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BRIEF REPORT

Improved Treatment Effect of Triamcinolone Acetonide Extended-Release in Patients with Concordant Baseline Pain Scores on the Average Daily Pain and Western Ontario and McMaster Universities Osteoarthritis Index Pain Scales

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ABSTRACT

Introduction: A phase 3 randomized controlled study comparing triamcinolone acetonide extended-release (TA-ER) to conventional TA crystalline suspension (TAcs) reported variable efficacy results. Enrollment criteria may have contributed to this discrepancy, as moderate-to-severe average daily pain (ADP) was required at baseline, whereas no limitations were placed on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-A) pain severity. We conducted a post hoc sensitivity analysis to compare treatment effects in patients reporting moderate-to-severe osteoarthritis (OA) pain on both scales.

Methods: Participants > 40 years old with symptomatic knee OA were randomly assigned to a single intra-articular injection of TA-ER 32 mg, TAcs 40 mg, or saline-placebo and followed for 24 weeks. Patient-reported ADP, WOMAC-A, rescue medication usage, and adverse events (AEs) were assessed. Participants who reported moderate-to-severe OA pain at baseline using both instruments (ADP $\geq$ 5 to $\leq$ 9, maximum 10 and WOMAC-A $\geq$ 2,

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maximum 4) were categorized as "concordant" pain reporters; patients with baseline moderate-to-severe OA on ADP only were termed "discordant" pain reporters.

Results: Two-hundred-ninety-two concordant pain reporters of 484 total subjects received TA-ER 32 mg ($n = 95$), TAcs 40 mg ($n = 100$), or saline-placebo ($n = 97$). Baseline characteristics and AE profiles of the concordant and discordant pain responders were consistent with the full analysis population. Among concordant pain reporters, TA-ER significantly ($p < 0.05$) improved ADP scores vs. TAcs (weeks 5–19; area-under-the-effect $[AUE]_{weeks1–12}$; $AUE_{weeks1–24}$) and saline-placebo (weeks 1–20; $AUE_{weeks1–12}$; $AUE_{weeks1–24}$). At week 12, a higher proportion reported no knee pain (ADP = 0) with TA-ER ($\sim$ 28%) vs. TAcs ($\sim$ 8%). TA-ER significantly improved WOMAC-A vs. TAcs at weeks 4, 8, and 12, with significant reduction in rescue medication usage observed with TA-ER from weeks 2 to 20 vs. TAcs.

Conclusions: In patients reporting moderate-to-severe knee OA pain at baseline based on concordant ADP and WOMAC-A scores, TA-ER provided statistically significant pain relief for $\geq$ 12 weeks compared with conventional TAcs.

Trial Registration: ClinicalTrials.gov Identifier: NCT02357459.

PLAIN LANGUAGE SUMMARY

Osteoarthritis is a chronic condition that greatly impacts patients. Pain is the most common symptom of osteoarthritis. Clinical trials evaluating the effects of new drugs to treat osteoarthritis pain frequently use scales to rate overall pain following treatment. Patients may rate their pain using a number that best describes their pain, with the lowest number typically meaning "no pain," and the highest number typically meaning "pain as bad as you can imagine." Other rating scales may be used to rate pain in situations commonly associated with osteoarthritis.

Results from a large clinical trial demonstrated that injection of an extended-release steroid significantly reduced pain compared with a conventional steroid injection on only one of the two pain-reporting scales used in the trial. A closer look found that some patients reported their pain differently on the two rating scales at the start of the trial, with some reporting moderate-to-severe pain using one questionnaire and mild pain using the other. Here, we focused on those patients who reported having moderate-to-severe osteoarthritis knee pain on both pain scales at the start and found that the pain relief benefit associated with the extended-release steroid injection was greatly improved compared with the conventional steroid injection with both measures. Patients receiving the extended-release steroid injection also decreased their use of rescue medication for pain relief.

Keywords: Corticosteroid; Intra-articular; Knee osteoarthritis; Pain; Triamcinolone acetonide extended-release

Key Summary Points

Why carry out this study?

Average daily pain (ADP) using a numeric rating scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-A subscale) are often used to assess osteoarthritis (OA) knee pain.

In a previous phase 3 study of patients with OA of the knee and well-balanced entry demographics, differing efficacy results were observed with the two different pain-reporting instruments when triamcinolone acetonide extended-release (TA-ER) was compared with conventional TA crystalline suspension (TAcs).

As trial enrollment criteria may have contributed to that discrepancy, we conducted a post hoc analysis to assess treatment effects in those patients who reported moderate-to-severe OA pain at baseline on both ADP and WOMAC-A (pain) scales (concordant pain reporters).

What was learned from the study?

In concordant pain reporters, TA-ER provided statistically significant and clinically meaningful pain relief for at least 12 weeks compared with conventional TAcs, suggesting that patients with knee OA pain who rated their pain consistently across two reporting instruments were better able to discern treatment effect.

Results of this post hoc analysis have implications for study design and patient recruitment of future trials evaluating the efficacy of intra-articular interventions for OA knee pain.

INTRODUCTION

Osteoarthritis (OA) of the knee is a serious and prevalent chronic disease with pain as its primary symptom [1, 2], and analgesic responses are the key endpoints in OA clinical trials [3–5]. The general, single-item, 11-point numeric rating scale (NRS) instrument, which can be used to report average daily pain (ADP) [6, 7], is applicable to a variety of disorders, and as a simple, unidimensional scale, it provides a fast and reliable method for measuring pain that is particularly useful for determining onset of effect [7, 8]. The disease-specific, five-item Western Ontario and McMaster Universities Osteoarthritis Index pain subscale (WOMAC-A) has also been frequently used in OA clinical trials, as part of a tool that assesses broader OA symptoms of stiffness and functioning (WOMAC-B and WOMAC-C, respectively) [9].

Conventional intra-articular corticosteroid (IACS) injections, such as triamcinolone acetonide crystalline suspension (TAcs), have been shown to reduce pain in patients with knee OA; however, questions remain about the duration and consistency of analgesic treatment effect given the paucity of high-quality prospective clinical trials [10, 11]. A microsphere-based extended-release formulation of triamcinolone acetonide (TA-ER) has consistently shown $\geq 50\%$ reduction in pain from baseline as measured by ADP and WOMAC-A across several randomized controlled clinical trials in patients with knee OA [12–15], with durations of effect lasting up to 16 weeks when compared to saline placebo [14, 15]. However, in the pivotal phase 3 trial, when TA-ER was compared with conventional TAcs, differing efficacy results were observed with ADP and WOMAC-A [14]. At week 12, a single intra-articular (IA) injection of TA-ER did not demonstrate a significant difference in ADP intensity as assessed by the NRS tool, but TA-ER significantly ($p < 0.05$) reduced pain compared with TAcs as assessed via the WOMAC-A subscale at the same landmark week 12 time point [14].

We hypothesized that trial enrollment criteria may have contributed to the inconsistent results observed across pain reporting

instruments. In this trial, ADP scores ≥ 5 to ≤ 9 reflecting moderate-to-severe pain were required for inclusion in the study; however, no qualifying WOMAC-A score was required for randomization. Inclusion of these patients who reported their pain inconsistently across the two instruments may have masked the true treatment effects and complicated interpretation of the phase 3 results. Therefore, we conducted a post hoc analysis focused on assessing treatment effects in those patients who reported moderate-to-severe knee OA pain according to both ADP and WOMAC-A scales (concordant pain reporters), with a secondary focus on those patients from the analysis who reported mild pain at baseline based on the WOMAC-A scale (discordant pain reporters).

METHODS

Ethics Compliance

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. The study protocol was approved by governing ethics bodies at the participating sites, and patients provided written informed consent before participating in any study-related procedures.

Study Design

This was a post hoc analysis of a phase 3 multicenter, randomized, double-blind study (ClinicalTrials.gov Identifier NCT02357459). Full details on patient eligibility, study design, and interventions have been reported elsewhere [14]. Briefly, men and women aged ≥ 40 years with body mass index ≤ 40 kg/m^2 with symptomatic knee OA and balanced demographics were randomly assigned to receive a single IA injection of TA-ER 32 mg (n = 161), TAcs 40 mg (n = 161), or saline-placebo (n = 162). Patients had symptomatic knee OA defined by American College of Rheumatology criteria for ≥ 6 months [16], Kellgren–Lawrence grade 2/3 OA based on screening index-knee radiography [17], and an average daily baseline ADP score ≥ 5 to ≤ 9 for ≥ 5 of the 7 days prior to study enrollment [6, 7]. Although captured at baseline, no qualifying WOMAC-A (pain) score was required for enrollment. All patients enrolled in the original study underwent the same protocols regardless of baseline pain reporting.

Patients were defined as concordant pain reporters if they had reported moderate-to-severe pain on both ADP (average daily score ≥ 5 to ≤ 9) and the WOMAC-A pain subscale (average score ≥ 2) at baseline (n = 292/484). Patients with a baseline ADP score ≥ 5 to ≤ 9, but who reported "mild" baseline pain on the WOMAC-A subscale (WOMAC-A < 2) [18] were considered discordant pain reporters (n = 192/484).

Study Assessments

ADP intensity was assessed daily on an NRS of 0 (no pain) to 10 (pain as bad as you can imagine) for 7 days prior to study enrollment. Patients called into an interactive voice-response system every day (4:00 p.m. to 12:00 a.m. locally) from screening to week 24 to report their ADP scores. The weekly mean of the mean daily ADP intensity scores was calculated from baseline through week 24. WOMAC-A (pain) scores were assessed using Likert 3.1, five-point subscales ranging from 0 (no symptoms) to 4 (extreme) [9], and measured at baseline and weeks 4, 8, 12, 16, 20, and 24. If patients were included in either the concordant or discordant group, their ADP and WOMAC-A scores were included regardless of responsiveness to the treatment.

Rescue analgesic medication usage was monitored throughout the study via a daily diary reporting system, and pill counts were confirmed at each clinical visit. The mean number of rescue medication tablets used per week was computed for each patient by summing the number of tablets used in each weekly interval and dividing by the number of days of non-missing responses in the weekly interval.

Treatment-emergent adverse events (TEAEs)—defined as any adverse event (AE) with onset after the administration of study treatment or any AE that was present at baseline but worsened in intensity through the end of the study—were analyzed.

Statistical Analysis

The effects of IA injection treatment were measured by least-squares means (LSM) at each week through week 24 for TA-ER vs. saline-placebo and TAcs and evaluated using a longitudinal mixed-effects model for repeated measures (MMRM) with fixed effects for study time point, study site, and baseline pain score. Area-under-the-effect (AUE) curves of change in weekly mean ADP intensity scores from weeks 1 to 12 ($AUE_{weeks1–12}$) and weeks 1 to 24 ($AUE_{weeks1–24}$) were analyzed using analysis of covariance with study site as a covariate.

A direct comparison of the ADP and WOMAC-A pain reporting instruments was carried out based on data from the entire phase 3 population. WOMAC-A scores at baseline were standardized to NRS-approximate equivalents on a 0–10 scale by multiplying WOMAC-A average scores by 2.5. Agreement between the adjusted WOMAC-A and ADP scores was assessed by calculation of Pearson correlation coefficients (r). Effect sizes based on r statistics are generally considered to be small, medium, or large based on cutoffs of 0.10, 0.30, and 0.50, respectively [19].

RESULTS

Patient Disposition and Baseline Characteristics

This post hoc analysis identified 292 patients (TA-ER, $n = 95$; saline-placebo, $n = 97$; TAcs, $n = 100$) from the phase 3 full analysis set (FAS; $n = 484$) who reported moderate-to-severe knee OA pain at baseline on both ADP and WOMAC-A (pain) scales (ADP ≥ 5 to ≤ 9 and WOMAC-A ≥ 2; concordant pain reporters); 192 patients (39.7%) who reported moderate-to-severe knee OA on the ADP scale but mild knee OA pain on the WOMAC-A scale (discordant pain reporters) were also assessed. Patient demographics and baseline characteristics are shown in Table 1. Patients ranged from 40 to 83 years of age (mean, 61.1 years), the majority were female (62.3%), and had a mean body mass index of approximately 30 kg/m^2. Figure 1 shows the correlation of ADP and WOMAC-A scores at baseline for the entire phase 3 study population (FAS; $n = 484$). After normalization to a common scale, ADP intensity scores using the NRS were approximately 23% higher than WOMAC-A scores at baseline (Pearson correlation coefficient [r] = 0.402).

Treatment Outcomes

For concordant pain reporters, change from baseline in ADP score was significantly ($p < 0.05$) improved with TA-ER compared with TAcs each week from weeks 5 to 19 and compared with saline-placebo each week from weeks 1 to 20 (Fig. 2). Analysis of the frequency distribution of ADP intensity scores demonstrated that ~ 28% of patients treated with TA-ER reported that they had no pain at week 12, compared with only ~ 8% of patients who received TAcs (Fig. 3). Lack of pain was maintained at week 16 in ~ 20% of patients treated with TA-ER (compared with ~ 9% of patients who received TAcs) (data not shown).

For concordant pain reporters, LSM differences (95% CI) in change from baseline in ADP score at week 12 were greater (TA-ER vs. TAcs: −0.87 [−1.54, −0.20], $p = 0.0105$; TA-ER vs. saline-placebo: −1.75 [−2.44, −1.06], $p < 0.0001$) than for discordant pain reporters (TA-ER vs. TAcs: 0.45 [−0.28, 1.17], $p = 0.2285$; TA-ER vs. saline-placebo: −0.01 [−0.73, 0.70]; $p = 0.9707$) (Table 2).

The AUE for the ADP intensity curves reflects the totality of the treatment effect. For concordant pain reporters, $AUE_{weeks1–12}$ and $AUE_{weeks1–24}$ treatment effects were statistically significant for TA-ER compared with TAcs (LSM differences [95% CI]: −47.7 [−94.4, −1.0] and −98.4 [−194.5, −2.3], respectively; $p < 0.05$ for both) and TA-ER compared with saline-placebo

Table 1 Demographic and baseline characteristics of concordant pain reporters

	TA-ER 32 mg *n* = 95	Saline-placebo *n* = 97	TAcs 40 mg *n* = 100
Sex, *n* (%)			
Male	33 (34.7)	37 (38.1)	40 (40.0)
Female	62 (65.3)	60 (61.9)	60 (60.0)
Age, years, mean (SD)	61.1 (9.2)	61.3 (8.9)	61.0 (10.1)
Race, *n* (%)			
American Indian or Alaska Native	0	0	0
Asian	9 (9.5)	9 (9.3)	10 (10.0)
Black or African American	9 (9.5)	3 (3.1)	9 (9.0)
Native Hawaiian or other Pacific Islander	3 (3.2)	1 (1.0)	2 (2.0)
White	74 (77.9)	84 (86.6)	79 (79.0)
Other	0	0	0
BMI (kg/m^2), mean (SD)	30.3 (5.0)	30.4 (4.8)	30.9 (4.7)
Years since primary diagnosis, mean (SD)	8.3 (7.4)	6.3 (5.8)	7.6 (7.0)
Kellgren–Lawrence grade, *n* (%)			
2	49 (51.6)	44 (45.4)	43 (43.0)
3	46 (48.4)	53 (54.6)	56 (56.0)
4	0	0	1 (1.0)
Unilateral/bilateral knee OA, *n* (%)			
Unilateral	33 (34.7)	37 (38.1)	42 (42.0)
Bilateral	62 (65.3)	60 (61.9)	58 (58.0)
Weekly ADP intensity score at baseline, mean (SD)	6.42 (0.94)	6.54 (1.01)	6.49 (0.95)
WOMAC-A (pain) score, mean (SD)	2.37 (0.34)	2.36 (0.35)	2.37 (0.32)

ADP average daily pain, *BMI* body mass index, *OA* osteoarthritis, *SD* standard deviation, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

(−136.1 [−184.2, −88.0] and −212.1 [−311.1, −113.1], respectively; $p < 0.0001$ for both) (Table 2). For comparison, among discordant pain reporters, LSM differences (95% CI) in $AUE_{weeks1–12}$ and $AUE_{weeks1–24}$ for TA-ER compared with TAcs were 12.3 (−41.6, 66.3; $p = 0.6518$) and 77.1 (−26.1, 180.2; $p = 0.1419$), respectively, and LSM differences for TA-ER compared with saline-placebo were −58.2 (−111.2, −5.3; $p < 0.05$) and −37.7 (−139.0, 63.6; $p = 0.4635$), respectively.

In concordant pain reporters, TA-ER also demonstrated statistically significant ($p < 0.05$) improvements over both TAcs and saline-placebo in WOMAC-A (pain) scores (weeks 4, 8, and 12 vs. TAcs; weeks 4, 8, 12, and 16 vs.

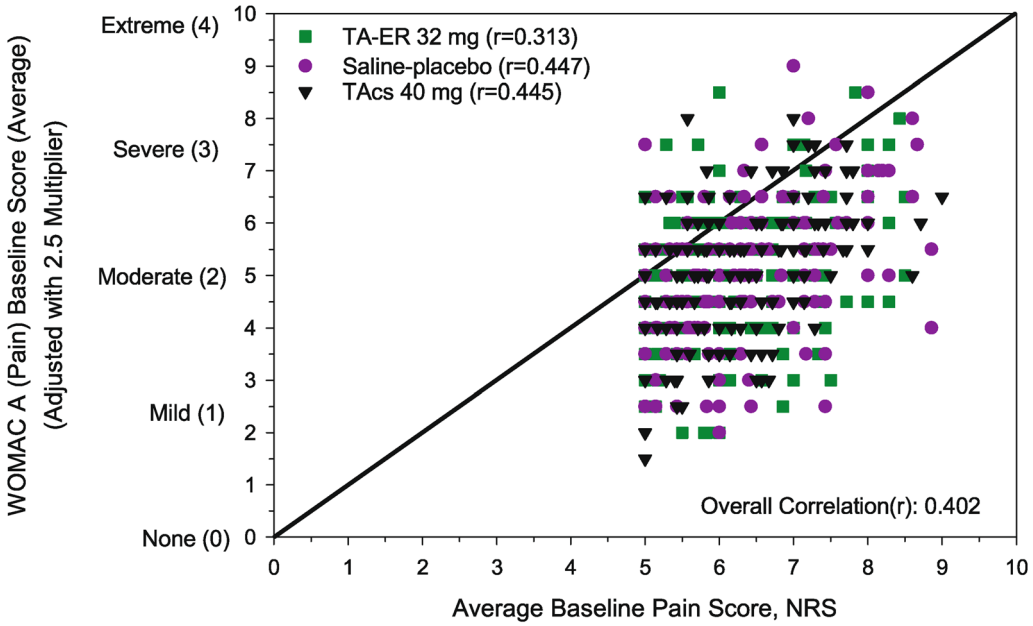

Fig. 1 Correlation between ADP and normalized WOMAC-A-derived baseline pain assessments in the phase 3 full analysis set. *NRS* numeric rating scale, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index. Data from the phase 3 FAS population: TA-ER (n = 161), saline-placebo (n = 162), TAcs (n = 161) [14]

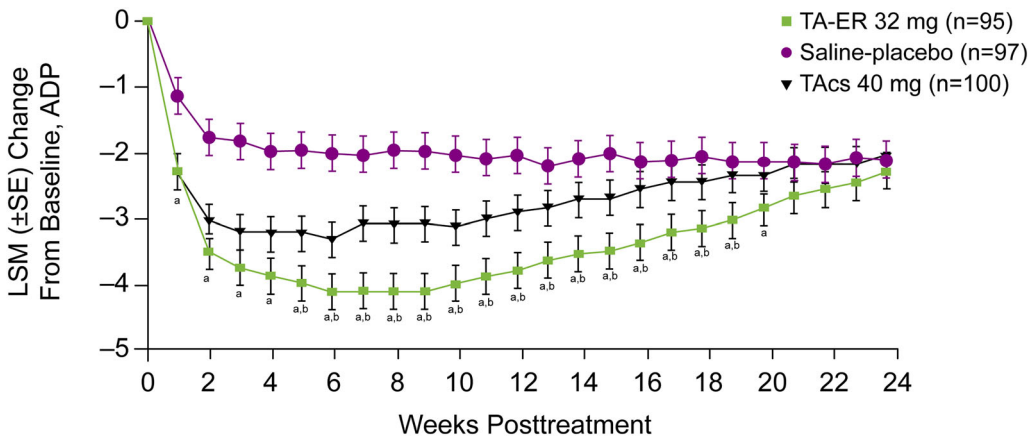

Fig. 2 Mean changes from baseline in ADP scores over time among concordant pain reporters. [a]$p < 0.05$ vs. saline-placebo; [b]$p < 0.05$ vs. TAcs. *ADP* average daily pain, *LSM* least-squares mean, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release

saline-placebo) (Fig. 4). For concordant pain reporters, TA-ER reduced pain (WOMAC-A) from baseline by as much as 59% (week 4); the largest reduction in pain resulting from TAcs treatment was 46% (week 4). In contrast, among discordant pain reporters, mean changes from baseline in WOMAC-A scores were not statistically significant vs. TAcs at any time point ($p > 0.1$ for weeks 4, 8, 12, 16, 20, and 24); changes were statistically significant vs. saline-placebo at week 4 only ($p = 0.0011$).

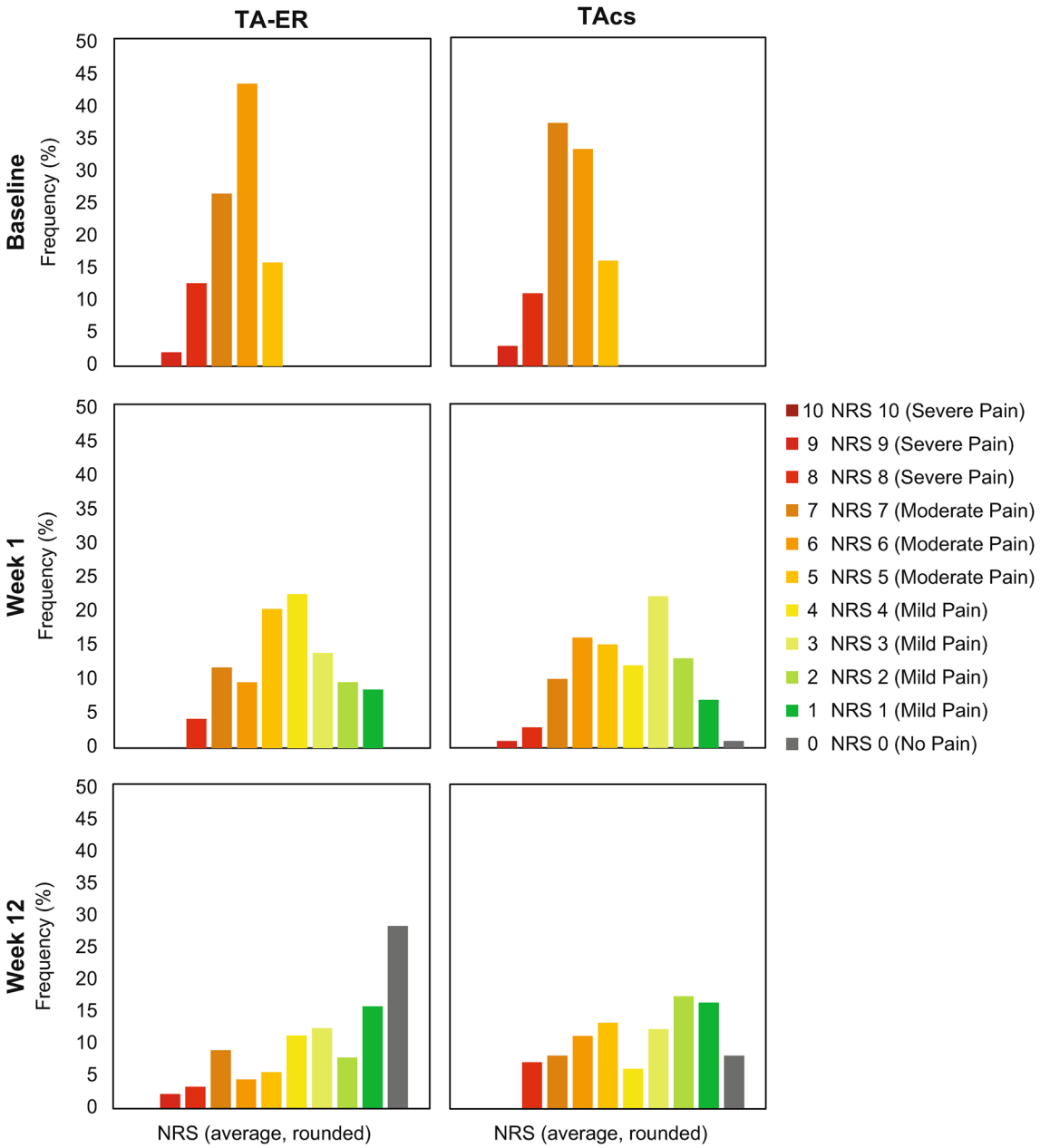

Fig. 3 Frequency distribution of ADP scores at baseline, week 1, and week 12 among concordant pain reporters. ADP scores rated on a 0–10 NRS, with 0 indicating "no pain" and 10 indicating "pain as bad as you can imagine." *ADP* average daily pain, *NRS* numeric rating scale, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release

Concordant pain reporters treated with TA-ER used significantly fewer rescue medication tablets each week from weeks 2 to 20 compared with TAcs and each week from weeks 1 to 24 compared with saline-placebo (Fig. 5). Among discordant pain reporters, no significant differences were noted between TA-ER and TAcs or between TA-ER and saline-placebo at any time point ($p > 0.05$ vs. both TAcs and saline-placebo at all time points).

Table 2 Differences in ADP scores at week 12 and area-under-the-effect curve

	LSM difference in ADP (95% CI); *p* value					
	Concordant pain reporters TA-ER (*n* = 95) Saline-placebo (*n* = 97) TAcs (*n* = 100)		Discordant pain reporters TA-ER (*n* = 66) Saline-placebo (*n* = 65) TAcs (*n* = 61)		Phase 3 FAS[a] TA-ER (*n* = 161) Saline-placebo (*n* = 162) TAcs (*n* = 161)	
	TA-ER vs. saline-placebo	TA-ER vs. TAcs	TA-ER vs. saline-placebo	TA-ER vs. TAcs	TA-ER vs. saline-placebo	TA-ER vs. TAcs
LSM difference at week 12	−1.75 (−2.44, −1.06); < 0.0001	−0.87 (−1.54, −0.20); 0.0105	−0.01 (−0.73, 0.70); 0.9707	0.45 (−0.28, 1.17); 0.2285	−0.98 (−1.47, −0.49); < 0.0001	−0.26 (−0.74, 0.23); 0.2964
$AUE_{weeks1–12}$	−136.1 (−184.2, −88.0); < 0.0001	−47.7 (−94.4, −1.0); 0.0451	−58.2 (−111.2, −5.3); 0.0314	12.3 (−41.6, 66.3); 0.6518	−102.0 (−136.8, −67.3); < 0.0001	−15.3 (−49.8, 19.2); 0.3827
$AUE_{weeks1–24}$	−212.1 (−311.1, −113.1); < 0.0001	−98.4 (−194.5, −2.3); 0.0447	−37.7 (−139.0, 63.6); 0.4635	77.1 (−26.1, 180.2); 0.1419	−135.5 (−205.9, −65.2); 0.0002	−13.2 (−83.0, 56.7); 0.7111

[a]Data from the phase 3 FAS population [14]

ADP average daily pain, *AUE* area-under-the-effect curve, *CI* confidence interval, *FAS* full analysis set, *LSM* least-squares mean, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release

Safety

Safety profiles were similar among treatment groups and consistent with those of the overall phase 3 safety population (Table 3) [14]. The incidence of TEAEs was comparable between treatment groups, with most TEAEs being grade 1 or 2, non-serious, and unrelated to study drug. The one exception was index-knee TEAEs, which largely comprises reports of mild-moderate arthralgia, wherein 19% of those receiving TA-ER showed ≥ 1 index-knee TEAE, compared with 9% and 10% of those receiving saline-placebo and TAcs, respectively (Table 3). Index-knee arthralgia is notable in the mean timing of onset in the three treatment groups (21.5 days for saline-placebo, 57 days for TAcs, and 78 days for TA-ER), suggesting these reports may represent waning of pain relief.

DISCUSSION

In a large phase 3 study of TA-ER, although the study population was limited, as intended, to patients with moderate-to-severe OA pain at baseline (based on ADP score ≥ 5 to ≤ 9), nearly 40% of the patients had reported their pain as "mild" on the WOMAC-A scale (< 2). In patients who reported moderate-to-severe baseline knee OA pain as assessed using both ADP (≥ 5 to ≤ 9) and WOMAC-A (≥ 2) instruments, a single IA TA-ER injection provided statistically significant ($p < 0.05$) improvements in patient-reported OA outcomes compared with TAcs and saline-placebo. These included reductions in pain and rescue medication usage. TA-ER treatment effects generally persisted for 16 weeks or longer; an ADP-based AUE analysis showed significant differences between TA-ER and both

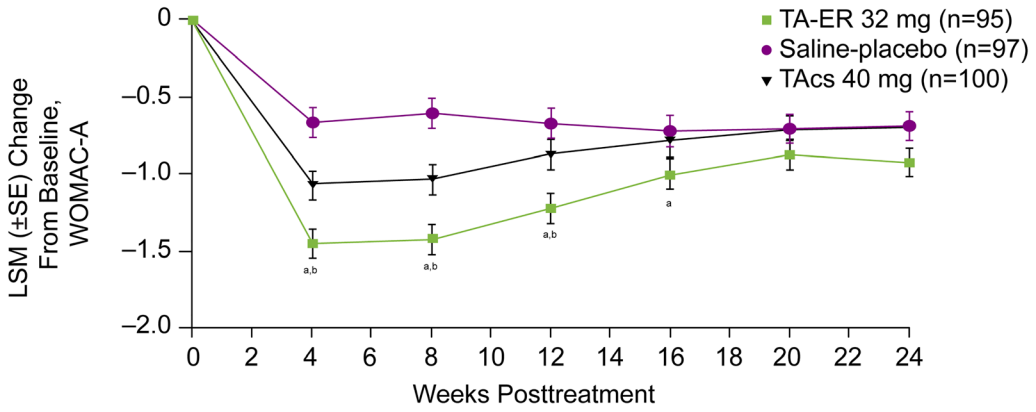

Fig. 4 Mean change from baseline in WOMAC-A (pain) score among concordant pain reporters. [a]$p < 0.05$ vs. saline-placebo; [b]$p < 0.05$ vs. TAcs. *LSM* least-squares mean, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

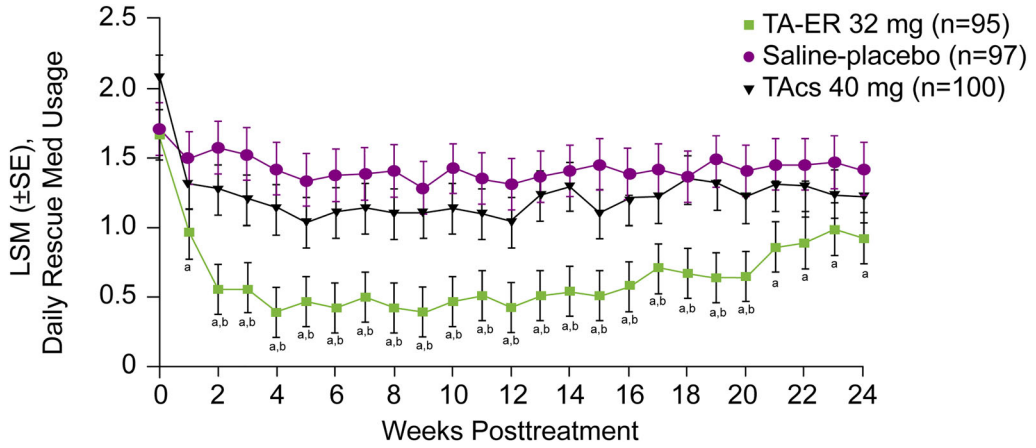

Fig. 5 Mean rescue medication usage among concordant pain reporters. [a]$p < 0.05$ vs. saline-placebo; [b]$p < 0.05$ vs. TAcs. *LSM* least-squares mean, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release

comparators through week 24, confirming the totality of the TA-ER treatment effect over time. The LSM difference at 12 weeks and the AUE for ADP results were enhanced in concordant pain reporters compared with those observed in the phase 3 FAS (Table 2) [14]. These results, demonstrating the persistence of the TA-ER effect, are consistent with the mechanism of action of an extended-release IACS [20, 21].

The magnitude of pain relief associated with TA-ER was substantial. TA-ER reduced pain (based on ADP intensity) from baseline by ≥ 50% from weeks 2 to 16 (inclusive), whereas TAcs reduced pain by ≥ 50% at week 6 only. There was a clear shift in the distribution of ADP intensity scores toward mild-to-no-pain from baseline to week 12 with both TA-ER and TAcs treatment; however, more than three times as many patients receiving TA-ER reported no knee pain at week 12 compared with TAcs. The magnitude of this TA-ER treatment effect was sustained through week 16, with approximately 20% of patients in the TA-ER group still reporting no pain.

The magnitude and duration of the analgesic effects of TA-ER observed in this post hoc analysis have not been attained, to our knowledge, in studies evaluating conventional IACS

Table 3 Summary of adverse events among concordant pain reporters

	TA-ER 32 mg *n* = 95	Saline-placebo *n* = 97	TAcs 40 mg *n* = 100
≥ 1 TEAE, *n* (%)	50 (52.6)	48 (49.5)	56 (56.0)
Grade 1	19 (20.0)	20 (20.6)	20 (20.0)
Grade 2	25 (26.3)	26 (26.8)	33 (33.0)
Grade 3	5 (5.3)	2 (2.1)	3 (3.0)
Grade 4	1 (1.1)	0	0
≥ 1 serious TEAE	5 (5.3)	2 (2.1)	3 (3.0)
≥ 1 TEAE leading to study discontinuation	0	0	1 (1.0)
TEAE by maximum relationship			
Not related[a]	45 (47.4)	45 (46.4)	52 (52.0)
Related[b]	5 (5.3)	3 (3.1)	4 (4.0)
≥ 1 index-knee TEAE	18 (18.9)	9 (9.3)	10 (10.0)
Index-knee arthralgia	11 (11.6)	6 (6.2)	4 (4.0)
≥ 1 index-knee TEAE leading to study discontinuation	0	0	1 (1.0)

[a]Includes "not related" and "unlikely" related
[b]Includes "possibly," "probably," or "definitely" related
ADP average daily pain, *TAcs* triamcinolone acetonide crystalline suspension, *TA-ER* triamcinolone acetonide extended-release, *TEAE* treatment-emergent adverse event

injections. These drugs are often associated with only moderate treatment effects and typically offer pain relief that is < 6 weeks in duration [10]. Results of a recent meta-analysis suggest that although smaller studies tend to demonstrate a moderate pain-relief benefit of conventional IACS injections, such benefits were relatively diminished among the few moderate-to-large trials (≥ 50 patients per trial group) that have been conducted so far [10, 11]. In addition, in this analysis the treatment groups were balanced in numbers of patients with unilateral or bilateral knee OA, meaning that treatment effects observed are not subject to differences associated with patients with unilateral disease being better able to self-assess changes in index knee pain than patients with bilateral disease [22].

The magnitude and duration of pain relief observed in this post hoc analysis were enhanced compared with those observed for the phase 3 FAS [14], suggesting that patients with concordant reporting of moderate-to-severe OA pain at baseline were better able to discern treatment effect. Instrument characteristics may have played a role in the variability of the patient's assessment of their pain at baseline. The ADP tool is not disease-specific, and data is captured using a single-item measure (11-point NRS scale) [6, 7]. This is in contrast to pain outcomes captured using the WOMAC-A tool, which assesses joint pain related to walking, using stairs, being in bed, sitting or lying down, and standing (each item scored individually) [9]. Results of this study have implications for the design of future trials to evaluate the efficacy of analgesics. In particular, the results highlight important considerations for patient recruitment and enrollment, such as the need to confirm the presence of moderate-to-severe pain by using more than one assessment tool. Further, results of this study emphasize

potential value of keeping both patients and trial sites blinded to study enrollment criteria as it relates to pain scores in order to minimize potential for inflated baseline pain scores.

The current analysis is limited in its post hoc, retrospective nature, which makes the applicability and generalizability of the findings unclear. Prospective studies are needed to confirm the results obtained.

CONCLUSIONS

TA-ER provided statistically significant and clinically meaningful pain relief for at least 12 weeks compared with conventional TAcs in patients who reported moderate-to-severe knee OA pain at baseline concordantly on two different scales (ADP for consistency of pain response and WOMAC-A for pain measurement specifically in OA). Treatment effects were enhanced compared with those observed for the phase 3 FAS, suggesting that patients with concordant reporting of pain across two instruments were better able to discern treatment effect. In these patients, TA-ER reduced pain from baseline by $\geq$ 50% extending to week 16, with approximately 20% of patients reporting no pain at week 16. The magnitude and duration of pain relief observed with TA-ER in this study highlights the potential substantial benefits over conventional TAcs. Results of this analysis also have implications for study design and patient recruitment of future trials evaluating efficacy of analgesic interventions for OA knee pain. Trial and instrument characteristics, including pain-based eligibility criteria, scale differences, and measurement variability, must be considered when selecting instruments and end points in clinical trials comparing the magnitude of analgesic benefit observed between active therapies.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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