ORIGINAL ARTICLE

A randomized, open-label, multicenter trial comparing once-a-day AVINZA® (morphine sulfate extended-release capsules) versus twice-a-day OxyContin® (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: Improved physical functioning in the ACTION trial

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ABSTRACT

This multicenter trial compared the efficacy, safety, and effect on quality of life and work limitation of once-daily extended-release morphine sulfate capsules (AVINZA®, A-MQD) and twice-daily controlled-release oxycodone HCl tablets (OxyContin®, O-ER) in subjects with chronic, moderate to severe low back pain. After randomization and a period of opioid dose titration, subjects (n = 266) underwent an eight-week evaluation phase and an optional four-month extension phase (n = 174 in extension phase). Subjects were assessed using the 12-item Short-Form Health Survey® (SF-12) and the Work Limitations Questionnaire® (WLQ). In both groups, significant improvements were observed in the SF-12 mean scores for physical functioning ($p < 0.001$), role physical ($p < 0.0001$), bodily pain ($p < 0.0001$), physical summary ($p < 0.001$), and mental component summary ($p < 0.005$). At the end of the titration period, greater relative improvements from baseline were seen in the SF-12 section on physical components in the A-MQD group versus the O-ER group, with significant differences observed for physical functioning ($p = 0.0374$), role physical ($p = 0.0341$), bodily pain ($p = 0.0001$), and physical summary ($p = 0.0022$). In both groups, SF-12 mean scores improved significantly for mental health ($p < 0.01$), role emotional ($p < 0.01$), social functioning ($p < 0.0005$), vitality ($p < 0.005$), and the mental component summary ($p < 0.005$), but no significant differences were noted between the two groups. Both groups reported improvement from baseline in WLQ physical demands scores, with no significant differences noted between the two groups. At the end of the evaluation phase, fewer subjects were unable to work due to illness or treatment in the A-MQD group than in the O-ER group (8.5 percent versus 19.4 percent, respectively; $p = 0.0149$). In conclusion, compared to twice-daily OxyContin, once-daily AVINZA resulted in significantly better and earlier improvement of physical function and ability to work.

Key words: morphine sulfate, oxycodone HCl, AVINZA, ACTION trial, low back pain, chronic pain, physical functioning, quality of life

INTRODUCTION

The ACTION trial was a randomized, parallel-group, open-label, multicenter study comparing the efficacy and safety of two sustained-release opioids—once-daily A-MQD (AVINZA®, Ligand Pharmaceuticals, San Diego, CA) and twice-daily O-ER (OxyContin®, Purdue Pharma LP, Stamford, CT)—in patients with chronic, moderate to severe low back pain. The study consisted of an opioid dose titration period followed by an eight-week in-depth evaluation phase and an optional four-month extension phase. The objective of the study was to compare the long-term efficacy and safety of A-MQD and O-ER in this patient population. We have recently reported the final efficacy and safety results of this trial.[1,2] The study

showed that both A-MQD and O-ER significantly improve pain and sleep scores. During the evaluation phase of the study, these improvements were significantly greater in the A-MQD group than in the O-ER group, with a significantly lower morphine-equivalent daily dose and fewer ibuprofen rescue doses.[1] Better results in the A-MQD group continued to be observed during the extension phase of the study.[2] This report presents the final results of the trial, examining assessments of quality of life and work limitation in the study population.

METHODS

Population and study design

Detailed information about the patient population and trial design has been reported previously.[1] Eligible subjects between the ages of 30 and 70 with a history of low back pain of at least six months' duration who were not being treated with an extended-release opioid were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER every 12 hours. Subjects were instructed to take their study medication at the same time each day, ± 30 minutes. Ibuprofen was the only rescue medication permitted for breakthrough pain during the study. Subjects were allowed to enter the evaluation phase if their pain was stabilized by the study medication during the titration phase; stabilization was defined as the combination of 1) pain scores no greater than 4 on three consecutive days, based on a visual analogue scale ranging from 0 (no pain) to 10 (worst pain); 2) the same daily dose of study medication for seven consecutive days; and 3) two or fewer ibuprofen rescue doses needed over three consecutive days. During the eight-week evaluation phase of the study, detailed subject-derived information on pain, sleep, ibuprofen use for breakthrough pain, and daily opioid dose was obtained. Subjects who agreed to enroll in the optional four-month extension phase continued on the same study medication, with ibuprofen rescue as needed. Except for the first four weeks of the evaluation phase, the daily dose of study medication (but not the frequency of daily administration) was adjusted at the discretion of the treating physician to maintain an optimal balance of pain control and tolerability.

Assessing quality of life and ability to work

The Short-Form Health Survey® (SF-12) is a validated, multipurpose, self-administered, 12-item health questionnaire derived from the more detailed SF-36 questionnaire.[3] It evaluates, for the preceding week, four physical domains (physical functioning, role physical, bodily pain, general health), four mental domains (vitality, social functioning, role emotional, mental health), and two summary health measures (physical component, mental component), with higher scores indicating better results. The Work Limitations Questionnaire® (WLQ) is a validated, self-administered questionnaire evaluating the subject's ability to work over the preceding two weeks.[4] It consists of 25 items that aggregate in four scales—time management, physical demands, mental-interpersonal demands, and output demands—with the scale score ranging from 0 (limited none of the time) to 100 (limited all of the time). The WLQ was administered only to the subset of subjects who identified themselves as being employed full time or part time upon entry into the study. The licensed version of both questionnaires was used, and no translations were made.

Both questionnaires were administered at baseline, at the end of the opioid dose titration period, at the end of Weeks 4 and 8 of the evaluation phase, and monthly during the extension phase, from Month 1 (i.e., Week 12 of the evaluation phase) to Month 4 (Week 24). Data input was performed by the subjects during monthly office visits using a handheld electronic diary specifically programmed for this study (PHT Corp., Charlestown, MA), without interference or assistance from healthcare providers.

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. The SF-12 and WLQ variables were analyzed as absolute values and as absolute and relative changes from baseline values, with baseline values defined as those obtained upon enrollment in the study. Comparison of the baseline scores between the two groups was performed using the Wilcoxon t-test; comparison of the differences between groups for subsequent evaluations was performed with ANOVA, using baseline values as covariates; and within-group comparisons of changes over time were performed using the pairwise t-test. All comparisons were two-sided, and significance was attributed to p values less than 0.05.

RESULTS

Subject disposition

A total of 392 subjects were randomized (203 to A-MQD and 198 to O-ER). Of those, 268 subjects entered the evaluation phase, 220 completed the evaluation phase, 174 continued into the optional four-month extension phase, and 132 completed the extension phase. The baseline demographics of the two study groups were comparable except for the number of African-American subjects (31.1 percent in the A-MQD group versus 15.7 percent in the O-ER group, $p < 0.02$) and subjects with

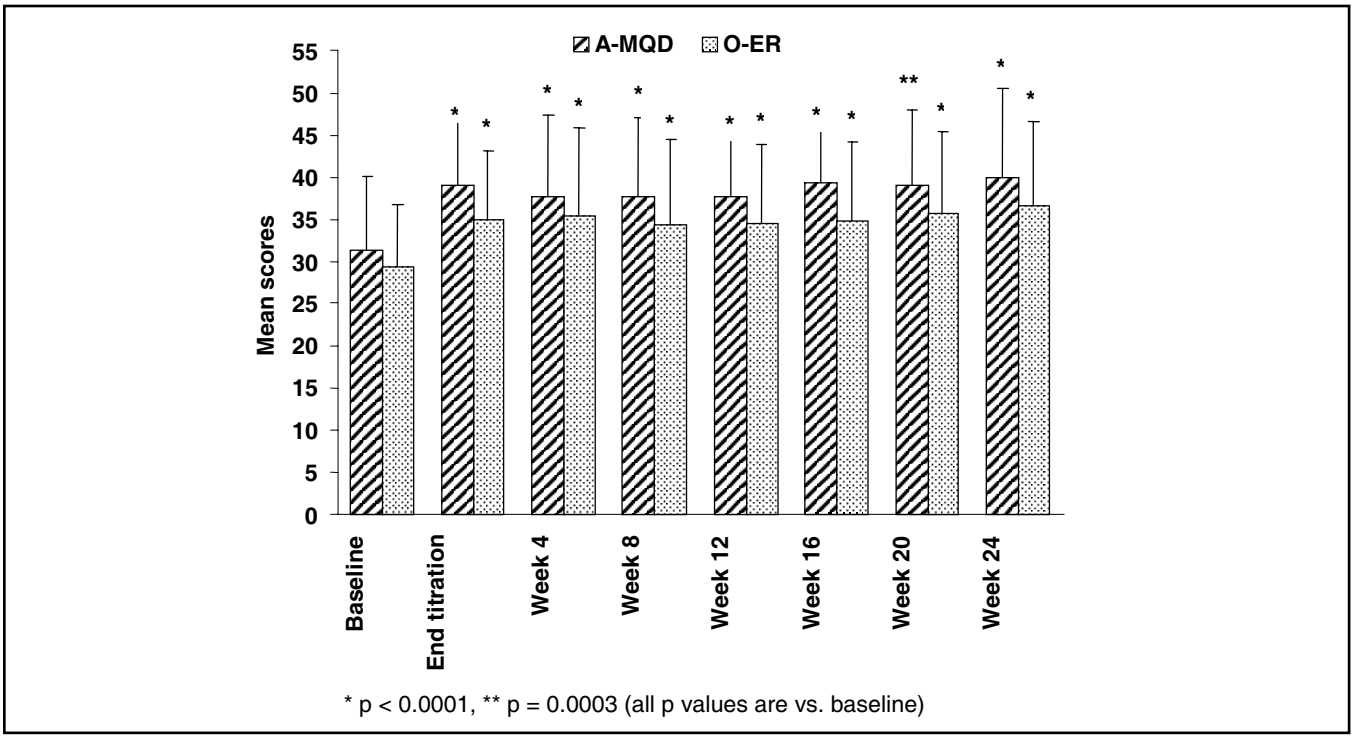

Figure 1. SF-12 physical component summary (mean scores ± standard deviations).

back pain associated with nerve involvement (36.9 percent in the A-MQD group versus 27 percent in the O-ER group, $p < 0.04$). Details on reasons for withdrawal from study and subject characteristics at different stages of the study were reported previously.[1,2]

SF–12 assessments

Adherence to answering the SF-12 questionnaires was high in both groups, ranging in the A-MQD group from 95 percent at baseline to 82 percent at Week 24 and in the O-ER group from 91 percent at baseline to 78 percent at Week 24. In both groups, there were significant improvements compared to baseline in the mean scores for all monthly SF-12 physical domain assessments for physical functioning ($p < 0.001$), role physical ($p < 0.0001$), bodily pain ($p < 0.0001$), and the physical component summary ($p < 0.001$). For the general-health physical domain, mean scores were significantly improved in the A-MQD group at the end of the opioid dose titration phase ($p = 0.0001$) and at Week 16 ($p = 0.0174$), and in the O-ER group at the end of the opioid dose titration phase ($p = 0.0052$), Week 4 ($p = 0.031$), and Week 8 ($p = 0.0435$). In all physical domains, most of the improvement was achieved during opioid dose titration in the first weeks of treatment (Figure 1). The mean relative score improvements were generally better in the A-MQD group than in the O-ER group, and the differences were significant between the two groups at the end of the opioid dose titration period for all five physical domains (Table 1). The greatest relative score changes from baseline were noted in the bodily pain domain and were significantly better in the A-MQD group as compared to the O-ER group at the end of opioid dose titration ($p = 0.0002$), at evaluation Week 8 ($p = 0.0002$), and at Month 1 ($p = 0.0433$) and Month 2 ($p = 0.0171$) of the extension phase.

In both groups, there were significant improvements from baseline in the mean scores for all monthly SF-12 assessments for the five mental domains: mental health ($p < 0.01$), role emotional ($p < 0.01$), social functioning ($p < 0.0005$), vitality ($p < 0.005$), and the mental component summary ($p < 0.005$) (Figure 2). However, there were no differences between the two groups in terms of relative score changes from baseline in any of the mental domains (Table 2).

WLQ assessments

All four demands scores, as well as the summary index scores, remained stable throughout the study in both treatment groups, with no significant differences noted between the two groups (Table 3). At baseline, the two groups were comparable in terms of the proportion of responses to the question, "During the past four weeks, did you work or did you not work at all due to illness or treatment?" (Table 4). At evaluation Week 8, however, 19.4 percent of subjects in the O-ER group were unable to work, versus 8.5 percent in the A-MQD group ($p = 0.0149$).

Table 1. SF-12 physical domain components

Time	Group	Mean relative change from baseline (percent)				
		Physical functioning	**Role physical**	**Bodily pain**	**General health**	**Physical summary**
End of titration	A-MQD (n = 121)	33.2	26.2	45.8	14.3	30.8
	O-ER (n = 112)	27.9	21.8	27.6	10.3	22.9
	p value*	**0.0278**	**0.0127**	**0.0002**	**0.0264**	**0.0017**
Evaluation Week 4	A-MQD (n = 100)	25.4	20.5	36.9	9.7	19.8
	O-ER (n = 84)	25.9	24.9	28.0	10.1	21.3
	p value	NS	NS	0.081	NS	NS
Evaluation Week 8	A-MQD (n = 93)	27.8	27.3	43.2	10.4	22.6
	O-ER (n = 84)	24.3	23.7	25.5	10.2	18.6
	p value	NS	NS	**0.0065**	NS	NS
Extension Month 1	A-MQD (n = 69)	25.2	26.8	40.1	10.8	21.5
	O-ER (n = 71)	19.0	22.8	26.4	5.8	17.6
	p value	NS	NS	**0.0433**	NS	NS
Extension Month 2	A-MQD (n = 55)	31.0	27.9	44.3	14.4	25.3
	O-ER (n = 70)	21.9	22.0	27.5	2.5	19.4
	p value	NS	NS	**0.0171**	NS	NS
Extension Month 3	A-MQD (n = 50)	25.3	27.7	44.5	4.6	18.7
	O-ER (n = 69)	23.1	23.2	32.1	2.8	22.6
	p value	NS	NS	NS	NS	NS
Extension Month 4	A-MQD (n = 43)	33.8	24.5	45.4	6.0	22.8
	O-ER (n = 54)	28.0	28.2	31.8	4.8	27.3
	p value	NS	NS	NS	NS	NS

* p values for between-treatment differences constructed for an ANOVA with baseline value as a covariate; NS = not significant ($p \geq 0.05$).

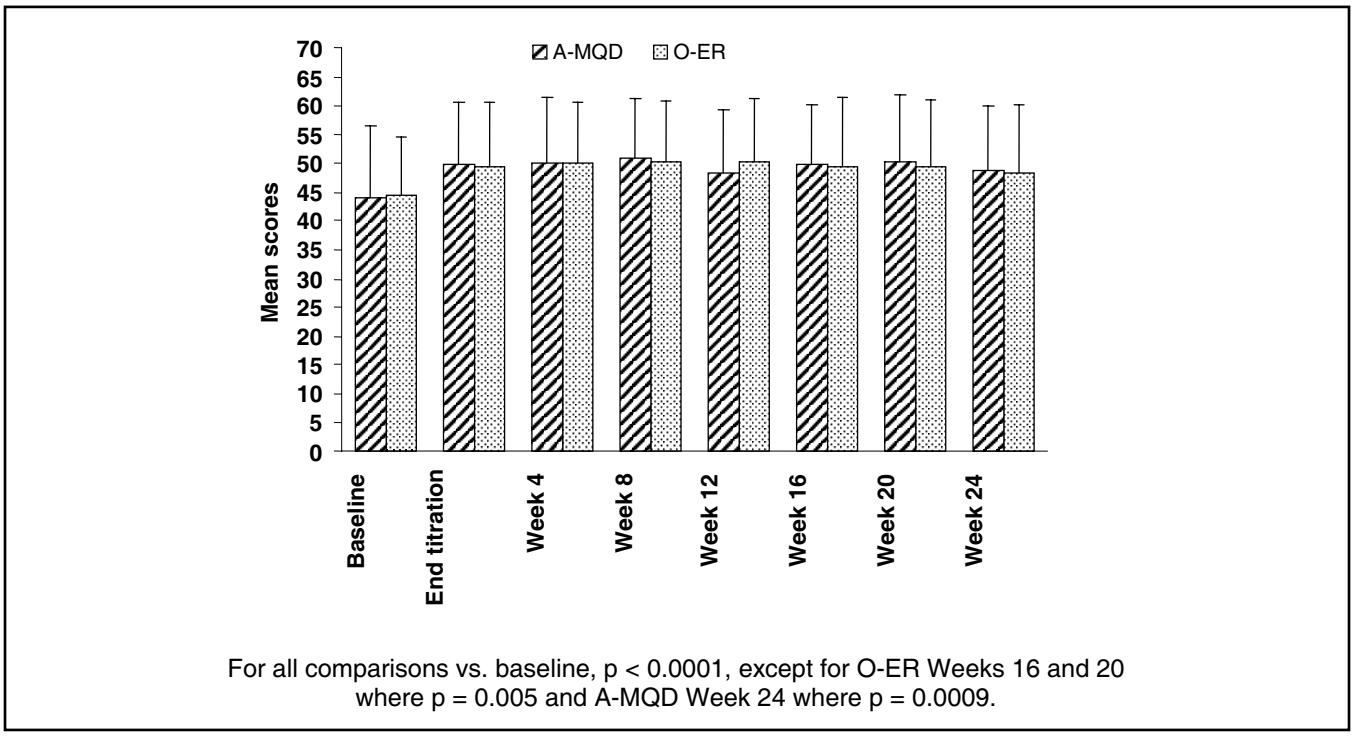

Figure 2. SF-12 mental component summary (mean scores ± standard deviations).

DISCUSSION

The ACTION trial compared the effectiveness of once-daily A-MQD and twice-daily O-ER, each with a unique modified-release profile, in the management of chronic, moderate to severe low back pain. We have previously reported that both A-MQD and O-ER significantly improved pain and sleep scores during the eight-week evaluation phase of the study, that A-MQD resulted in significantly better improvement in pain and sleep scores while requiring a significantly lower daily morphine dose, and that the two study medications resulted in comparable incidence and severity of opioid-induced side effects.[1,2]

Chronic low back pain is not only a cause of significant suffering; it is often associated with disability, resulting in a considerable socioeconomic impact. One study has estimated the total healthcare expenditures incurred by individuals with low back pain at $90.7 billion and the total incremental expenditures attributable to back pain at $26.3 billion.[5] Low back pain is one of the most common causes of work disability and accounts for about a quarter of workers' compensation costs.[6] Therefore, clinical management of low back pain should aim at providing the best possible pain relief as well as at preserving physical function, with the goal of preventing disability or reducing its severity. Several trials have studied short-acting and extended-release opioids for chronic non-cancer pain and have reported improvement in patient self-reports of pain intensity, but few trials have assessed whether pain relief is also associated with functional gains. Where specific functional assessments have been performed, findings have been equivocal, with functional improvements noted in some studies but not in others.[7-10] Since opioids have been shown to provide significant pain relief in most studies, divergence in functional outcomes is likely due to reasons other than lack of pain control, such as the small number of subjects evaluated in a study, the heterogeneity in the patient population, and incomplete functional-data collection. It may also be that in some individuals, disability is too advanced to be reversible.

The ACTION trial was well suited to an evaluation of the effect of opioid therapy on functional status because it enrolled a large number of subjects who were treated for several months and because it involved a randomized study design that mitigated the risk of patient-selection bias. Two validated and complementary functional questionnaires were used in the study, in accordance with the IMMPACT recommendations for outcome measures in clinical trials involving patients with chronic pain.[11] We selected the SF-12, a disease-nonspecific functional health survey, instead of the more commonly used SF-36 because it is briefer and amenable to repeated testing, as confirmed by the adherence rate of between 80 and 90 percent observed in the trial. The study did not include objective functional capacity assessments, such as measurement of active range of motion of the lumbar spine, or static and dynamic strength testing because their impact on this large trial would have been prohibitive in terms of both subject time demands and cost.

Table 2. SF-12 mental domain components						
Time	**Group**	**Mean relative change from baseline (percent)**				
		Vitality	**Social functioning**	**Role emotional**	**Mental health**	**Mental summary**
End of titration	A-MQD (n = 121)	15.6	29.1	27.4	21.5	18.2
	O-ER (n = 112)	14.7	25.8	23.1	14.9	13.0
	p value*	NS	NS	NS	0.0578	NS
Evaluation Week 4	A-MQD (n = 100)	15.2	26.1	26.7	24.0	21.2
	O-ER (n = 84)	14.6	27.7	26.5	18.9	16.2
	p value	NS	NS	NS	NS	NS
Evaluation Week 8	A-MQD (n = 93)	16.9	32.8	30.4	25.5	23.0
	O-ER (n = 84)	13.8	20.7	31.5	17.5	16.4
	p value	NS	**0.0087**	NS	NS	NS
Extension Month 1	A-MQD (n = 69)	17.8	34.1	35.4	25.5	25.9
	O-ER (n = 71)	14.5	26.0	23.3	15.2	14.8
	p value	NS	NS	NS	NS	NS
Extension Month 2	A-MQD (n = 55)	20.6	30.4	33.6	27.9	24.8
	O-ER (n = 70)	12.1	25.0	22.3	11.1	11.2
	p value	NS	NS	NS	NS	NS
Extension Month 3	A-MQD (n = 50)	23.5	35.3	40.7	31.5	32.1
	O-ER (n = 69)	12.7	23.3	21.3	10.9	10.0
	p value	NS	NS	NS	NS	NS
Extension Month 4	A-MQD (n = 43)	16.5	30.9	34.6	28.7	25.0
	O-ER (n = 54)	14.3	23.9	17.1	11.6	9.3
	p value	NS	NS	NS	NS	NS

* p values for between-treatment differences constructed for an ANOVA with baseline value as a covariate; NS = not significant ($p \geq 0.05$).

Table 3. Work Limitations Questionnaire						
Time	**Group**	**Mean demands score***				
		Time	**Physical**	**Mental**	**Output**	**Index**
Baseline	A-MQD	54.9	40.5	72.6	67.3	18.2
	O-ER	53.3	43.7	74.2	67.1	18.3
End of titration	A-MQD	72.1	26.4	84.6	82.9	21.5
	O-ER	73.5	29.3	81.9	76.9	20.5
Evaluation Week 4	A-MQD	74.1	24.2	84.9	83.0	21.3
	O-ER	71.1	27.2	80.6	78.6	20.1
Evaluation Week 8	A-MQD	74.4	26.4	87.4	87.0	22.1
	O-ER	75.3	24.2	85.5	78.0	20.9
Extension Month 1	A-MQD	73.3	26.1	83.3	80.7	21.1
	O-ER	79.9	23.0	85.3	78.2	20.9
Extension Month 2	A-MQD	78.4	24.3	83.9	81.0	21.2
	O-ER	79.3	20.8	84.6	77.3	21.0
Extension Month 3	A-MQD	72.4	23.4	86.1	83.7	21.8
	O-ER	77.9	29.7	81.1	78.7	20.8
Extension Month 4	A-MQD	79.2	23.1	88.9	86.0	22.6
	O-ER	70.6	22.6	81.3	79.4	19.6

* Scale: 0 (limited none of the time) to 100 (limited all of the time).

This study showed that both A-MQD and O-ER led to significant improvement on both the physical and mental components of the SF-12. Physical functioning scores improved by approximately 20 to 30 percent, and almost all of the gains were already achieved by the end of the opioid dose titration phase, when the first post-baseline assessment was performed. Improved physical functioning continued to be noted in subsequent monthly assessments made over a total of more than seven months of follow-up study. At the end of dose titration, subjects treated with A-MQD reported significantly better improvement in all physical component scores than subjects treated with O-ER, with an average summary physical score improvement of 30.8 percent in the A-MQD group versus 22.9 percent in the O-ER group ($p = 0.0017$). The relative advantage of A-MQD continued to be seen during the evaluation and extension phases of the study, but the difference with O-ER was no longer significant, possibly due to subject withdrawal having reduced the statistical power of the study.

Within the SF-12 physical domain components, the main difference between the two study groups was noted

Table 4. Subjects' inability to work due to illness or treatment			
	A-MQD	**O-ER**	**p value***
Baseline			
Worked during past four weeks	56 (90.3 percent)	41 (93.2 percent)	NS
Did not work during past four weeks	6 (9.7 percent)	3 (6.8 percent)	
End of titration			
Worked during past four weeks	64 (97.0 percent)	39 (97.5 percent)	NS
Did not work during past four weeks	2 (3.0 percent)	1 (2.5 percent)	
Evaluation Week 4			
Worked during past four weeks	48 (90.6 percent)	34 (94.4 percent)	NS
Did not work during past four weeks	5 (9.4 percent)	2 (5.6 percent)	
Evaluation Week 8			
Worked during past four weeks	43 (91.5 percent)	25 (80.6 percent)	0.0149
Did not work during past four weeks	4 (8.5 percent)	6 (19.4 percent)	
* Calculated by Cochran Mantel Haenszel test; NS = not significant.			

in the relative improvement from baseline for bodily pain scores, which were better in the A-MQD group at each of the six follow-up assessments, with a significant difference achieved at the end of opioid dose titration, Week 8 of the evaluation phase, and Months 1 and 2 of the extension phase. This outcome corroborates the findings of the visual analogue pain scale from the Brief Pain Inventory, which also showed significantly better results in the A-MQD group.[1] Using two independent evaluation methodologies, the SF-12 and the WLQ pain scale, the study has confirmed that once-daily A-MQD results in better pain control than twice-daily O-ER in patients with chronic low back pain.

Other studies have also shown improved physical function associated with pain relief after therapy with A-MQD in patients with different types of chronic, moderate to severe noncancer pain. In a randomized, double-blind, Phase III trial conducted in osteoarthritic subjects, Caldwell et al.[12] showed that the mean WOMAC physical function score improved by 18 percent at Week 4 with A-MQD, compared to an improvement of 8 percent with placebo. In a real-world-conditions, single-arm study of 492 subjects with nonmalignant chronic pain, Adams et al.[13] showed that A-MQD significantly increased the proportion of subjects who reported an improvement in ability for moderate-intensity activities such as "climbing one flight of stairs" ($p = 0.008$) and "bending, kneeling, or stooping" ($p = 0.0005$). In addition, treatment with A-MQD significantly decreased the proportion of subjects who reported that "problems with functioning occurred 7 days a week," from 81 percent at baseline to 67 percent at Month 3 ($p < 0.01$).

In a randomized trial conducted in subjects with various chronic, nonmalignant pains that compared O-ER given every eight or 12 hours to polymer-coated extended-release morphine sulfate (Kadian®, Alpharma Branded Products Division, Inc., Piscataway, NJ) given every 12 or 24 hours, functional status was evaluated by the SF-36 health questionnaire at baseline, Week 4, and Week 24.[14] In 43 evaluable subjects treated with O-ER, the physical component summary scores improved by a modest 7 percent, from a mean of 31.1 at baseline to a mean of 33.2 at Week 24 ($p < 0.05$), and there were no significant improvements in the mental component summary scores.

CONCLUSION

The ACTION trial has shown that in subjects with chronic, moderate to severe low back pain who are stabilized on opioid therapy, both AVINZA® and OxyContin® significantly improve pain, sleep, and physical functioning for up to seven months on study. The study also showed that AVINZA® results in significantly better pain

relief, sleep, physical function, and ability to work than does OxyContin.® The results seen with the patients taking AVINZA® were achieved with significantly lower morphine-equivalent daily doses, less frequent ibuprofen use for breakthrough pain, and a comparable safety profile.

FINANCIAL DISCLOSURE

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