MQD, using a two-sided test and an alpha error of 0.05.

Randomization was performed centrally for all study sites, with no stratification factors. Because the number of subjects withdrawn from study during titration could differ between the two study groups, an interactive voice response system was used for subject registration and randomization, and this system was programmed to calibrate the randomization ratio as needed to achieve an equal number of subjects from each group at the start of the evaluation phase.

For data analysis, two populations were distinguished: the "all subjects treated" (AST) population, defined as all randomized subjects who received at least one dose of either study drug; and the "intent to treat" (ITT) population, defined as subjects who entered the eight-week evaluation phase. Standard descriptive statistics were used to report baseline demographic variables. Comparison between groups was performed by the Wilcoxon two-sample test for continuous variables and the Pearson's chi-square test for categorical variables.

Efficacy variables (raw scores from BPI, PSQI, and a brief sleep questionnaire) were analyzed for the ITT population only. These variables were analyzed and compared between groups for predefined assessment time

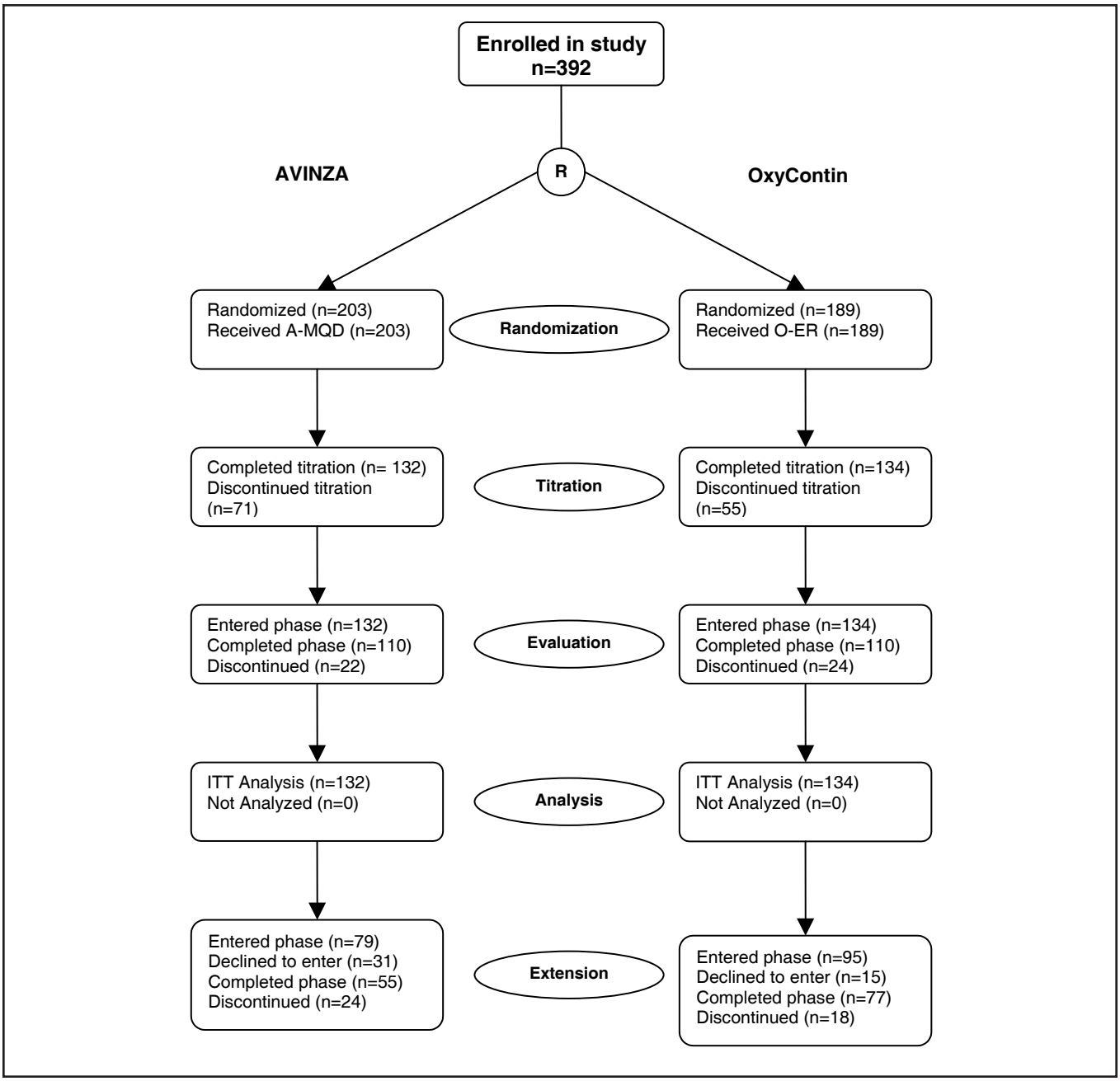

Figure 1: Patient disposition diagram.

points and presented both as absolute values and as relative changes from baseline, defined as the values obtained at enrollment. Daily and weekly averages during the eight-week evaluation phase were computed. Baseline scores were compared between the two groups using the Wilcoxon two-sample test. Categorical efficacy variables were compared using the Cochran-Mantel-Haenzel test. Within-group continuous efficacy variables were compared by the paired t-test or the Wilcoxon signed rank test. Differences between treatments and 95 percent confidence intervals for predefined pain assessment time points were compared by ANOVA, with patient baseline characteristics tested as covariates. All comparisons between groups were two-sided and considered significant for p values < 0.05. No adjustment was made for multiple comparisons or for one interim analysis, as the penalty spent for the latter was deemed negligible.

Safety information was analyzed for the AST and ITT populations. Standard descriptive statistics were used to describe the incidence and severity of the elicited opioid-related side effects. In the case of multiple occurrences of the same event within the same subject, the event was only counted once, and the highest reported severity grade was counted. In tables where severity or relationships were

Table 3. Exposure to study medication

		AST population		ITT population	
		A-MQD (n = 203)	O-ER (n = 189)	A-MQD (n = 132)	O-ER (n = 134)
Days to dose stabilization	Mean	28.6	30.6	28.6	30.6
	Median (range)	28 (6 – 50)	29 (12 – 56)	28 (6 – 50)	29 (12 – 56)
Days on study medication	Mean	62.9	64.2	83.8	82.2
	Median (range)	76 (2 – 134)	78 (0 – 114)	83 (17 – 134)	85 (17 – 114)
Total daily opioid dose (mg)	Mean	63.7	53.3	69.9	60.7
	Median (range)	56 (30 – 360)	40 (16 – 233)	58 (30 – 360)	56 (16 – 233)
Daily dose in morphine-equivalents* (mg)	Mean**	63.7	80	69.9	91
	Median (range)	56 (30 – 360)	60 (24 – 349)	58 (30 – 360)	84 (24 – 349)

* Using American Pain Society conversion factor 1:1.5 for oxycodone:morphine; ** p = 0.001 for ATT, p = 0.0125 for ITT by ANOVA.

tabulated, the adverse event with the greatest severity or strongest relationship to study drug was the event counted.

This report presents the final results of the first part of the study, i.e., the titration and evaluation phases. An interim analysis of the evaluation phase for the first 329 subjects enrolled in the study has been previously presented.[17] As extensive quality-of-life data were collected in the study, these analyses will be the subject of a future report. A preliminary analysis of the data from the extension phase of the study was presented recently and will also be the subject of a future report.[18]

RESULTS

Between May and November 2004, 392 eligible subjects were enrolled at 35 study sites and randomized to treatment with A-MQD (n = 203) or O-ER (n = 189). During the dose-titration phase, 126 subjects (32.1 percent) left the study, 71 (35 percent) in the A-MQD arm and 55 (29 percent) in the O-ER arm. The remaining 266 subjects met the criteria for stabilized opioid dose and entered the evaluation phase, with 132 in the A-MQD group and 134 in the O-ER group. These 266 subjects correspond to the ITT population that served to evaluate and compare the efficacy and safety of the two study drugs during the evaluation phase. Forty-six subjects (17.3 percent of the ITT population) left the study before completing the eight-week evaluation phase, 22 in the A-MQD group and 24 in the O-ER group, and the remaining 220 subjects (110 per group) completed the evaluation phase. Subject disposition is shown in Figure 1, and reasons for leaving the study are shown in Table 1.

Baseline characteristics

Subject demographics and baseline characteristics for the AST and ITT populations are shown in Table 2. The demographics of the two study groups were comparable except for the number of African Americans in the ITT population (31.1 percent in the A-MQD group vs. 15.7 percent in the O-ER group, $p < 0.02$), nonmechanical back pain in the AST population (23.6 percent in the A-MQD group vs. 15.3 percent in the O-ER group, $p < 0.04$), and back pain associated with nerve involvement, which was higher in the A-MQD group both in the AST population (36.9 percent vs. 27 percent, respectively, $p < 0.04$) and the ITT population (40.9 percent vs. 28.4 percent, respectively, $p = 0.03$).

Exposure to study drug

Table 3 summarizes the exposure to study medication in the AST and ITT population. There were no differences in the number of days of opioid use between the two treatments, both in terms of total length of therapy (mean in the ITT of 83.8 and 82.2 days for A-MQD and O-ER, respectively) and of the length of the titration phase (mean in the ITT of 28.6 and 30.6 days for A-MQD and O-ER,

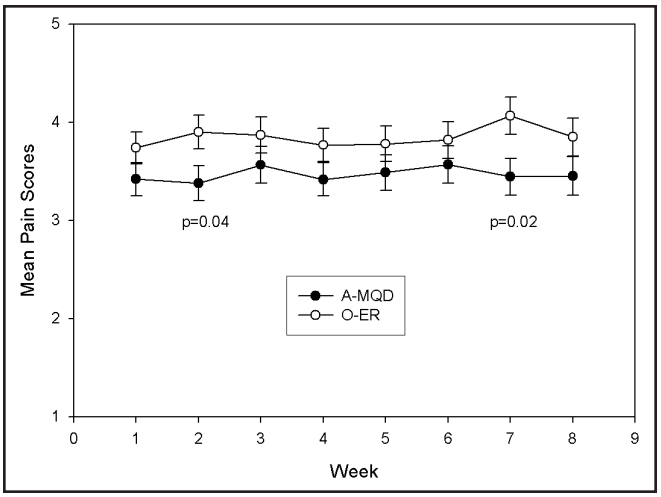

Figure 2. Mean weekly BPI pain scores during the evaluation phase for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

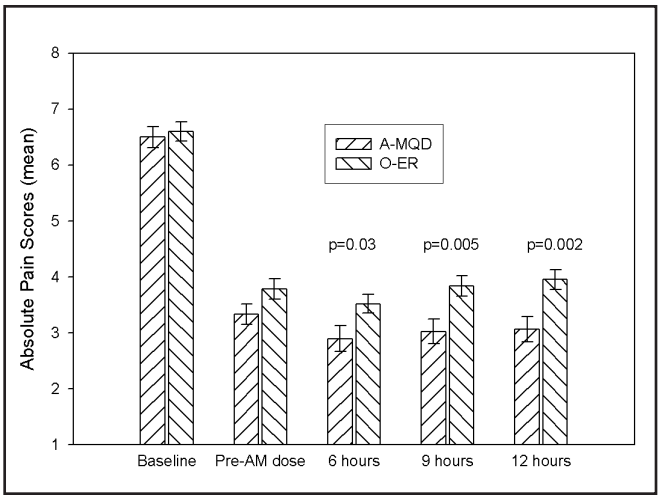

Figure 3. Mean weekly BPI pain scores averaged for the evaluation phase weeks one, four, and eight for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

respectively). For the ITT population, the mean total daily opioid dose was 69.9 mg of morphine (range, 30 to 360 mg) in the A-MQD group and 60.7 mg of oxycodone (range, 16 to 233 mg) in the O-ER group. When converting the oxycodone dose into an equianalgesic morphine dose using the ratio of 1:1.5 (i.e., 1 mg oxycodone equivalent to 1.5 mg morphine) recommended by the APS,[1] the morphine-equivalent dose used by the O-ER group in the ITT population was significantly higher (mean = 91 mg) compared to the morphine dose used in the A-MQD group (mean = 69.9 mg, p = 0.0125).

Pain assessments

The mean pain scores at baseline (i.e., at enrollment) were comparable in the two groups (6.5 in the A-MQD group and 6.6 in the O-ER group). Pain scores had decreased to 4 or less in all subjects who entered the evaluation phase as required by study design. During the eight-week evaluation phase, the weekly average BPI pain scores remained at less than 4 in both groups (Figure 2)—with mean weekly scores consistently lower in the A-MQD group compared to the O-ER group—for the full duration, with the difference reaching significance at weeks two (p = 0.04) and seven (p = 0.02). The BPI pain scores obtained four times a day for seven consecutive days on weeks one, four, and eight were averaged for all three weeks and were found to be significantly lower in the A-MQD group compared to the O-ER group at six hours (p = 0.03), nine hours (p = 0.005), and 12 hours (p = 0.002) after the morning dose (Figure 3).

There was a difference between the two groups in the pain score profiles observed over 24 hours (Figure 3). In the A-MQD group, the mean pain scores six, nine, and 12 hours after the morning dose were consistently lower than the mean pain scores prior to the morning dose, suggesting that pain relief was maintained or further improved throughout the day. By contrast, in the O-ER group, only the mean pain score six hours after the morning dose was lower than the mean pain score prior to the morning dose, whereas the mean pain scores nine and 12 hours after the morning dose were higher than the mean pain score prior to the morning dose, suggesting a gradual loss of the analgesic effect.

Figure 4 reports the mean absolute change in the BPI pain scores between the first assessment at entry on study (baseline) and the pain scores averaged for weeks one, four, and eight and shows a significant difference in favor of the A-MQD group for the six-hour (p = 0.038), nine-hour (p = 0.005), and 12-hour (p = 0.002) time points after the morning dose.

A responder analysis was performed for the ITT population, with a responder defined as a subject whose average weekly pain score had improved by at least 2 points from entry on study at week one to week eight of the evaluation phase or the week of the last visit. In the A-MQD group, 73 of 132 subjects (55.3 percent) were identified as responders, compared to 59 of 134 subjects (44.0 percent) in the O-ER group (p = 0.03).

Sleep assessments

Both treatments resulted in improved sleep scores as assessed by the PSQI assessments, evaluated every four weeks, with improvement noted by the end of titration and continuing during the eight-week evaluation phase. As shown in Figure 5, the relative changes in PSQI scores from entry on study were significantly better in the A-MQD group compared to the O-ER group at week four (30 percent

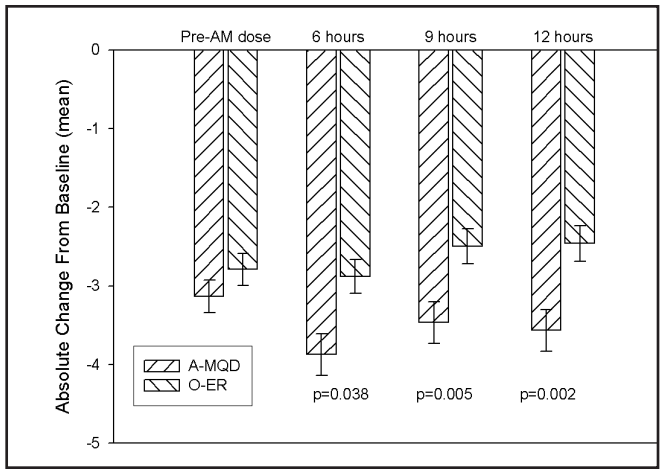

Figure 4. Mean absolute change from baseline in BPI pain scores averaged for the evaluation phase weeks one, four, and eight for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

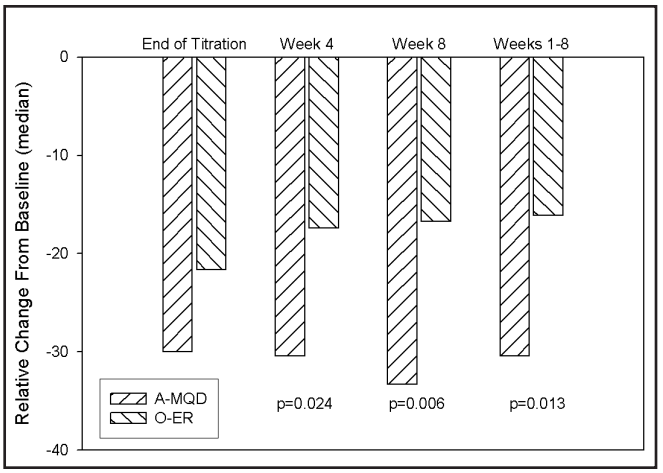

Figure 5. Median relative change in PSQI scores from baseline in the ITT population. Comparison between groups was performed by the Brown-Mood test, and only significant p values for comparison between treatment groups are shown

improvement vs. 17 percent, p = 0.024), week eight (33 percent vs. 17 percent, p = 0.006) and weeks one, four, and eight combined (30 percent vs. 16 percent, p = 0.013).

Rescue medications

Ibuprofen (200-mg capsules) was the only analgesic permitted as rescue medication for breakthrough pain. Ibuprofen use during the eight-week evaluation phase was low in both groups, with a mean of four to six doses/patient/week (Figure 6). There were fewer total rescue doses in the A-MQD group (2,595 doses) compared to the O-ER group (3,154 doses), and the difference was significant ($p < 0.0001$) when ibuprofen doses were normalized to the number of patient days on study (A-MQD = 83,124 and O-ER = 81,268).

Safety assessments

The incidence and severity of elicited opioid side effects were comparable between the two groups both in the AST and ITT populations, as shown in Table 4. Sixteen SAEs were reported (seven from A-MQD and nine from O-ER). Eight of these 16 SAEs were considered probably or possibly related to study drug, two in the A-MQD group (one case each of hypersensitivity and hypoxia) and six in the O-ER group (one case each of intestinal obstruction and respiratory failure and four cases of drug abuse or diversion). Drug abuse or diversion was described by the investigator as intentional misuse (n = 1), drug abuse (n = 1), or theft (n = 2). No cases of drug abuse or diversion were reported in the A-MQD group.

DISCUSSION

The ACTION study, a randomized, two-arm, open-label, multicenter trial, was conducted to compare the effectiveness of two SROs, each with a unique modified-release profile, and to evaluate the pattern of SRO use over several months in patients with chronic, moderate to severe low back pain. Our aims in conducting this trial were: 1) to verify that A-MQD provides 24-hour around-the-clock pain relief with a single daily dose, and 2) to compare the clinical benefits of A-MQD given once a day to those of O-ER given twice a day. Our working hypothesis was that, as A-MQD dosed once daily provides plasma concentrations with narrower fluctuations and with a single "peak and trough" profile over 24 hours compared to O-ER dosed twice daily, it is better at maintaining morphine concentrations within a patient-specific effective therapeutic range, resulting in superior pain relief, fewer breakthrough pain episodes, and possibly less dose increase over the long term.

We conducted this trial in subjects with chronic low back pain because it is the single most common reason for SRO prescriptions in the United States. In addition, as subjects with low back pain are usually younger and healthier than subjects with chronic pain due to cancer or osteoarthritis, the risk of confounding factors due to comorbidities was expected to be lower. To our knowledge, this is the largest randomized trial comparing two SROs and also the first trial to compare the efficacy and safety of A-MQD and O-ER in treating low back pain.

Our goal was also to design a pragmatic trial consistent with the clinical management of low back pain in the general population; specifically, the protocol 1) allowed up to six weeks for opioid dose titration to increase the proportion of subjects continuing into the evaluation phase; 2) extended the evaluation period to eight weeks instead of four weeks as seen in most other studies; 3) offered an optional four-month extension phase to replicate "real world" treatment conditions; and 4) selected

Table 4. Incidence and severity score of elicited opioid side effects during the titration plus evaluation phase								
	ITT population				AST population			
	Incidence (percent)		Mean severity score*		Incidence (percent)		Mean severity score*	
	A-MQD (n = 113)	O-ER (n = 115)	A-MQD (n = 113)	O-ER (n = 115)	A-MQD (n = 175)	O-ER (n = 164)	A-MQD (n = 175)	O-ER (n = 164)
Constipation	87	89	3.3	2.9	92	90	3.8	3.2
Dizziness	58	64	0.9	1.0	67	71	1.3	1.1
Drowsiness	85	84	2.0	1.9	85	88	2.3	2.0
Dry mouth	82	76	2.2	2.0	85	81	2.6	2.1
Itchiness	65	57	1.2	1.3	67	62	1.4	1.4
Nausea	50	47	0.8	0.7	60	564	1.1	0.9
Vomiting	24	19	0.3	0.2	28	23	0.5	0.2
* Using a scale from 0 to 10 where 0 = "not at all" to 10 = "an awful lot".								

commonly used scales to measure pain, sleep, quality of life, and functional status. Because double-blinded, double-dummy clinical trials are difficult to manage and execute, we opted for an open-label design for this Phase IV trial. We assumed that the large size of the trial, the multiplicity of study sites, the matching of the number of subjects entering the evaluation phase, and the use of an independent CRO to manage the study would largely offset any potential bias resulting from the open-label design. In fact, the similarity of baseline characteristics between the two groups argues against a systematic bias introduced in patient selection. That unmasking study drugs led to differences between the two groups in early discontinuations cannot be ruled out.

The large number of study sites and the diversity of practices represented led to the enrollment of a study population fairly representative of the general population of subjects with chronic low back pain about to switch to a SRO. This population was characterized by a preponderance of women (60 percent) and middle-aged patients (median of 50 years), a protracted history of back complaints (median of six to seven years), and back problems due to mechanical causes (75 to 85 percent) and with moderate to severe symptoms (pain scores 6 to 7). The two study groups had comparable characteristics at enrollment, except for a higher percentage of Black/African-American patients, back pain of nonmechanical origin, and back pain with nerve involvement in the A-MQD group. Differences in some baseline characteristics sometimes occur when central randomization is performed without stratification by study site, as was the case in this study. These few imbalances in patient demographics, however, do not account for the differences in efficacy perceived between the two SROs, as the superior efficacy of A-MQD over O-ER persists with or without covariate adjustment.

Of the 392 patients enrolled, a sizeable proportion (32 percent) withdrew prematurely from study, mostly during the titration phase (73 percent). The three most frequent reasons cited for early withdrawal add up to 70 percent of the total, with adverse reactions being the most common (37.8 percent), followed by withdrawal of consent (21.5 percent) and refusal to follow-up (11 percent), the last two reflecting an active decision on the part of the subject (32.5 percent combined). In contrast, persistent pain was cited as the cause for early discontinuation in only 9.3 percent of the cases. These drop-out rates are not unique to this trial and are consistent with those observed in patients treated with SROs outside clinical trials as well as in those enrolled in other randomized and single-arm studies of various SROs.[19-21] This substantial drop-out rate may reflect: 1) the low acceptance of subjects suffering from pain, with or without functional disability, of the demands of clinical trials, particularly when the study involves drugs readily available without participation in a clinical trial; 2) the poor tolerability profile of SROs in some patients; and 3) the failure of these drugs to meet overall patient expectations. Reducing patient attrition from SRO therapy might be achieved by better preparing them to accept the early, but usually reversible, opioid-related adverse reactions and by tailoring opioid dose titration according to individual patient needs and characteristics of the SRO.

Two-thirds of subjects (67.9 percent) enrolled in this trial completed the titration phase, and a large majority (57 percent) completed the eight-week evaluation phase. These patients clearly benefited from taking their prescribed SRO dose, as their pain scores significantly decreased from entry on study to completion of titration, with a 49 percent improvement (from a mean score of 6.5 to 3.4) in the A-MQD group and a 43 percent improvement (from a mean score of 6.6 to 3.7) in the O-ER group. In both groups, the mean pain scores remained low during the evaluation phase. In addition, these patients had few episodes of breakthrough

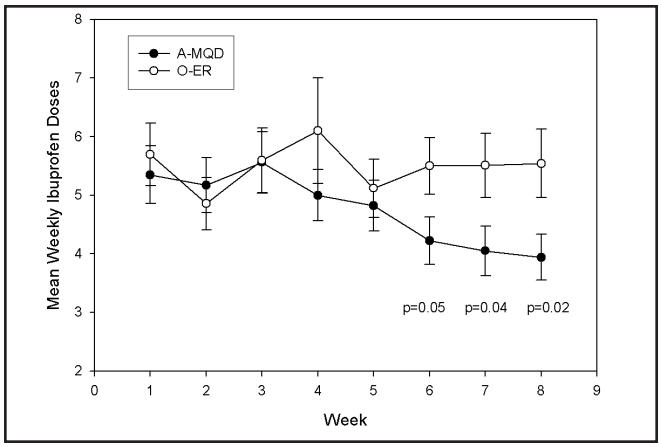

Figure 6. Mean weekly number of ibuprofen rescue doses in the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

pain, as suggested by the average of less than one daily ibuprofen rescue, and reported better quality of sleep. This was accomplished with an acceptable safety profile. Thus, SROs represent an effective approach for the symptomatic treatment of the majority of patients with chronic, moderate to severe low back pain, with the prerequisite that the titration phase be conducted carefully and the patients are properly supervised for the duration of their therapy.

This study also confirmed our hypothesis that A-MQD given once every 24 hours provides significantly better pain management compared to O-ER given once every 12 hours. When we designed this study, we were aware of data suggesting that two-thirds of subjects treated with O-ER for chronic pain required more than twice-daily dosing to achieve pain control, with dosing every eight hours reported as the most common method.[22] To avoid variations in dosing intervals between patients within each treatment group, we required that A-MQD and O-ER be administered according to their approved doses. Since we did not compare the pharmacokinetics of A-MQD and O-ER in this trial, we cannot prove that the superior efficacy results are correlated to more uniform opioid plasma concentrations and fewer fluctuations over 24 hours. The clinical evidence, however, strongly supports this explanation, as patients in the A-MQD group showed around-the-clock pain relief consistently throughout the evaluation period, with lower mean pain scores six, nine, and 12 hours after the morning dose compared to the pre-morning dose mean pain scores, with no rebound in mean pain scores 24 hours later. Furthermore, prior pharmacokinetic studies have already documented that A-MQD has a reduced fluctuation index (i.e., less difference between peak and trough plasma concentrations) than twice-daily O-ER despite being administered only once daily.[14] Our study extends the findings of pharmacokinetic studies and documents, in a large number of patients, the added benefits in terms of better pain relief, improved sleep, and lower daily opioid dose over those achieved with an SRO given twice daily.

A significant finding of this trial is that patients in the A-MQD group had better pain relief and at the same time required a lower daily opioid dose compared to patients in the O-ER group (when the dose in the latter group was converted into morphine equivalents). One possible explanation is that the conversion factor recommended by the APS of 1:1.5 for oxycodone:morphine does not apply to sustained-release opioids. Another possible explanation is that for patients to achieve consistent pain control over 24 hours with A-MQD dosed once daily, they are likely to have had uniform morphine plasma concentrations within the therapeutic range throughout 24 hours, possibly leading to slower development of tolerance to morphine.

Another key study finding was the beneficial effect on sleep noted with both SROs. We believe that improved sleep quality was due to less frequent awakenings from breakthrough pain episodes. Improved sleep could also be ascribed to subjects' not needing to wake up in the night to take additional doses of analgesic, as is observed with short-acting opioids or nonopioid analgesics. Patients in the A-MQD group had significantly better sleep scores compared to patients in the O-ER group in week four, week eight, and weeks one through eight of the evaluation phase. Improved sleep in the A-MQD group confirms and extends the sleep findings reported by Caldwell et al.[10] A recently reported polysomnography study confirmed these subjective sleep findings and provided objective measurements of the effects of A-MQD on various sleep parameters, including decreased latency to persistent sleep, number of night awakenings, and total wake time.[23] This study also demonstrated increased sleep efficiency, total sleep time, and Stage 2 sleep duration, with no significant decrease in REM duration from baseline.

It has been argued that SROs' only advantage over short-acting opioids is convenience, and that the abuse liability negates the value of SROs. In our opinion, the results of the ACTION trial refute this assertion. The convenience of SRO dosing may improve the compliance with the prescribed SRO dosing schedule. Fewer peak-to-trough fluctuations over 24 hours result in more uniform pain control, which in turn lead to more normalization of daily activities, better sleep, and less potential for overshooting of medication secondary to poor pain control. Lastly, fewer daily doses simplifies the assessment of a patient's compliance with therapy as a result of easier pill counts.

In conclusion, the ACTION trial demonstrated that SROs are effective agents for the symptomatic management of the majority of patients with chronic, moderate to severe low back pain. Furthermore, the study clearly documented that A-MQD provides 24-hour around-the-clock pain relief with a once-a-day dose and results in better pain control, better quality of sleep, a lower daily opioid dose, and a comparable safety profile compared to patients receiving twice-daily O-ER.

DISCLOSERS

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Richard L. Rauck, MD, Carolinas Pain Institute, Winston-Salem, North Carolina.
Stephen A. Bookbinder, MD, Ocala Rheumatology Research Center, Ocala, Florida.
Timothy R. Bunker, MD, The Birmingham Pain Center, Birmingham, Alabama.
Christopher D. Alftine, MD, Medford Medical Clinic, Medford, Oregon.
Richard Ghalie, MD, Ligand Pharmaceuticals Inc., San Diego, California.
Andres Negro-Vilar, MD, PhD, Ligand Pharmaceuticals Inc., San Diego, California.
Egbert de Jong, MD, Organon Pharmaceuticals USA Inc., Roseland, New Jersey.
Steven Gershon, MD, Advanced Pain Management and Rehabilitation PC, Virginia Beach, Virginia.

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The ACTION Trial Study Group consisted of the following co-investigators: J. Adler (Colorado Springs, CO), L. Alwine (Downingtown, PA), D. Auzine II (New Orleans, LA), V. Carrigan (Clarksville, TN), C. Codding (Oklahoma City, OK), P. Coleman (Lansing, MI), W. Cox (Cincinnati, OH), R. Dahmes (New Orleans, LA), M. Drass (Altoona, PA), W. Eider (Yakima, WA), L. Gilderman (Pembroke Pines, FL), P. Ginsberg (Hollywood, FL), I. Goldsmith (Las Vegas, NV), M. Hale (Plantation, FL), W. Harper (Raleigh, NC), C. Herring (Wilmington, NC), D. Herrington (San Angelo, TX), W. Keeton (Decatur, GA), V. Kumar (Las Vegas, NV), J. Pottanat (Newburgh, IN), R. Rapoport (Fall River, MA), W. Rayner (Jenkintown, PA), D. Riff (Anaheim, CA), G. Rothbaas (Perrysburg, OH), J. Rubino (Raleigh, NC), W. Seger (Ft. Worth, TX), G. Silver (Clearwater, FL), J. Sutherland (Waterloo, IA), E. Thomas (Prairie Village, KS), A. Weil (Marietta, GA).

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