



Efficacy of Triamcinolone Acetonide Extended-Release in Participants with Unilateral Knee Osteoarthritis: A Post Hoc Analysis

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ABSTRACT

Introduction: Osteoarthritis (OA) is common and its prevalence is increased in military service members. In a phase 3 randomized controlled trial (NCT02357459), a single intra-articular injection of an extended-release formulation of triamcinolone acetonide (TA-ER) in

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participants with unilateral or bilateral knee OA demonstrated substantial improvement in pain and symptoms. Bilateral knee pain has emerged as a confounding factor in clinical trials when evaluating the effect of a single intra-articular injection. Furthermore, unilateral disease is frequently first to emerge in active military personnel secondary to prior traumatic joint injury. In this post hoc analysis, we assessed efficacy and safety of TA-ER in a subgroup of participants with unilateral knee OA.

Methods: Participants ≥ 40 years of age with symptomatic knee OA were randomized to a single intra-articular injection of TA-ER 32 mg, TA crystalline suspension (TAcS) 40 mg, or saline-placebo. Average daily pain (ADP)-intensity and rescue medication use were collected at each of weeks 1–24 postinjection; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-A (pain), WOMAC-B (stiffness), WOMAC-C (function), and Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QoL) were collected at weeks 4, 8, 12, 16, 20, and 24 postinjection. Adverse events (AEs) were assessed throughout the study. Participants with unilateral knee OA were selected for this analysis.

Results: Of 170 participants with unilateral OA (TA-ER, $N = 51$; saline-placebo, $N = 60$; TAcS, $N = 59$), 42% were male and 89% were white. TA-ER significantly ($p < 0.05$) improved ADP-intensity vs. saline-placebo (weeks 1–24) and TAcS (weeks 4–21). TA-ER significantly

($p < 0.05$) improved WOMAC-A vs. saline-placebo (all time points) and TAcS (weeks 4, 8, 12, 24). Consistent outcomes were observed for rescue medication, WOMAC-B, WOMAC-C, and KOOS-QoL. AEs were similar in frequency/type across treatments.

Conclusion: TA-ER provided 5–6 months' pain relief that consistently exceeded saline-placebo and TAcS, suggesting that TA-ER injected intra-articularly into the affected knee may be an effective non-opioid treatment option. Although the participants included in this analysis did not fully represent the diverse demographics of active service members, the substantial unmet medical need in the military population suggests that TA-ER may be an important treatment option; additional studies of TA-ER in active military patients are needed.

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PLAIN LANGUAGE SUMMARY

Osteoarthritis is a common chronic condition that many people experience as pain, swelling, and stiffness in a variety of joints. Osteoarthritis can develop over time because of many reasons including repeated minor trauma or the result of a single major injury. This could help explain why osteoarthritis happens at a higher rate in military members compared with civilian populations. The risk of developing osteoarthritis increases the longer a person serves in the military and is the leading cause of medical discharge. There is no cure for osteoarthritis, but many treatments are available that reduce pain including acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, and steroid injections. Injecting steroids into the joint has been shown to reduce pain, but is typically short-lived. A long-acting form of steroid injection that releases the active ingredient slowly over

3 months from a biodegradable bead has been shown to be effective in patients with osteoarthritis in one or both knees. This paper examines the extended-release steroid injection in people with osteoarthritis in one knee. People receiving the extended-release steroid injection had greater improvements in osteoarthritis pain, stiffness, function, and knee-related quality of life compared with people who received saline-placebo or a short-acting steroid injection. These benefits lasted around 5–6 months after the injection. Safety was similar among all three treatment groups with most events being mild or moderate. These data suggest that for military and civilian populations suffering with osteoarthritis in one knee, the extended-release steroid injection may be an effective and well-tolerated treatment option. More research using the extended-release steroid injection in active military patients is needed.

INTRODUCTION

Osteoarthritis (OA) is a serious disease that affects more than 30 million US adults and is characterized by chronic pain, stiffness, and swelling that leads to reduced mobility and impaired quality of life (QoL) [1–3]. Active duty service members experience OA at a significantly higher rate than the civilian population, likely due to extreme physical demands and an increased frequency of joint trauma that occurs throughout military service [4]. In a retrospective analysis of 1566 combat-injured soldiers, the prevalence of posttraumatic OA was 28%, compared with 12% in the civilian trauma population [5]. Extensive years of military service are associated with an increased risk of developing OA, and being in the army, marines, or air force branches of service further increases this risk [6]. In addition to active duty service members, members of the military reserves, who comprise approximately one-third of the armed forces, are typically older than their active-duty counterparts, putting them at an increased risk of developing OA [7, 8]. The ubiquity of posttraumatic OA among active duty service members and its association with

high disability rates make OA the most common reason soldiers are medically discharged from the US military [5, 9, 10].

Posttraumatic OA develops because of residual joint abnormalities and degeneration following acute injury or repetitive joint trauma, and the knee is one of the most commonly affected joints [5, 9]. Obesity is recognized as a primary risk factor of OA of the knee due to abnormally high joint stress [11]. The modern combat load for deployed military forces can exceed 100 lb, mimicking the excess physiologic burden of obesity and inducing premature degenerative changes [11, 12]. Repetitive joint stress from kneeling, squatting, and long marches with overloaded joints also increases the risk of knee OA in military service members [12]. Joint trauma can also contribute to increased risk of developing knee OA, and anterior cruciate ligament (ACL) injuries occur four to five times more frequently among active duty service members compared with the general population [13]. While most individuals return to active duty following treatment for ACL injuries, a large proportion of those affected will develop posttraumatic OA within 2 decades of ACL reconstruction [14, 15]. Acute joint injury during combat also frequently leads to OA, with combat injuries (high-energy injuries most commonly caused by explosion) of the knee joint ($n = 37$) leading to OA in 100% of participants in one retrospective analysis [5].

Chronic pain is reported in more than 40% of soldiers following deployment and is significantly associated with injury during combat and combat intensity [16]. Pain is the primary symptom of knee OA, and analgesic interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and traditional intra-articular corticosteroids (IACS) are used for short-term pain management [17]. Opioids are often prescribed for chronic pain in service members, and 15.1% of postdeployment soldiers report opioid use, although research has not shown them to be an effective long-term solution [16]. Additionally, opioid use is associated with cognitive and psychological side effects that may limit neurologic assessment and combat effectiveness [18, 19]. Opioid abuse and misuse are a significant military health

concern, with 21.5% of army personnel reporting opioid misuse in the past 12 months [20]. There is a need for long-acting, non-opioid approaches to knee pain management for active duty service members and veterans with knee OA.

The American College of Rheumatology (ACR) and the Osteoarthritis Research Society International [21, 22] recommend traditional IACS for short-term management of OA pain, although their efficacy beyond 12 weeks is controversial [23, 24]. Traditional IACS (e.g., triamcinolone acetonide crystalline suspension [TAcS]) rapidly efflux from the joint, limiting the duration of pain relief [25]. Triamcinolone acetonide extended-release (TA-ER) is a poly(lactic-co-glycolic acid) (PLGA) microsphere-based formulation of triamcinolone acetonide that is approved by the US Food and Drug Administration for the management of OA knee pain [26]. TA-ER extends the intra-articular (IA) residence time of the active pharmacologic agent (TA) to at least 12 weeks and reduces the plasma exposure to TA following injection compared with TAcS [25, 26]. The extended-release mechanism of TA-ER did translate into durable (3–4 months) efficacy in a phase 3, randomized, placebo-controlled trial in participants with symptomatic knee OA [27]. In that study, a single IA TA-ER injection significantly improved mean average daily pain (ADP)-intensity score compared with saline-placebo at the 12-week primary end point ($p < 0.0001$) and extended through week 16 [27]. Additionally, TA-ER significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS-QoL) scores compared with both saline-placebo and TAcS at week 12 (prespecified secondary exploratory end points; $p < 0.05$) [27].

The phase 3 study included participants with both unilateral (35.1% [170/484]) and bilateral disease (64.9% [314/484]). Per protocol, TA-ER was injected into only one knee (the index knee, reported by the participant as the knee with more pain at screening) [27]. Several sources suggest that self-report measures used to evaluate treatment of one knee may be

influenced by the presence of pain in the contralateral limb, making therapeutic response difficult to interpret [28, 29]. Further, bilateral pain has emerged as a confounding factor in clinical trials where the impact of intra-articular injections was evaluated in only one of two painful knees [30, 31]. Given the urgent need for non-opioid approaches to the treatment of OA and that unilateral OA pervades the US active duty and veteran populations, the objective of this post hoc analysis was to assess the efficacy and safety of a single IA TA-ER injection in the subgroup of participants with unilateral knee OA included in the phase 3 study.

METHODS

Study Design

A phase 3, randomized, double-blind, single-dose study assessed the safety and efficacy of TA-ER in participants with knee OA. Full details of the phase 3 trial have been published elsewhere [27]. In brief, participants were centrally randomized (1:1:1) to receive a single IA injection of TA-ER (32 mg), TAcS (40 mg), or saline-placebo. Randomization was stratified by baseline weekly mean ADP-intensity score (5 to < 6, 6 to < 7, and \geq 7). Analgesic medications were withheld starting at screening with a washout period equal to five times the agent's half-life, except for acetaminophen or paracetamol (\leq 3000 mg/day; 500-mg tablets provided as rescue treatment). Participants were monitored for a total of 24 weeks following a single IA injection. This study was registered on ClinicalTrials.gov (NCT02357459) before the first participant was enrolled. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Quorum Review IRB and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol received institutional review board approval (Quorum Review IRB, Seattle, WA, USA; #30017) before commencement of any study procedures, and participants provided written informed consent before any study-

related procedures. Informed consent was obtained from all individual participants included in the study.

Study Population

Eligible participants were men and women \geq 40 years of age with symptomatic knee OA per ACR criteria for \geq 6 months before screening, Kellgren-Lawrence grade 2 or 3 osteoarthritis in the index knee as assessed on the screening radiograph, participant-reported index knee pain for > 15 days in the previous month, and a baseline 24-h ADP-intensity score ranging from 5 to 9. Participants treated with IACS in any joint within 3 months of screening or IA hyaluronic acid in the index knee within 6 months of screening were excluded. Participants included in this subgroup analysis were those with unilateral knee OA as reported by the participant and confirmed using medical records.

Procedures

Participants received a single IA injection into the index knee of TA-ER 32 mg (5 mL injection volume), saline-placebo (5 mL), or TAcS 40 mg (1 mL) using standard injection technique following an attempt at synovial fluid aspiration. The use of ultrasound guidance was at the discretion of the investigator. Commercially available Kenalog-40 injectable suspension was used as the current standard of care TAcS [32]. TA-ER powder was reconstituted in 5 mL diluent immediately before IA injection. Kenalog-40 was prepared per the manufacturer's instructions [32]. Treatments were prepared and administered by designated unblinded personnel who had no other participant contact.

Study Assessments

The primary outcome of the phase 3 study was a landmark analysis of the least-squares mean (LSM) change from baseline to week 12 in weekly ADP-intensity scores for TA-ER compared with saline-placebo. ADP-intensity score was assessed daily via an interactive voice-response system

according to an 11-point numeric rating scale ranging from 0 = no pain to 10 = pain as bad as you can imagine. Average daily pain (ADP)-intensity and rescue medication use were collected at each of weeks 1–24 postinjection. WOMAC Likert 3.1, 5-point subscales (higher scores indicate worse status) were used to evaluate pain (WOMAC-A), stiffness (WOMAC-B), and function (WOMAC-C). Quality of life was assessed using the KOOS-QoL subscale (four questions with five options for each question), with a higher score indicating better quality of life; a normalized score (0–100 with 0 = extreme symptoms and 100 = no symptoms) was calculated using the formula $\text{KOOS-QoL} = 100 - \text{Average}(\text{Question1} - \text{Question4})/4 \times 100$. WOMAC-A, WOMAC-B, and WOMAC-C were evaluated at outpatient visits day 1 (baseline) and weeks 4, 8, 12, 16, 20, and 24; KOOS-QoL was evaluated at all outpatient visits except for weeks 16 and 20 and only measured in participants where a local language-validated questionnaire was available. Rescue medication use was reported daily by the participant using an interactive voice-response system and measuring returned medication at study visits.

Statistical Analysis

In the full analysis population, key secondary end points were evaluated in a step-down manner as reported previously [27]: area under the effect (AUE) curves of the change in weekly mean ADP-intensity scores from baseline to week 12 ($\text{AUE}_{\text{week1-12}}$) for TA-ER compared with saline-placebo; $\text{AUE}_{\text{week1-12}}$ for TA-ER compared with TAcS; an analysis at week 12 of the change in weekly mean ADP-intensity scores from baseline for TA-ER compared with TAcS; and AUE curves of the change in weekly mean ADP-intensity scores from baseline to week 24 for TA-ER compared with saline-placebo ($\text{AUE}_{\text{week1-24}}$). Prespecified secondary exploratory end points were evaluated using inferential testing and included change from baseline over time (each week from week 1 to 24) for ADP-intensity scores, WOMAC (–A, –B, and –C), KOOS-QoL, and use of rescue medication. In this post hoc analysis of participants with

unilateral OA, ADP-intensity, WOMAC-A, WOMAC-B, WOMAC-C, KOOS-QoL, and rescue medication usage were evaluated. LSM change from baseline was analyzed with a longitudinal mixed-effects model for repeated measurements using observed data, with fixed effects for treatment group, study week, treatment-by-week interaction, study site and baseline pain, and a random participant effect.

Safety was evaluated on the basis of adverse events, physical examinations, index knee assessments, vital signs, and clinical laboratory evaluations on day 1 and through the final visit.

RESULTS

Participants and Baseline Characteristics

A total of 486 participants were randomly assigned in the phase 3 trial, of whom 484 were treated: 161 participants received TA-ER, 162 participants received saline-placebo, and 161 participants received TAcS; 2 participants did not receive treatment and were not included in the full analysis or safety populations. Of the full analysis population, 170 participants (35.1%) reported unilateral OA (TA-ER, $N = 51$; saline-placebo, $N = 60$; TAcS, $N = 59$). In the unilateral knee OA subgroup, the treatment groups were well balanced with respect to baseline characteristics (Table 1). Participants ranged from 40 to 85 years of age (mean, 61 years), the majority were female (58.2%), and 48.8% had obesity.

Analgesia

In the subset of participants with unilateral disease, ADP-intensity scores were significantly improved with TA-ER compared with saline-placebo from weeks 1 to 24 and TAcS from weeks 4 to 21 ($p < 0.05$); numeric improvements vs. TAcS continued through the end of study (Fig. 1, Table 2). Further, TA-ER significantly improved WOMAC-A scores compared with saline-placebo at all time points and at weeks 4, 8, 12, and 24 compared with TAcS; numeric decreases vs. TAcS were observed at the

Table 1 Demographics and baseline characteristics in the unilateral subgroup

	TA-ER 32 mg (N = 51)	Saline-placebo (N = 60)	TAcS 40 mg (N = 59)	Total (N = 170)
Sex, <i>n</i> (%)				
Male	19 (37.3)	24 (40.0)	28 (47.5)	71 (41.8)
Female	32 (62.7)	36 (60.0)	31 (52.5)	99 (58.2)
Age (years), mean (SD)	60.0 (8.78)	61.2 (9.16)	60.4 (10.69)	60.6 (9.57)
Race, <i>n</i> (%)				
Asian	0	1 (1.7)	3 (5.1)	4 (2.4)
Black or African American	3 (5.9)	2 (3.3)	6 (10.2)	11 (6.5)
Native Hawaiian or other Pacific Islander	3 (5.9)	0	1 (1.7)	4 (2.4)
White	45 (88.2)	57 (95.0)	49 (83.1)	151 (88.8)
BMI (kg/m ²), mean (SD)	30.3 (4.95)	29.5 (4.56)	30.6 (4.57)	30.1 (4.68)
BMI category, <i>n</i> (%)				
Normal (BMI 18.5–24.9 kg/m ²)	7 (13.7)	9 (15.0)	7 (11.9)	23 (13.5)
Overweight (BMI 25.0–29.9 kg/m ²)	21 (41.2)	24 (40.0)	19 (32.2)	64 (37.6)
Class I obese (BMI 30.0–34.9 kg/m ²)	13 (25.5)	21 (35.0)	22 (37.3)	56 (32.9)
Class II obese (BMI 35.0–39.9 kg/m ²)	10 (19.6)	6 (10.0)	11 (18.6)	27 (15.9)
Years since primary diagnosis, mean (SD)	7.5 (6.44)	6.9 (6.44)	6.0 (4.53)	6.8 (5.85)
K-L grade, <i>n</i> (%)				
2	26 (51.0)	30 (50.0)	21 (35.6)	77 (45.3)
3	25 (49.0)	30 (50.0)	37 (62.7)	92 (54.1)
4	0	0	1 (1.7)	1 (0.6)
ADP-intensity (0–10 NRS), mean (SD)	6.4 (0.81)	6.3 (0.93)	6.4 (0.87)	6.3 (0.87)
WOMAC (0–4 Likert scale), mean (SD)				
WOMAC-A (pain)	2.1 (0.53)	2.1 (0.55)	2.1 (0.49)	2.1 (0.52)
WOMAC-B (stiffness)	2.4 (0.82)	2.5 (0.67)	2.5 (0.70)	2.5 (0.72)
WOMAC-C (function)	2.2 (0.58)	2.1 (0.54)	2.2 (0.49)	2.1 (0.54)
KOOS-QoL subscale (0–4 Likert scale), ^a mean (SD) ^b	30.0 (16.32)	32.2 (16.59)	30.8 (14.65)	31.1 (15.80)

ADP average daily pain, BMI body mass index, K-L Kellgren-Lawrence, KOOS-QoL Knee Injury and Osteoarthritis Outcome Score-Quality of Life, NRS numeric rating scale, SD standard deviation, TAcS triamcinolone acetonide crystalline suspension, TA-ER triamcinolone acetonide extended-release, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

^a Reported as the cumulative score (0–100) for all KOOS-QoL subscale items

^b TA-ER, *N* = 50; saline-placebo, *N* = 60; TAcS, *N* = 57

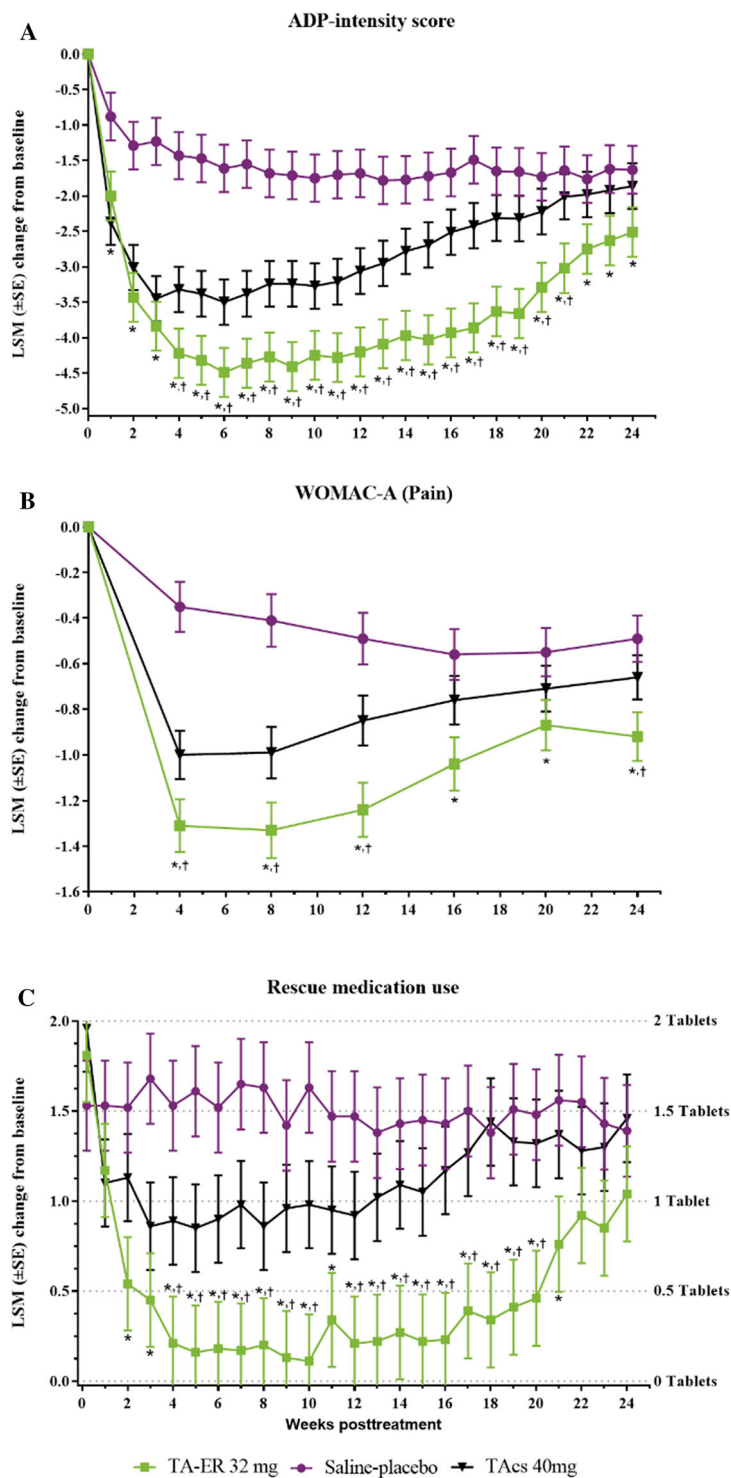


Fig. 1 Change in ADP-intensity score (a), WOMAC-A (pain) score (b), and rescue medication use (c) over time in participants with unilateral knee OA. * $p < 0.05$ vs. saline-placebo. † $p < 0.05$ vs. TAcS. ADP average daily pain, LSM least-squares mean, SE standard error, TA triamcinolone

acetonide, TAcS triamcinolone acetonide crystalline suspension, TA-ER triamcinolone acetonide extended-release, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Table 2 LSM differences in ADP-intensity, WOMAC (–A, –B, –C), KOOS-QoL subscale, and rescue medication use at week 12

End point	TA-ER vs. saline-placebo		TA-ER vs. TAcS	
	LSM difference (95% CI)	<i>p</i> value	LSM difference (95% CI)	<i>p</i> value
ADP-intensity	– 2.52 (– 3.38, – 1.65)	< 0.0001	– 1.14 (– 2.00, – 0.28)	0.0097
WOMAC-A	– 0.76 (– 1.06, – 0.45)	< 0.0001	– 0.39 (– 0.70, – 0.09)	0.0121
WOMAC-B	– 0.84 (– 1.20, – 0.49)	< 0.0001	– 0.36 (– 0.71, – 0.01)	0.0461
WOMAC-C	– 0.75 (– 1.05, – 0.44)	< 0.0001	– 0.35 (– 0.65, – 0.05)	0.0246
KOOS-QoL ^a	19.39 (11.77, 27.02)	< 0.0001	8.18 (0.56, 15.80)	0.0354
Rescue medication use	– 1.26 (– 1.91, – 0.60)	0.0002	– 0.71 (– 1.36, – 0.06)	0.0335

ADP average daily pain, KOOS-QoL Knee Injury and Osteoarthritis Outcome Score-Quality of Life, LSM least-squares mean, TAcS triamcinolone acetonide crystalline suspension, TA-ER triamcinolone acetonide extended-release, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

^a TA-ER, *N* = 50; saline-placebo, *N* = 60; TAcS, *N* = 57

remaining time points assessed (Fig. 1). The impact of TA-ER on pain relief was also demonstrated by a persistent decrease in rescue medication usage compared with baseline throughout the duration of the study (Fig. 1), with significant reductions compared with saline-placebo from weeks 2 to 21 and with TAcS from week 4 to 10 and from week 12 to 20 ($p < 0.05$).

Stiffness and Physical Function

TA-ER improved stiffness and function as evidenced by significant ($p < 0.05$) reductions in WOMAC-B and WOMAC-C scores compared with saline-placebo at all study visits (Fig. 2, Table 2). Improvements were significant ($p < 0.05$) compared with TAcS for WOMAC-B at weeks 4, 8, 12, 16, and 20 and for WOMAC-C at weeks 4, 8, and 12. WOMAC-B and WOMAC-C scores continued to numerically favor TA-ER compared with TAcS at all other time points assessed.

Knee-Related Quality of Life

Significant improvements ($p < 0.05$) in KOOS-QoL scores were observed for TA-ER compared with both saline-placebo and TAcS at weeks 4, 8, and 12 and with saline-placebo at week 24;

numeric improvements were maintained at week 24 compared with TAcS (Fig. 2, Table 2).

Safety

AEs were reported in 47.1% (24/51), 50.0% (30/60), and 50.8% (30/59) of participants with unilateral OA treated with TA-ER, saline-placebo, and TAcS, respectively (Table 3). Across treatment groups, most AEs were mild or moderate and unrelated to study agent. There were no serious AEs or AEs that led to study discontinuation in the active treatment groups. In the saline-placebo group, 1.7% (1/60) of participants had a serious AE, and 1.7% (1/60) of participants had an AE that led to study discontinuation. Index-knee-related AEs occurred in 7.8% (4/51), 8.3% (5/60), and 15.3% (9/59) of participants in the TA-ER, saline-placebo, and TAcS treatment groups, respectively. No index-knee-related AEs were serious, and only led to discontinuation in 1.7% (1/60) of participants receiving saline-placebo.

DISCUSSION

In participants with unilateral knee OA, a single IA injection of TA-ER provided significant improvements in OA symptoms and QoL

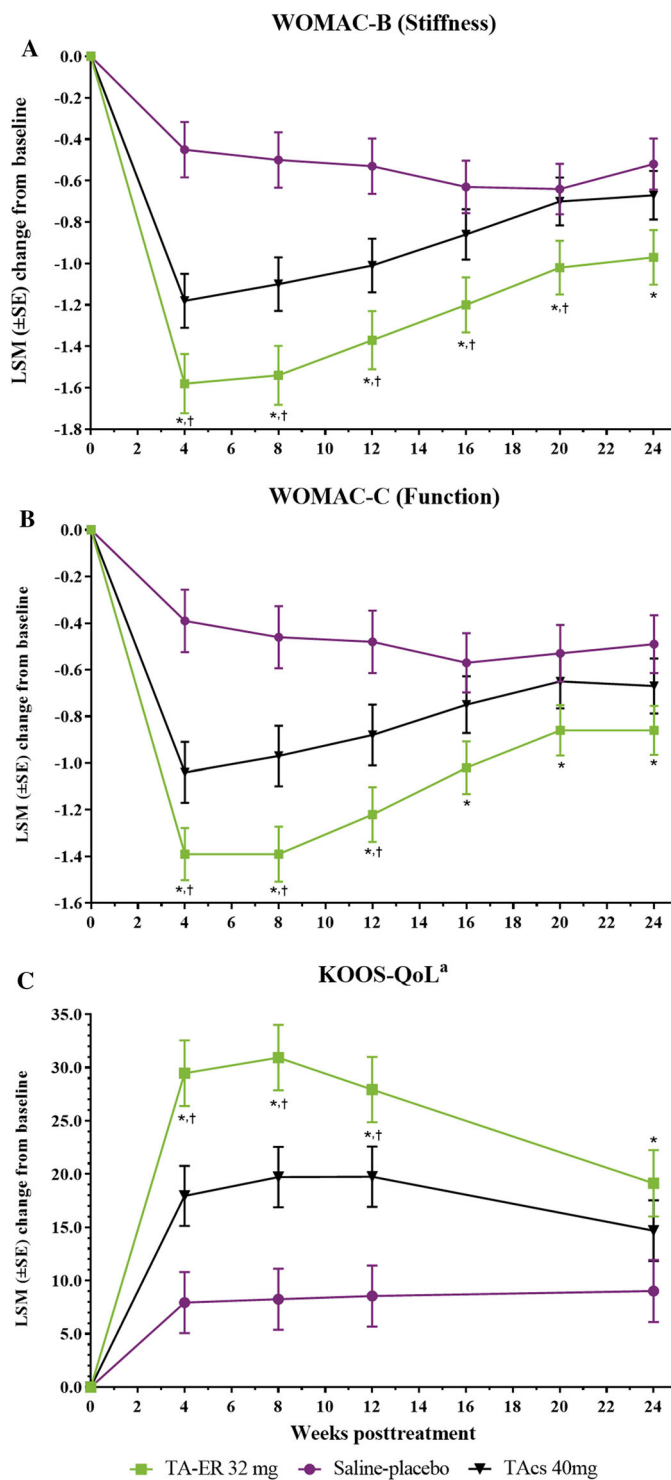


Fig. 2 Change in WOMAC-B (stiffness) (a), WOMAC-C (function) (b), and KOOS-QoL (c) scores over time in participants with unilateral knee OA. * $p < 0.05$ vs. saline-placebo. † $p < 0.05$ vs. TAcS. ^aTA-ER, $N = 50$; saline-placebo, $N = 60$; TAcS, $N = 57$. KOOS-QoL Knee Injury

and Osteoarthritis Outcome Score Quality of Life, LSM least-squares mean, OA osteoarthritis, SE standard error, TAcS triamcinolone acetonide, TA-ER triamcinolone acetonide extended-release, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

Table 3 Summary of adverse events

	TA-ER 32 mg (N = 51)	Saline-placebo (N = 60)	TAcS 40 mg (N = 59)
≥ 1 AE	24 (47.1)	30 (50.0)	30 (50.8)
≥ 1 common AE (> 5% in any treatment group)			
Arthralgia	4 (7.8)	8 (13.3)	5 (8.5)
Gastroesophageal reflux	0	3 (5.0)	0
Headache	5 (9.8)	5 (8.3)	5 (8.5)
Joint effusion	0	0	3 (5.1)
Nasopharyngitis	1 (2.0)	3 (5.0)	5 (8.5)
Sciatica	1 (2.0)	0	3 (5.1)
Upper respiratory tract infection	0	5 (8.3)	2 (3.4)
≥ 1 serious AE	0	1 (1.7)	0
≥ 1 AE leading to study discontinuation	0	1 (1.7)	0
AEs by maximum severity			
Grade 1	12 (23.5)	10 (16.7)	17 (28.8)
Grade 2	12 (23.5)	19 (31.7)	11 (18.6)
Grade 3	0	1 (1.7)	2 (3.4)
Grade 4	0	0	0
AEs by maximum relationship to study agent			
Not related	19 (37.3)	28 (46.7)	26 (44.1)
Unlikely related	2 (3.9)	1 (1.7)	3 (5.1)
Possibly, probably, or definitely related	3 (5.9)	1 (1.7)	1 (1.7)
≥ 1 index-knee-related AE	4 (7.8)	5 (8.3)	9 (15.3)
≥ 1 serious index-knee AE	0	0	0
≥ 1 index-knee AE leading to discontinuation	0	1 (1.7)	0
≥ 1 AE related to injection procedure	1 (2.0)	2 (3.3)	1 (1.7)

AE adverse event, TAcS triamcinolone acetonide crystalline suspension, TA-ER triamcinolone acetonide extended-release. The values are given as the number of participants, with percentages in parentheses

compared with saline-placebo and TAcS, with treatment effects that generally persisted 5–6 months following administration. The magnitude of analgesic effect from TA-ER was profound: pain scores were reduced by > 60% at week 3–17 for ADP-intensity and > 50% at week 4–16 for WOMAC-A. TA-ER also reduced the

need for rescue medication tablets, further demonstrating the greater analgesic benefit associated with TA-ER. Marked improvements in stiffness and function were also observed after TA-ER treatment, with maximal reductions of 65% and 64% for WOMAC-B and WOMAC-C scores, respectively. Additionally, KOOS-QoL

subscale scores more than doubled following treatment with TA-ER. The outcomes in this post hoc subgroup analysis were improved compared with the full analysis population and may reflect the ability of participants with unilateral OA to better self-assess changes in index-knee pain, after a single injection, in the absence of pain in the contralateral knee [27, 28]. Additional studies designed to proactively assess the impact of a single TA-ER injection in participants with unilateral OA, or of simultaneous TA-ER injections in each knee of participants with bilateral disease, are warranted.

Non-opioid interventions that are successful in providing sustained relief from OA pain are needed, and as such the ability of TA-ER to significantly reduce the use of pain-relieving rescue medication is of particular interest. Analgesic interventions such as NSAIDs, IACS, and opioids are used for short-term pain management of knee OA [21, 22], but opioids are also often prescribed for chronic OA pain in service members [16]. Given that traditional IACS (e.g., TAcS) provide only short-term pain relief in OA, it is unlikely that treatment would result in a longer-term, opioid-sparing effect in the context of chronic pain. Indeed, data from the current analysis suggest that TAcS has a minimal effect on reducing pain medication usage which tapers off by approximately 12 weeks after injection, whereas TA-ER consistently and significantly reduces pain medication usage by > 75% at weeks 2 to 20 after injection. Data on whether or not TA-ER demonstrates a true opioid-sparing effect should be collected.

Limitations of this post hoc subgroup analysis include the relatively small unilateral knee OA sample sizes and the selection of participants based on self-reported unilateral pain without confirmation of unilateral OA using x-ray evaluation of the contralateral knee. In addition, the age, sex, and racial distribution of the participants in this study does not correlate with the demographics of the active duty military population. Although the active duty force is composed of 84.1% men, only 37.3% of participants who received TA-ER in this analysis were male [33]. Likewise, the population in this

study was 11.2% nonwhite, whereas approximately one-third of active duty members identify as a racial minority [33]. Furthermore, the average age of participants receiving TA-ER (60 years) may be older than military members seeking treatment for OA given the increased incidence of OA in younger age groups for military members compared with the general population [4]. Prospective studies of TA-ER outcomes in a military-specific population are needed.

CONCLUSION

In a phase 3 subgroup analysis in a general population of participants with unilateral knee OA, TA-ER provided significant reductions in pain compared with TAcS and saline-placebo, as measured by ADP-intensity, WOMAC-A score, and rescue medication use. Stiffness, function, and knee-related QoL were also significantly improved with TA-ER treatment compared with saline-placebo and TAcS. Treatment effects were generally durable for 5–6 months following TA-ER administration. These clinical data suggest that TA-ER injected intra-articularly into the affected knee may be an effective non-opioid treatment option for patients with unilateral OA, including members of the military. Given the unmet need among members of the military, TA-ER may present an important non-opioid alternative for treatment of knee OA pain.

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

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