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ORIGINAL RESEARCH

Enthesitis and Dactylitis Resolution with Risankizumab for Active Psoriatic Arthritis: Integrated Analysis of the Randomized KEEPsAKE 1 and 2 Trials

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ABSTRACT

Introduction: The presence (vs absence) of enthesitis/dactylitis is associated with greater psoriatic arthritis (PsA) activity and reduced health-related quality of life. Risankizumab, an interleukin 23 antagonist, demonstrated superior treatment efficacy over placebo in patients with PsA, including enthesitis/dactylitis. Herein, we report the efficacy of risankizumab on complete resolution of enthesitis and/or dactylitis and improvements in patient-reported outcomes in patients with PsA.

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Methods: This integrated post hoc analysis of data from KEEPsAKE 1 and KEEPsAKE 2 included patients with baseline enthesitis (Leeds Enthesitis Index > 0) and/or dactylitis (Leeds Dactylitis Index > 0). Efficacy outcomes at weeks 24 and 52 included proportion of patients achieving enthesitis and/or dactylitis resolution and minimal clinically important differences (MCID) in pain, Health Assessment Questionnaire-Disability Index, and Functional Assessment of Chronic Illness Therapy-Fatigue.
Results: Of 1407 patients, approximately 63%, 28%, and 20% had baseline enthesitis, dactylitis, and both enthesitis/dactylitis, respectively. At week 24, higher response rates were observed for risankizumab vs placebo for resolution of enthesitis, dactylitis, and both enthesitis/dactylitis (differences of 13.9%, 16.9%, and 13.3%, respectively; $p < 0.05$). By week 52, risankizumab treatment resulted in complete resolution of enthesitis, dactylitis, and both enthesitis and dactylitis in 55.0%, 76.1%, and 52.3% of patients; similar resolution rates occurred among patients who switched from placebo to risankizumab. Among risankizumab-treated patients who achieved resolution of enthesitis and/or dactylitis, MCIDs were also attained in patient-reported pain, disability, and fatigue at week 24 (all $p < 0.05$; except fatigue in patients with resolution of both enthesitis/dactylitis); responses were sustained through week 52.
Conclusions: Higher proportions of risankizumab-treated (vs placebo-treated) patients achieved enthesitis and/or dactylitis resolution and meaningful improvements in patient-reported outcomes at week 24 and generally sustained responses at week 52. Thus, risankizumab may result in sustained alleviation of PsA-related pathognomonic musculoskeletal lesions of enthesitis/dactylitis.
Clinicaltrials.gov identifiers: NCT03675308, and NCT03671148.

Keywords: Biologic; Interleukin 23; Psoriasis; Psoriatic arthritis; Risankizumab; Enthesitis; Dactylitis

Key Summary Points

Why carry out this study?

Patients with psoriatic arthritis often have musculoskeletal symptoms such as periarticular manifestations of enthesitis and dactylitis, which have been associated with increased overall disease burden (e.g., higher potential for joint damage) and reduced health-related quality of life (e.g., limitations with daily function), especially if treatment is delayed.

The pathogenesis of enthesitis and dactylitis has been linked to the interleukin 23 pathway, making interleukin 23 agonists, such as risankizumab, a potential interest for investigation.

We report on integrated data from two clinical studies in patients with psoriatic arthritis evaluating the efficacy of risankizumab on the complete resolution of enthesitis and/or dactylitis and the associated improvements in patient-reported outcomes.

What was learned from the study?

Patients treated with risankizumab achieved higher response rates for resolution of enthesitis, dactylitis, and enthesitis/dactylitis vs patients who received placebo and demonstrated clinically meaningful improvements in patient-reported assessments, including pain, disability, and fatigue.

INTRODUCTION

Enthesitis and dactylitis are common periarticular manifestations and are considered the cardinal musculoskeletal lesions in early active psoriatic arthritis (PsA) [1–3]. The worldwide prevalence of enthesitis and dactylitis in patients with PsA ranges from 25% to 44% and 8% to 48%, respectively [4–6]. PsA with enthesitis and/or dactylitis is associated with

increased disease activity and overall disease burden and reduced health-related quality of outcomes compared with PsA without these features [7]. Additionally, enthesitis severity and acute dactylitis are associated with greater radiographic joint and digit damage, and a delay in initiating treatment may result in greater radiographic damage, functional limitation, and reduced health-related quality of life [4, 8, 9]. Accordingly, drugs that treat these periarticular manifestations in PsA may be relevant in psoriasis for the prevention of the development of enthesitis or dactylitis. The immunopathogenesis of enthesitis and dactylitis in PsA is centrally linked to the interleukin 23 (IL-23) pathway [10], which makes research into the impact of IL-23 inhibition of special interest for treating these conditions.

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that inhibits IL-23 by binding to its p19 subunit [11]. Results from the KEEPsAKE 1 and KEEPsAKE 2 studies at week 24 demonstrated superior efficacy of risankizumab over placebo to treat the signs and symptoms of PsA, including enthesitis and dactylitis [12–14]. The aim of this integrated analysis was to evaluate the efficacy of risankizumab on the complete resolution of enthesitis and/or dactylitis and the associated improvements in patient-reported outcomes using data from the KEEPsAKE 1 and KEEPsAKE 2 studies.

METHODS

Study Design and Patients

Detailed descriptions of KEEPsAKE 1 (NCT03675308) and KEEPsAKE 2 (NCT03671148) study designs and patient populations have been previously reported [12, 13]. Briefly, enrolled patients were aged ≥ 18 years, had a confirmed clinical diagnosis of PsA (symptom onset ≥ 6 months prior to screening, met the Classification Criteria for Psoriatic Arthritis and active disease [defined as ≥ 5 tender joints based on 68 joint counts with ≥ 5 swollen joints based on 66 joint counts], and active plaque or nail psoriasis), had an inadequate response or intolerance to ≥ 1 conventional synthetic disease modifying antirheumatic drugs (csDMARD; KEEPsAKE 1 and KEEPsAKE 2 studies), and/or had an inadequate response or intolerance to 1 or 2 biologic therapies (KEEPsAKE 2 study). Patients were randomized (1:1) to receive double-blind, subcutaneously administered risankizumab 150 mg or placebo at weeks 0, 4, and 16. At week 24, patients previously randomized to placebo received a blinded dose of risankizumab 150 mg, and patients randomized to risankizumab received a blinded dose of placebo. All patients were then eligible to receive open-label risankizumab 150 mg every 12 weeks from weeks 28 to 52. For the remainder of this report, patients who were initially randomized to risankizumab will be referred to as the "continuous risankizumab" cohort, and those patients who started on placebo and switched to risankizumab will be referred to as the "placebo-risankizumab" cohort. Patients with enthesitis (Leeds Enthesitis Index [LEI] > 0), dactylitis (Leeds Dactylitis Index [LDI] > 0), or both enthesitis/dactylitis at baseline were included in this integrated post hoc analysis.

The clinical trials were conducted in accordance with the operations manual, protocol, International Council for Harmonisation guidelines, and applicable guidelines and regulations governing ethical principles and study conduct originating in the Declaration of Helsinki. Independent ethics committees/institutional review boards ensured the ethical, scientific, and medical appropriateness of the study before it was conducted and approved all relevant documentation including the protocol, informed consent form(s), and all participant materials. Written informed consent was obtained from all patients before enrollment.

Assessments

All enthesitis and dactylitis assessments were performed by independent, qualified medical professionals (predominantly rheumatologists). Efficacy outcomes included resolution of enthesitis (LEI = 0), dactylitis (LDI = 0), or both enthesitis/dactylitis (LEI = 0 and LDI = 0) over time among those with baseline enthesitis and/

or dactylitis; median time to first achievement of resolution of enthesitis, dactylitis, or both enthesitis/dactylitis; enthesitis and/or dactylitis-free state (i.e., patients without baseline enthesitis and/or dactylitis [LEI = 0, LDI = 0, or LEI = 0 and LDI = 0] who remained free of enthesitis, dactylitis, or both enthesitis/dactylitis, respectively) at weeks 24 and 52; and mean change from baseline in LEI or LDI. Patient-reported outcomes included proportion of patients who achieved a minimally clinical important difference (MCID) in pain (≥ 10-mm decrease on a 100-mm visual analog scale [scoring range, 0–100]) [15], Health Assessment Questionnaire-Disability Index (HAQ-DI; ≥ 0.35-unit decrease [scoring range, 0 – 3]) [16], or Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue; ≥ 4-point increase [scoring range, 0–52]) [17]. Lower scores indicate a more favorable health state for pain (less pain) and HAQ-DI (less disability), whereas higher scores indicate an improvement in FACIT-Fatigue (less fatigue). These patient-reported outcomes were assessed in patients with baseline enthesitis, dactylitis, or both enthesitis/dactylitis who achieved resolution of these manifestations over time. Additionally, the proportions of patients achieving MCID in pain, HAQ-DI, or FACIT-Fatigue were compared between patients who achieved resolution of enthesitis, dactylitis, or both enthesitis/dactylitis and patients who did not achieve resolution at weeks 24 and 52.

Statistical Analysis

For all analyses, data were pooled from the KEEPsAKE 1 and KEEPsAKE 2 studies. The analyses of enthesitis and/or dactylitis resolution at week 24 were prespecified in the KEEPsAKE 1 study (ranked secondary endpoints with multiplicity adjustment). Baseline demographics and clinical characteristics were evaluated using descriptive statistics (e.g., mean and SD, counts and percentages). For response rates, 95% CI was calculated based on normal approximation to the binomial distribution. Nominal p values were determined using the Cochran-Mantel-Haenszel test adjusting for the stratification factors of current use of csDMARD (0 vs ≥ 1 therapy) at baseline, extent of psoriasis (≥ 3% or < 3% affected body surface area) at baseline, and study (KEEPsAKE 1 or KEEPsAKE 2). The time to first achievement of resolution analyses was conducted during the double-blind period. A mixed-effect model for repeated measures was used for continuous variables collected up to week 24; data were analyzed as observed after week 24. For categorical variables, nonresponder imputation (NRI) incorporating multiple imputation to handle missing data due to COVID-19 was used up to week 24; NRI (as observed) was used after week 24.

RESULTS

Patients

Of 1407 patients treated in the KEEPsAKE 1 and 2 studies, 63% ($n = 892$), 28% ($n = 392$), and 20% ($n = 275$) had enthesitis, dactylitis, and both enthesitis/dactylitis at baseline, respectively. Baseline demographics and disease characteristics were generally well balanced among patients with (vs without) enthesitis, dactylitis, and both enthesitis/dactylitis (Table 1). As expected, patients with (vs without) enthesitis, dactylitis, or both enthesitis/dactylitis at baseline had numerically higher mean values in tender joint count, swollen joint count, patient's global assessment of disease activity, and physician's global assessment of disease activity.

Efficacy

Resolution of Enthesitis and/or Dactylitis Outcomes

Patients treated with risankizumab achieved higher response rates for resolution of enthesitis vs patients in the placebo group at week 24 (Fig. 1). Resolution of enthesitis response rates at week 24 was 48.4% vs 34.8% (risankizumab vs placebo, respectively; $p < 0.001$). Resolution of dactylitis response rates at week 24 was 68.1% vs 51.0% (risankizumab vs placebo; $p < 0.001$). For both enthesitis/dactylitis manifestations, week

24 resolution rates were 42.2% vs 28.6% (risankizumab vs placebo groups; $p<0.05$). Response rates for resolution of enthesitis, dactylitis, and both enthesitis/dactylitis at week 52 were generally sustained in the continuous risankizumab cohort or increased in the placebo-risankizumab cohort. In patients randomized to receive continuous risankizumab who achieved resolution of enthesitis, dactylitis, and both enthesitis/dactylitis at week 24 (as observed), maintenance of these response rates (NRI [as observed]) also occurred at week 52 (enthesitis, 80.6%; dactylitis, 88.7%; both enthesitis/dactylitis, 71.4%). Response patterns were generally similar in biologic-naïve and biologic-experienced patients (Supplementary Fig. 1).

Time to First Resolution of Enthesitis and/or Dactylitis

Treatment with risankizumab resulted in a shorter time to first resolution of enthesitis vs placebo (median time [95% CI], risankizumab, $n=444$, 22.9 [16.1–24.1] weeks; placebo, $n=448$, 24.1 [16.6–24.1] weeks; hazard ratio [HR; 95% CI], 1.21 [1.02–1.44]; $p<0.05$). Similarly, treatment with risankizumab resulted in shorter time to first resolution of dactylitis than placebo (median time [95% CI], risankizumab, $n=188$, 12.3 [12.1–12.9] weeks; placebo, $n=204$, 16.1 [13.1–16.6] weeks; HR [95% CI], 1.42 [1.12 – 1.81]; $p<0.01$). For resolution of both enthesitis/dactylitis, risankizumab treatment also resulted in shorter time to first resolution than placebo (median time [95% CI], risankizumab, $n=128$, 24.1 [17.6–24.7] weeks; placebo, $n=147$, 24.4 [24.1–25.0] weeks; HR [95% CI], 1.34 [0.95–1.89]); however, statistical significance was not met (nominal $p=0.11$).

Maintenance of Enthesitis- and/or Dactylitis-Free State

Among patients without baseline enthesitis, their enthesitis-free state remained generally stable up to week 52. At week 24, 81.0% (*n/N*, 213/263; 95% CI, 76.2%–85.7%) of patients receiving risankizumab and 76.2% (192/252; 70.9%–81.4%) of patients receiving placebo remained free of enthesitis. By week 52, 86.3% (227/263; 82.2%–90.5%) and 82.9% (209/252; 78.3%–87.6%) of patients in the continuous risankizumab and placebo-risankizumab cohorts remained enthesitis free, respectively. Similarly, in patients without baseline dactylitis at week 24, 87.1% (452/519; 84.2%–90.0%) and 82.4% (407/494; 79.0%–85.7%) of patients in the risankizumab and placebo cohorts, respectively, remained free of dactylitis. By week 52, the dactylitis-free patients comprised 88.6% (460/519; 85.9%–91.4%) of the continuous risankizumab cohort and 87.7% (433/494; 84.8%–90.6%) of the placebo-risankizumab cohort. When patients were evaluated who were free of both enthesitis/dactylitis at baseline, 79.8% (162/203; 74.3%–85.3%) of those patients treated with risankizumab and 73.7% (143/194; 67.5%–79.9%) of those patients receiving placebo remained free of both enthesitis/dactylitis at week 24. The proportions remained high at week 52 with 84.7% (172/203; 79.8%–89.7%) of the continuous risankizumab and 82.0% (159/194; 76.5%–87.4%) of placebo-risankizumab cohorts remaining both enthesitis/dactylitis free.

Improvement in Enthesitis and Dactylitis

By week 24 of treatment, greater improvements in LEI scores (as measured by least squared [LS] mean changes) were observed among patients with baseline enthesitis when treated with risankizumab vs placebo (LS mean [95% CI], −1.6 [−1.7, −1.4] vs −1.2 [−1.4, −1.0], respectively; $p<0.001$) (Fig. 2). Similarly, numerically greater improvements in LDI scores at week 24 were observed in patients with dactylitis at baseline in the risankizumab vs placebo groups (LS mean [95% CI], −71.9 [−80.8, −63.1] vs −65.2 [−74.0, −56.4], respectively; $p=0.23$). Continuous improvements in LEI and LDI scores were observed from weeks 24–52 in both groups. At week 52 in the continuous risankizumab and placebo-risankizumab cohorts, LS mean (95% CI) changes from baseline in LEI were −2.0 (−2.2, −1.9) and −1.8 (−2.0, −1.7) and in LDI were −84.2 (−102.1, −66.4) and −83.8 (−102.2, −65.5), respectively. Response patterns were generally similar among biologic-naïve and biologic-experienced patients (Supplementary Fig. 2).

Table 1 Baseline demographics and characteristics

Characteristic	With enthesitis[a]		With dactylitis[b]		With both enthesitis[a]/dactylitis[b]		Without enthesitis[c]		Without dactylitis[d]		Without enthesitis[c]/dactylitis[d]	
	RZB 150 mg *n* = 444	PBO *n* = 448	RZB 150 mg *n* = 188	PBO *n* = 204	RZB 150 mg *n* = 128	PBO *n* = 147	RZB 150 mg *n* = 263	PBO *n* = 252	RZB 150 mg *n* = 519	PBO *n* = 494	RZB 150 mg *n* = 203	PBO *n* = 194
Age, years, mean (SD)	52.8 (12.2)	52.1 (12.5)	50.6 (12.2)	51.2 (12.2)	52.6 (11.8)	51.8 (12.6)	50.3 (12.4)	51.0 (11.8)	52.4 (12.4)	51.9 (12.3)	51.5 (12.3)	51.4 (11.9)
Male, *n* (%)	210 (47.3)	197 (44.0)	110 (58.5)	103 (50.5)	78 (60.9)	72 (49.0)	142 (54.0)	136 (54.0)	242 (46.6)	230 (46.6)	110 (54.2)	105 (54.1)
White, *n* (%)	418 (94.1)	420 (93.8)	170 (90.4)	189 (92.6)	114 (89.1)	137 (93.2)	254 (96.6)	241 (95.6)	502 (96.7)	470 (95.1)	198 (97.5)	188 (96.9)
BMI, kg/m^2, mean (SD)	31.1 (7.1)	31.3 (6.7)	30.7 (6.6)	30.9 (6.4)	31.2 (7.1)	31.3 (6.8)	30.8 (6.7)	29.2 (5.7)	31.1 (7.1)	30.5 (6.4)	31.0 (7.1)	29.1 (5.9)
PsA duration, years, mean (SD)	7.6 (7.1)	7.7 (8.4)	6.9 (6.2)	7.5 (7.4)	7.1 (5.9)	7.5 (7.7)	7.2 (7.9)	6.9 (7.0)	7.7 (7.8)	7.4 (8.1)	7.4 (8.1)	6.8 (7.2)
Concomitant csDMARD, *n* (%)												
Any csDMARD	310 (69.8)	313 (69.9)	133 (70.7)	142 (69.6)	88 (68.8)	106 (72.1)	197 (74.9)	180 (71.4)	374 (72.1)	350 (70.9)	152 (74.9)	143 (73.7)
Any methotrexate	250 (56.3)	260 (58.0)	109 (58.0)	118 (57.8)	69 (53.9)	86 (58.5)	174 (66.2)	154 (61.1)	315 (60.7)	296 (59.9)	134 (66.0)	122 (62.9)
None	134 (30.2)	135 (30.1)	55 (29.3)	62 (30.4)	40 (31.3)	41 (27.9)	66 (25.1)	72 (28.6)	145 (27.9)	144 (29.1)	51 (25.1)	51 (26.3)
TJC,[e] mean (SD)	25.3 (15.1)	24.2 (13.6)	26.0 (15.9)	25.0 (14.1)	30.0 (15.8)	27.3 (14.5)	14.9 (9.9)	15.5 (10.2)	19.8 (13.4)	19.4 (12.3)	14.1 (9.0)	14.5 (9.8)

Table 1 continued

Characteristic	With enthesitis[a]		With dactylitis[b]		With both enthesitis[a]/dactylitis[b]		Without enthesitis[c]		Without dactylitis[d]		Without enthesitis[c]/dactylitis[d]	
	RZB 150 mg *n* = 444	PBO *n* = 448	RZB 150 mg *n* = 188	PBO *n* = 204	RZB 150 mg *n* = 128	PBO *n* = 147	RZB 150 mg *n* = 263	PBO *n* = 252	RZB 150 mg *n* = 519	PBO *n* = 494	RZB 150 mg *n* = 203	PBO *n* = 194
SJC,[f] mean (SD)	13.6 (8.8)	13.7 (8.8)	15.8 (9.7)	16.7 (10.7)	17.6 (10.1)	17.4 (11.1)	10.2 (6.2)	10.9 (7.2)	11.1 (7.1)	11.0 (6.5)	9.7 (5.6)	9.8 (6.0)
PtGA, mean (SD)												
Pain[g]	58.9 (22.4)	57.6 (22.2)	62.0 (21.6)	60.4 (22.0)	65.2 (21.4)	62.4 (20.7)	52.2 (23.1)	56.1 (23.7)	54.4 (23.0)	55.8 (22.9)	51.3 (23.8)	56.6 (23.3)
Disease activity[g]	59.7 (21.1)	58.0 (22.0)	63.0 (20.4)	59.8 (21.6)	65.7 (19.5)	61.3 (21.0)	53.4 (22.3)	55.3 (23.0)	55.3 (21.9)	55.9 (22.5)	52.2 (22.4)	55.3 (22.9)
PGA disease activity,[g] mean (SD)	63.8 (17.5)	63.3 (16.6)	66.0 (15.6)	66.2 (15.6)	67.6 (15.1)	67.1 (15.2)	58.5 (16.9)	59.2 (16.9)	60.3 (17.8)	60.1 (16.9)	57.3 (16.9)	58.0 (16.8)
HAQ-DI, mean (SD)	1.2 (0.6)	1.2 (0.6)	1.3 (0.6)	1.2 (0.6)	1.4 (0.6)	1.3 (0.6)	1.0 (0.7)	1.0 (0.6)	1.1 (0.7)	1.1 (0.6)	1.0 (0.7)	1.0 (0.6)
FACIT-Fatigue, mean (SD)	27.3 (11.4)	27.1 (11.6)	27.4 (11.7)	27.3 (11.1)	26.1 (11.6)	26.1 (11.0)	32.0 (10.6)	31.8 (11.3)	29.7 (11.2)	29.4 (12.0)	32.6 (10.3)	32.1 (11.5)

BMI body mass index, *csDMARD* conventional synthetic disease-modifying, antirheumatic drug, *FACIT-Fatigue* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *LDI* Leeds Dactylitis Index, *LEI* Leeds Enthesitis Index, *PBO* placebo, *PGA* physician's global assessment, *PsA* psoriatic arthritis, *PtGA* patient's global assessment, *RZB* risankizumab, *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count

[a]Baseline LEI > 0. [b]Baseline LDI > 0. [c]Baseline LEI = 0. [d]Baseline LDI = 0. [e]Based on 68 joints. [f]Based on 66 joints. [g]Scored as millimeters on a 100-mm horizontal visual analog scale

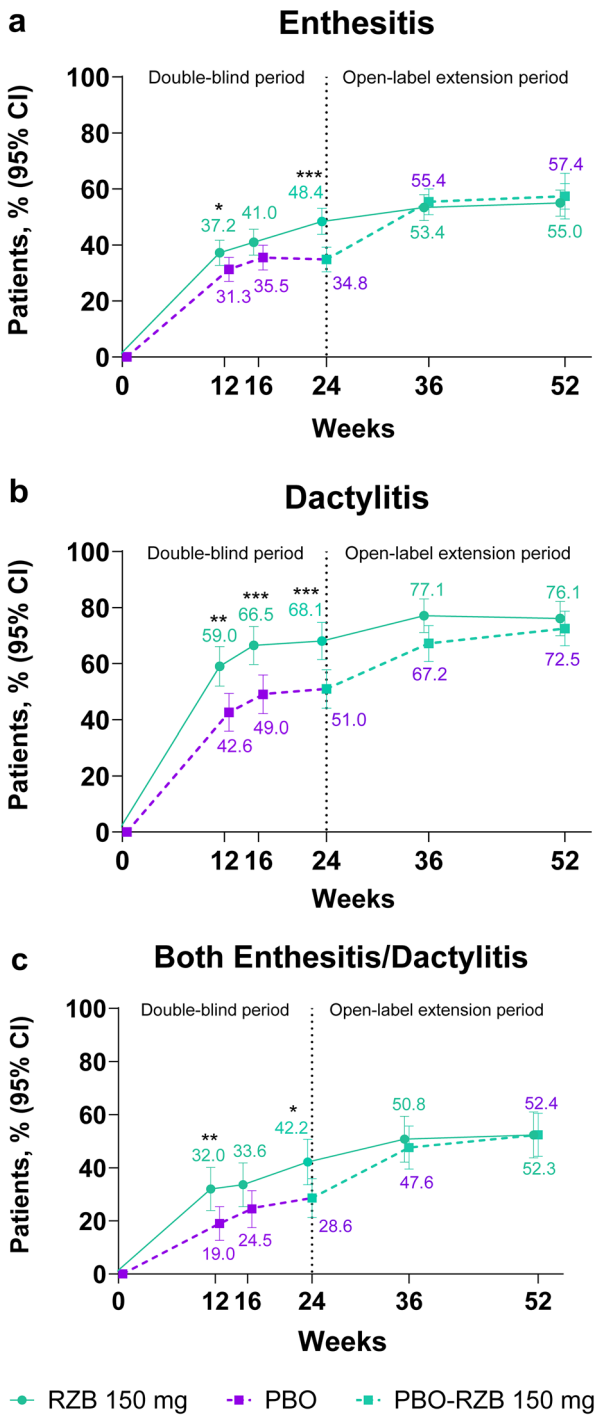

Fig. 1 Proportion of patients achieving resolution of enthesitis (randomized to RZB, $n = 444$; PBO, $n = 448$) (**a**), dactylitis (RZB, $n = 188$; PBO, $n = 204$) (**b**), and both enthesitis/dactylitis (RZB, $n = 128$; PBO, $n = 147$) (**c**). Missing data were imputed using nonresponder imputation incorporating multiple imputation to handle missing data resulting from COVID-19 in the double-blind period and nonresponder imputation (as observed) in the open-label extension period. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs PBO. *CI* confidence interval, *PBO* placebo, *RZB* risankizumab

Patient-Reported Outcomes

Among patients who achieved resolution of enthesitis and/or dactylitis at week 24 (as observed), greater proportions of patients treated with risankizumab achieved MCIDs in pain, HAQ-DI, and/or FACIT-Fatigue (NRI [as observed]) compared with placebo ($p < 0.05$; except for FACIT-Fatigue among patients who achieved resolution of both enthesitis/dactylitis) (Fig. 3). From weeks 24 to 52, response rates were consistent in the continuous risankizumab cohort and numerically increased in the placebo-risankizumab cohort. MCIDs in patient-reported outcomes were achieved by greater proportions of patients who achieved resolution of enthesitis and/or dactylitis compared with those patients who did not at weeks 24 and 52 (all $p \leq 0.05$; except for pain among patients who achieved resolution of both enthesitis/dactylitis at week 52) (Table 2).

DISCUSSION

Overall, these integrated analyses from the KEEPsAKE 1 and KEEPsAKE 2 studies support that risankizumab treatment resulted in the greater resolution of enthesitis, dactylitis, and both enthesitis/dactylitis compared with placebo at week 24, and response rates at week 52 were generally sustained in the continuous risankizumab cohort or numerically increased in the placebo-risankizumab cohort. Furthermore, improvements in these clinically relevant PsA domains among those patients who achieved resolution at week 24 were maintained at week 52 with continuous risankizumab treatment, supporting a central role of the IL-23 pathway in these distinct PsA manifestations. Shorter time to first resolution of enthesitis and/or dactylitis was achieved with risankizumab compared with placebo. In addition, most patients who were free of enthesitis, dactylitis, or both enthesitis/dactylitis at baseline remained generally stable up to 52 weeks.

In a real-world cohort of patients with PsA, enthesitis or dactylitis was associated with a high disease burden [7]. In our analysis,

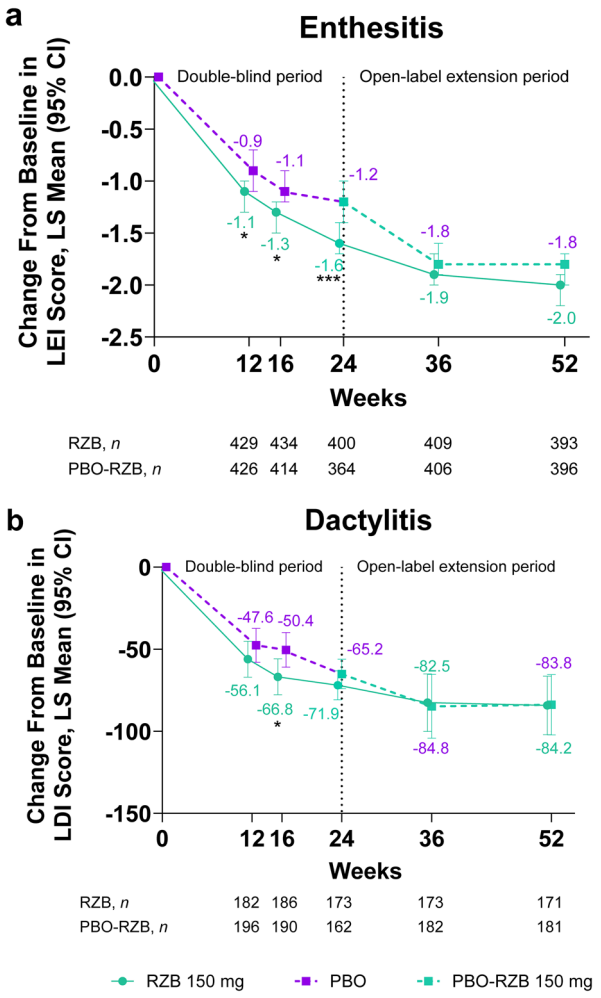

Fig. 2 Mean change in LEI among patients with baseline enthesitis (**a**) and in LDI among patients with baseline dactylitis (**b**). Mixed-effect model repeated measurement analysis was used for the double-blind period; as-observed data were used for the open-label extension period. $^{*}p < 0.05$; $^{***}p < 0.001$ vs PBO. *CI* confidence interval, *LDI* Leeds Dactylitis Index, *LEI* Leeds Enthesitis Index, *LS* least squares, *PBO* placebo, *RZB* risankizumab

risankizumab was efficacious in helping patients with enthesitis and/or dactylitis achieve clinically meaningful changes in patient-reported outcomes of physical function and health-related quality of life. We focused on MCID in patient-reported outcomes at weeks 24 and 52. In this integrated analysis, most patients who achieved resolution of enthesitis and/or dactylitis with risankizumab also achieved MCIDs in pain, disability, and fatigue at weeks 24 and 52. Additionally, patients who achieved resolution of enthesitis and/or dactylitis had higher rates of MCID in patient-reported outcomes compared with those patients who did not achieve such resolution.

The IL-23 pathway plays an important role in the pathogenesis of both enthesitis and dactylitis manifestations [18]. Early preclinical studies provide additional support for common mechanistic pathways (e.g., regulation of inducible IL-23–producing myeloid cells and IL-23 receptor-positive innate and adaptive T cells) in periarticular and articular joint inflammation, thus, providing a strong rational for IL-23 antagonism as a target therapy for enthesitis and dactylitis [3, 19, 20]. Other studies have demonstrated improvement in enthesitis and/or dactylitis with IL-23 inhibitors for the treatment of active PsA. Data from the phase 3 UltIMMa-1 and UltIMMa-2 studies showed that a greater proportion of patients treated with the IL–23 inhibitor risankizumab achieved complete resolution of psoriatic lesions compared with ustekinumab [21]. In the phase 3 PSUMMIT-1 and PSUMMIT-2 studies of the IL-12/23 inhibitor ustekinumab, significantly greater improvements in enthesitis and dactylitis were observed in ustekinumab-treated patients compared with those patients who received placebo [22, 23]. In the phase 3 DISCOVER-1 and DISCOVER-2 studies, the IL-23 inhibitor guselkumab demonstrated higher rates of enthesitis and dactylitis resolution compared with placebo [24, 25]. These results indicate that IL-23 inhibition is efficacious in improving and resolving enthesitis and/or dactylitis in patients with PsA. Efficacy comparisons with other PsA treatments have been previously reported in several meta-analyses; however, comparisons are limited because of differences in study designs with various scoring systems and treatment outcomes [26, 27].

A limitation of this analysis is that the KEEPsAKE 1 and KEEPsAKE 2 studies were performed during the COVID-19 pandemic, which resulted in missing data due to COVID-19–related logistical restrictions; however, these restrictions were addressed by implementing specific imputation methods to handle missing data resulting from the pandemic, and the number of patients who had missing data due to COVID-19 was small.

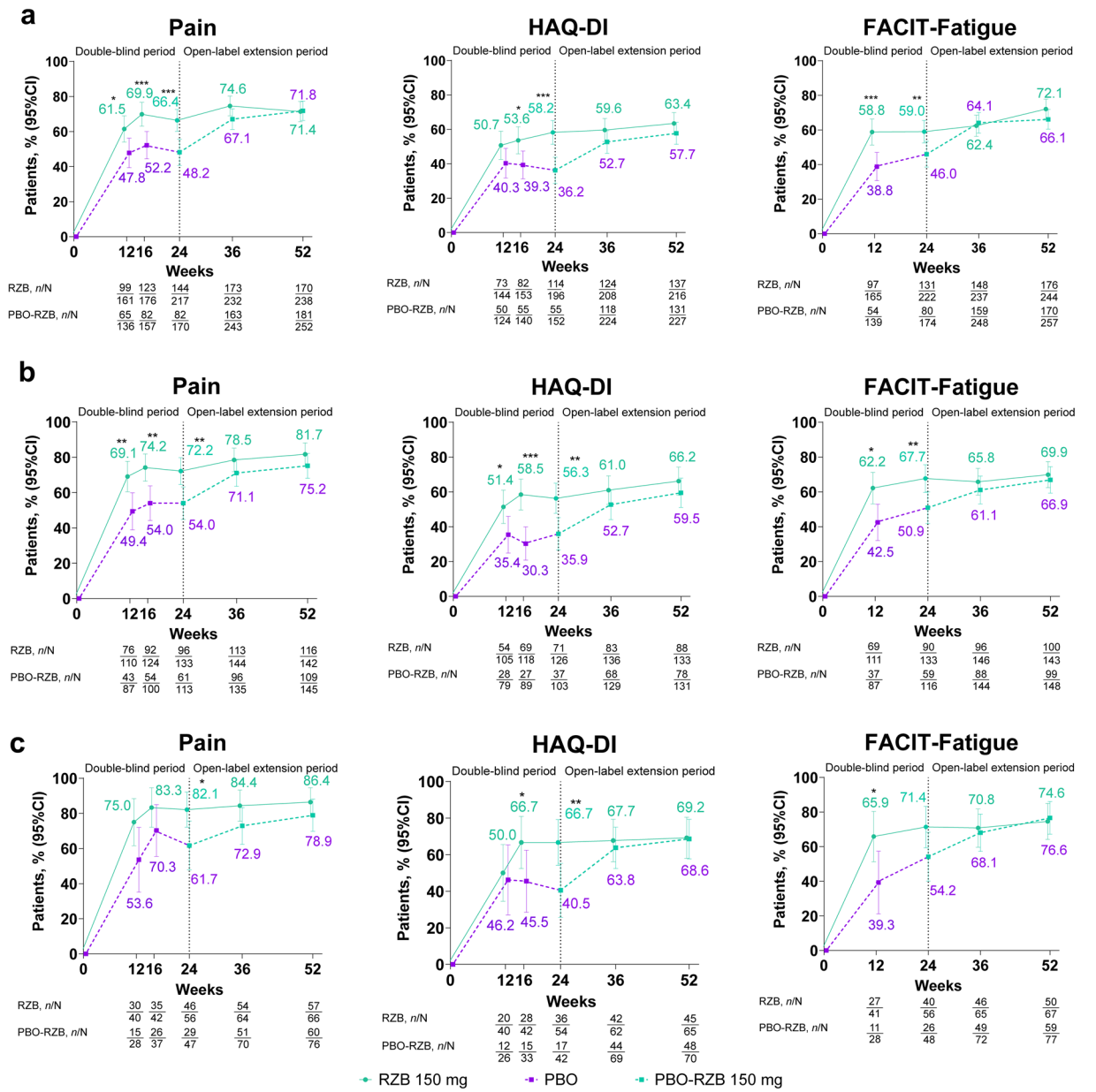

Fig. 3 Proportion of patients who achieved MCID in PROs among those who achieved resolution of enthesitis (**a**), dactylitis (**b**), and both enthesitis/dactylitis (**c**). MCID cutoffs are ≥ 10-mm decrease on a 100-mm visual analog scale (pain), ≥ 0.35-unit decrease (HAQ-DI), and ≥ 4-point increase (FACIT-Fatigue). Missing data were imputed using nonresponder imputation incorporating multiple imputation to handle missing data resulting from COVID-19 in the double-blind period and nonresponder imputation (as observed) in the open-label extension period. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs PBO. *CI* confidence interval, *FACIT-Fatigue* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *MCID* minimally clinical important difference, *PBO* placebo, *PRO* patient-reported outcome, *RZB* risankizumab

Table 2 Proportion of patients achieving MCIDs in PROs among those who achieved vs those who did not achieve resolution of enthesitis and/or dactylitis as observed at weeks 24 and 52

MCID[a]	Week 24		Week 52	
	Achieved resolution	Did not achieve resolution	Achieved resolution	Did not achieve resolution
Enthesitis, *n/N* (%)[b]				
Pain	226/387 (58.4)***	183/441 (41.5)	351/490 (71.6)*	182/286 (63.6)
HAQ-DI	169/348 (48.6)***	116/409 (28.4)	268/443 (60.5)***	122/265 (46.0)
FACIT-Fatigue	211/396 (53.3)***	183/446 (41.0)	346/501 (69.1)***	151/288 (52.4)
Dactylitis, *n/N* (%)[c]				
Pain	157/246 (63.8)***	55/122 (45.1)	225/287 (78.4)***	41/101 (40.6)
HAQ-DI	108/229 (47.2)*	35/108 (32.4)	166/264 (62.9)***	24/90 (26.7)
FACIT-Fatigue	149/249 (59.8)*	57/124 (46.0)	199/291 (68.4)***	35/102 (34.3)
Both enthesitis/dactylitis, *n/N* (%)[d]				
Pain	75/103 (72.8)***	70/154 (45.5)	117/142 (82.4)	74/100 (74.0)
HAQ-DI	53/96 (55.2)**	52/147 (35.4)	93/135 (68.9)**	47/95 (49.5)
FACIT-Fatigue	66/104 (63.5)*	78/155 (50.3)	109/144 (75.7)**	59/100 (59.0)

FACIT-Fatigue Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *MCID* minimally clinical important difference, *PBO* placebo, *PRO* patient-reported outcome

Missing data were imputed using nonresponder imputation incorporating multiple imputation to handle missing data resulting from COVID-19 at week 24 and nonresponder imputation (as observed) at week 52

Nominal *p* values were determined using a chi-squared test

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs PBO

[a]MCID cutoffs are ≥ 10-mm decrease on a 100-mm visual analog scale (pain), ≥ 0.35-unit decrease (HAQ-DI), and ≥ 4-point increase (FACIT-Fatigue)

[b]Among patients with enthesitis at baseline, regardless of treatment group

[c]Among patients with dactylitis at baseline, regardless of treatment group

[d]Among patients with both enthesitis/dactylitis at baseline, regardless of treatment group

Lastly, the double-blind period lasted up to week 24; thus, patients were no longer blinded to the treatment after week 24, and the open-label extension period could be biased towards patients who responded to risankizumab. Reassuringly, patients initially randomized to receive placebo and then switched to risankizumab at week 24 experienced a similar trajectory of enthesitis and/or dactylitis improvements compared with those patients treated with continuous risankizumab from weeks 24 to 52.

CONCLUSIONS

Overall, treatment with risankizumab improves or resolves the clinical signs and symptoms of enthesitis and/or dactylitis. Most patients treated with risankizumab also achieved clinically meaningful responses in patient-reported outcomes for up to 52 weeks. These post hoc results, when complemented by primary efficacy data, support the use of risankizumab in improving long-term outcomes across multiple clinical domains of PsA.

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Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. These data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home."

Declarations

Conflict of Interest. Shawn G. Kwatra is an advisory board member/consultant and/or investigator for AbbVie, Arcutis, ASLAN, Celldex, Galderma, Genzada, Incyte, J&J, Novartis, Pfizer, Regeneron, and Sanofi. Saakshi Khattri is a speaker, serves as an advisory board member for, and/or has received research grants from AbbVie, BMS, Janssen, LEO, Lilly, Novartis, Pfizer, and UCB. Ahmad Z. Amin has received speaker or consulting fees from AbbVie, Amgen, BMS, Dermavant, Incyte, Janssen, LEO, Lilly, Regeneron, Sanofi-Genzyme, Pfizer, and UCB. Roberto Ranza is a consultant for AbbVie, Janssen, Novartis, and Pfizer, and is a member of speaker bureaus for AbbVie, Janssen, Novartis, and Pfizer. Blair Kaplan, Linyu Shi, Byron Padilla, and Ahmed M. Soliman are employees of AbbVie, and may hold AbbVie stock, stock options, and/or patents. Dennis McGonagle has received research grants from and/or is a member of speaker bureaus for AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, and UCB.

Ethical Approval. The clinical trials were conducted in accordance with the operations manual, protocol, International Council for Harmonisation guidelines, and applicable guidelines and regulations governing ethical principles and study conduct originating in the Declaration of Helsinki. Independent ethics committees/institutional review boards ensured the ethical, scientific, and medical appropriateness of the

study before it was conducted and approved all relevant documentation including the protocol, informed consent form(s), and all participant materials. Written informed consent was obtained from all patients before enrollment.

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