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CLINICAL SCIENCE

Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial

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ABSTRACT

Objective To evaluate risankizumab, a biological therapy that inhibits interleukin 23, in patients with active psoriatic arthritis (PsA) who have responded inadequately or are intolerant to ≥1 conventional synthetic disease-modifying antirheumatic drug (csDMARD).

Methods In the randomised, placebo-controlled, double-blind KEEPsAKE 1 trial, 964 patients with active PsA were randomised (1:1) to receive risankizumab 150 mg or placebo at weeks 0, 4 and 16. The primary endpoint was the proportion of patients achieving ≥20% improvement in American College of Rheumatology criteria (ACR20) at week 24. Here, we report the results from the 24-week double-blind period; the open-label period with all patients receiving risankizumab is ongoing.

Results At week 24, a significantly greater proportion of patients receiving risankizumab achieved the primary endpoint of ACR20 (57.3% vs placebo, 33.5%; p<0.001). Significant differences were also observed for risankizumab versus placebo for the first eight ranked secondary endpoints, including skin and nail psoriasis endpoints, minimal disease activity and resolution of enthesitis and dactylitis (p<0.001). Adverse events and serious adverse events were reported at similar rates in the risankizumab and placebo groups. Serious infections were reported for 1.0% and 1.2% of patients receiving risankizumab and placebo, respectively. There was one death in the risankizumab group (urosepsis deemed unrelated to the study drug).

Conclusions Risankizumab treatment results in significantly greater improvement of signs and symptoms of PsA compared with placebo and is well tolerated in patients with active PsA who have responded inadequately or are intolerant to ≥1 csDMARD.

Trial registration number NCT03675308.

Key messages

What is already known about this subject?

- Despite the range of available therapies for psoriatic arthritis, efficacious, well-tolerated therapeutic options are needed to treat the diverse disease manifestations in patients who have not responded adequately to standard treatment.

What does this study add?

- Risankizumab 150 mg at weeks 0, 4 and 16 significantly improved the signs and symptoms of psoriatic arthritis, including joint symptoms, enthesitis and dactylitis, and skin and nail manifestations of psoriasis, in patients with inadequate response or intolerance to ≥1 conventional synthetic disease-modifying antirheumatic drug.
- Risankizumab was well tolerated, with a safety profile similar to that observed in patients with psoriasis, and no new safety signals were identified.

How might this impact on clinical practice or future developments?

- The results from the phase 3 KEEPsAKE 1 trial demonstrate the efficacy of risankizumab to treat the diverse clinical manifestations of psoriatic arthritis.
- Risankizumab may provide an additional therapeutic option for patients in whom standard therapies are inadequate.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, inflammatory disease characterised by co-occurring musculoskeletal inflammation and psoriasis. The diverse clinical manifestations of PsA include arthritis, enthesitis, dactylitis, axial involvement, and skin and/or nail psoriasis. The impact of PsA on patients' function; pain; fatigue; emotional well-being and ability to participate in work, social and leisure activities reduces patients' quality of life[1] and contributes to the individual and societal burden of the disease.[2]

Treating all facets of PsA is important for meaningfully improving patients' quality of life. First-line PsA treatment includes non-steroidal anti-inflammatory drugs, local corticosteroid injections for musculoskeletal symptoms and topical therapies for psoriasis. For patients with poor prognostic factors or who do not respond adequately to first-line treatments, systemic therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), antitumour necrosis factor therapy and other biological therapies are recommended.[3] Despite the range of available PsA therapies,

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efficacious, well-tolerated therapeutic options are needed for patients who have experienced inadequate responses or intolerances to available therapies.

Risankizumab is a humanised IgG1 monoclonal antibody that specifically inhibits interleukin 23 (IL-23) by binding to its p19 subunit. Risankizumab is approved in multiple countries to treat moderate-to-severe plaque psoriasis.[4] The KEEPsAKE 1 trial is evaluating the efficacy and safety of risankizumab to treat active PsA in patients who had responded inadequately or were intolerant to ≥1 csDMARD. The companion KEEPsAKE 2 trial (NCT03671148) is evaluating similar endpoints in a patient population that includes patients with a history of inadequate response or intolerance to biological agents.[5] The results of the initial 24-week double-blind period of the ongoing KEEPsAKE 1 study are reported herein.

METHODS

Study design and treatment

This phase 3, global, multicentre study included a screening period; a 24-week double-blind, placebo-controlled, parallel-group period; and a 204-week open-label period. Patients were randomised (1:1, stratified by baseline psoriasis (≥3%/<3% body surface area), presence of dactylitis (yes/no), presence of enthesitis (yes/no) and current csDMARD use (0/≥1)) by interactive response technology to receive subcutaneously administered risankizumab 150 mg or matching placebo in a blinded fashion at weeks 0, 4 and 16 during the double-blind period. Study visits occurred at weeks 0, 4, 8, 12, 16 and 24. Patients who had not achieved ≥20% improvement in swollen and/or tender joint count at both weeks 12 and 16 could add or modify concomitant therapies. Except for the baseline and primary endpoint visits, study visits could be modified to accommodate COVID-19-related restrictions; these included out-of-window study visits, phone calls and/or at-home visits for patients unable to attend onsite visits. The study drug was not administered to patients with suspected or confirmed COVID-19 infection; study drug administration and study visits could be resumed after patients recovered from infection.

This study was conducted in accord with the protocol, operations manual, International Council for Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol, informed consent document and all study materials were reviewed and approved by the independent ethics committee or institutional review board. All patients provided written informed consent to participate in the study.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patients

Eligible patients were adults (aged ≥18 years) with active PsA (symptom onset ≥6 months, meeting the Classification Criteria for Psoriatic Arthritis, ≥5 of 68 tender and ≥5 of 66 swollen joints, ≥1 erosion based on centrally read radiograph (hands and/or feet) or high-sensitivity C reactive protein (hsCRP) ≥3.0 mg/L and active plaque psoriasis (≥1 psoriatic plaque(s) of ≥2 cm in diameter or nail psoriasis)). All patients had experienced an inadequate response, intolerance or contraindication to ≥1 csDMARD (csDMARD-IR). Continuation of concomitant therapy with ≤2 csDMARDs at protocol-approved doses was allowed. No prior exposure to biologics was permitted; however, prior exposure to targeted synthetic disease-modifying antirheumatic drug was allowed.

Assessments

Efficacy assessments

The primary endpoint was the proportion of patients who achieved ≥20% improvement in American College of Rheumatology criteria (ACR20) at week 24. Multiplicity-controlled ranked secondary endpoints included (1) change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI); (2) proportion of patients who achieved ≥90% reduction in Psoriasis Area and Severity Index 90 (PASI 90); (3) proportion of patients who achieved ACR20 at week 16; (4) proportion of patients who achieved minimal disease activity (MDA); (5) change from baseline in modified Nail Psoriasis Severity Index (mNAPSI), a composite score incorporating grading (0–3) of pitting, onycholysis and oil-drop dyschromia and crumbling and absence/presence (0/1) of leukonychia, splinter haemorrhages, hyperkeratosis and red spots in the lunula[6]; (6) change from baseline in Physician's Global Assessment of Fingernail Psoriasis Score (PGA-F), based on the worse of nail bed or nail matrix signs of disease severity (0 (clear) to 4 (severe)[7 8]), (7) proportion of patients who achieved resolution of enthesitis (Leeds Enthesitis Index=0; prespecified analysis of pooled data from KEEPsAKE 1 and KEEPsAKE 2); (8) proportion of patients who achieved resolution of dactylitis (Leeds Dactylitis Index=0; prespecified analysis of pooled data KEEPsAKE 1 and KEEPsAKE 2); (9) change from baseline in PsA-modified Total Sharp Score (PsA-mTSS)[9]; (10) change from baseline in 36-Item Short-Form Health Survey Physical Component Summary (SF-36 PCS) score; and (11) change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire (FACIT-Fatigue) score. Except for ACR20 at week 16, all ranked secondary endpoints were evaluated at week 24. Non-ranked secondary endpoints included the proportions of patients who achieved ≥50% and ≥70% improvement in ACR criteria (ACR50/70) at week 24. Post hoc analyses included the proportions of patients who achieved Disease Activity in Psoriatic Arthritis (DAPSA) remission (REM; DAPSA score ≤4), low disease activity (LDA) +REM (DAPSA score ≤14), ≥50% and ≥85% reduction in DAPSA.

Safety assessments

Safety was evaluated throughout the study and included adverse event (AE) monitoring, physical examinations, vital sign measurements and clinical laboratory testing for haematology and chemistry. An independent data monitoring committee periodically reviewed unblinded safety data until the week 24 interim analysis.

Statistical analysis

A sample size of 440 patients per treatment group was estimated to provide ≥90% power to detect a ≥25% difference in ACR20 response rates, assuming a placebo response rate of 35%. This sample size was estimated to provide approximately 80% power to detect a standardised effect size of 0.20 in change from baseline in PsA-mTSS.

Efficacy analyses were conducted on the full analysis set, which included all randomised patients who received one or more doses of the study drug. For categorical efficacy endpoints, missing data unrelated to COVID-19 were handled by non-responder imputation, and missing data due to COVID-19 (infection or

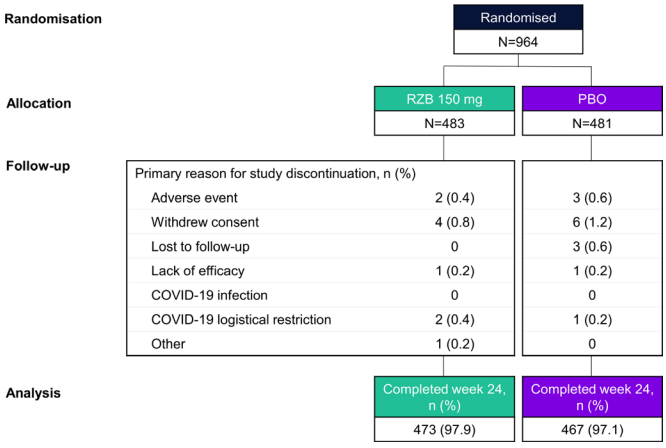

Figure 1 Patient disposition. PBO, placebo; RZB, risankizumab.

logistical restrictions) were handled by multiple imputation. Observations after patients initiated rescue therapy or concomitant medications for PsA that could have meaningfully impacted efficacy assessments were imputed as non-responders (categorical endpoints) or considered as missing and excluded from the model (continuous endpoints). Categorical efficacy endpoints were compared using the Cochran-Mantel-Haenszel test with adjustment for stratification factors. Continuous efficacy endpoints were analysed using mixed-effect model for repeated measures incorporating factors of treatment, visit, stratification factors and baseline values. Radiographic endpoints were analysed using an analysis of covariance model incorporating linear extrapolation to impute missing data or data after discontinuation of study drug or initiation of rescue medication. To increase sample size due to the smaller number of patients with enthesitis and dactylitis at baseline, data for the resolution of enthesitis and dactylitis were pooled from KEEPsAKE 1 and KEEPsAKE 2 (prespecified); these analyses were adjusted for common stratification factors and study. All primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment via a fixed sequence testing procedure to control the family-wise type I error rate at $\alpha=0.05$ (two-sided). Safety analyses were conducted on the safety analysis set, which included all patients who received one or more doses of study drug.

RESULTS

Patients

A total of 964 patients were enrolled at 186 sites in 38 countries, and 97.5% completed the double-blind period between 25 March 2019 and 8 October 2020 (figure 1). No patients withdrew due to COVID-19 infection, and three patients (<0.3%) withdrew due to COVID-19 logistical restrictions. Less than 3% of patients in either group had missing data due to COVID-19 or the primary and all secondary endpoints (online supplemental table S1).

Demographical and baseline characteristics were generally balanced between groups (table 1). Patients were considered csDMARD-IR based on inadequate response (85.2%), intolerance (14.4%) or contraindication (0.4%) to prior therapy with ≥1 csDMARD. csDMARDs used previously by >10% of patients included methotrexate (89.9%), sulfasalazine (21.5%) and leflunomide (12.8%). The proportion of patients using concomitant csDMARDs was similar between the risankizumab and placebo groups (76.0% vs 76.7%); of concomitant csDMARDs, only methotrexate was reported for >10% of patients (61.6%).

Table 1 Demographics and characteristics at baseline

Characteristic	RZB 150 mg N=483	Placebo N=481
Women, n (%)	231 (47.8)	247 (51.4)
Age (years), median (range)	52 (20–85)	52 (22–79)
Race, n (%)		
White	454 (94.0)	451 (93.8)
Black/African American	4 (0.8)	2 (0.4)
Asian	13 (2.7)	22 (4.6)
Native Hawaiian/Pacific Islander	3 (0.6)	1 (0.2)
American Indian/Alaskan Native	1 (0.2)	0
Multiple	8 (1.7)	5 (1.0)
Not Hispanic/Latino, n (%)	390 (80.7)	389 (80.9)
BMI, kg/m^2, mean (SD)	30.7 (6.4)	30.3 (6.2)
PsA duration, years, mean (SD)	7.1 (7.0)	7.1 (7.7)
Swollen joint count,* mean (SD)	12.1 (7.8)	12.2 (8.0)
Tender joint count,† mean (SD)	20.8 (14.1)	20.5 (12.8)
Patient's assessment of pain,‡ mean (SD)	57.1 (22.6)	57.1 (22.6)
PtGA of disease activity,‡ mean (SD)	57.9 (21.8)	57.4 (22.1)
PGA of disease activity,‡ mean (SD)	61.3 (17.6)	62.4 (17.0)
HAQ-DI, mean (SD)	1.15 (0.66)	1.17 (0.65)
hsCRP, mg/L, mean (SD)	11.9 (15.9)	11.3 (14.1)
PsA-mTSS, mean (SD)	13.0 (29.9)	13.5 (29.0)
Presence of psoriasis affecting ≥3% BSA, n (%)	273 (56.5)	272 (56.5)
BSA,§ %, mean (SD)	16.8 (19.7)	16.5 (20.8)
PASI,§ mean (SD)	10.9 (10.1)	10.0 (10.4)
Presence of nail psoriasis, n (%)	309 (64.0)	338 (70.6)
mNAPSI,¶ mean (SD)	18.1 (16.4)	16.6 (16.0)
PGA-F,¶ mean (SD)	2.1 (1.0)	2.0 (1.0)
MDA, n (%)	2 (0.4)	6 (1.2)
Presence of enthesitis,** n (%)	297 (61.5)	290 (60.3)
LEI,†† mean (SD)	2.7 (1.5)	2.6 (1.5)
Presence of dactylitis,‡‡ n (%)	148 (30.6)	147 (30.6)
LDI,§§ mean (SD)	98.6 (120.4)	92.5 (125.5)
SF-36 PCS, mean (SD)	35.2 (8.1)	35.2 (7.7)
FACIT-Fatigue, mean (SD)	29.4 (11.3)	29.3 (11.2)
Prior csDMARDs,¶¶ n (%)		
0	2 (0.4)	2 (0.4)
1	338 (70.0)	311 (64.7)
2	105 (21.7)	136 (28.3)
≥3	38 (7.9)	32 (6.7)
Concomitant medication use, n (%)		
MTX***	314 (65.0)	315 (65.5)
csDMARD other than MTX†††	52 (10.8)	49 (10.2)
MTX and another csDMARD	20 (4.1)	29 (6.0)
Oral corticosteroids	101 (20.9)	87 (18.1)
NSAID	296 (61.3)	314 (65.3)

*Based on 66 joints.
†Based on 68 joints.
‡Scored as millimetres on a 100 mm horizontal Visual Analogue Scale.
§Among patients with ≥3% BSA affected by psoriasis (RZB, n=273; PBO, n=271).
¶Among patients with nail psoriasis (RZB, n=309; PBO, n=338).
**LEI >0.
††Among patients with LEI >0.
‡‡LDI >0.
§§Among patients with LDI >0.
¶¶Includes 32 patients who reported prior treatment with apremilast (RZB, n=11 (2.3%); PBO, n=21 (4.4%)) and five patients who reported prior treatment with tofacitinib (RZB, n=2 (0.4%); PBO, n=3 (0.6%)).
***As monotherapy or in combination with another csDMARD.
†††Sulfasalazine, leflunomide or apremilast without MTX.
BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C reactive protein; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity for PsA; mNAPSI, modified Nail Psoriasis Severity Index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PBO, placebo; PGA, physician global assessment; PGA-F, Physician's Global Assessment of Fingernail Psoriasis; PsA, psoriatic arthritis; PsA-mTSS, PsA-modified Total Sharp Score; PtGA, patient's global assessment; RZB, risankizumab; SF-36 PCS, 36-Item Short-Form Health Survey Physical Component Summary.

Table 2 Primary and secondary efficacy endpoints

Parameter	RZB 150 mg N=483	Placebo N=481	Difference (95% CI)	P value
Primary endpoint				
ACR20 at week 24, n (%)	277 (57.3)	161 (33.5)	24.0 (18.0 to 30.0)	<0.001*
Ranked secondary endpoints				
Change in HAQ-DI at week 24, mean (95% CI)	−0.31 (−0.36,−0.27)	−0.11 (−0.16,−0.06)	−0.20 (−0.26 to 0.14)	<0.001*
PASI 90 at week 24,† n (%)	143 (52.3)	27 (9.9)	42.5 (35.6 to 49.3)	<0.001*
ACR20 at week 16, n (%)	272 (56.3)	161 (33.4)	23.1 (16.8 to 29.4)	<0.001*
MDA at week 24, n (%)	121 (25.0)	49 (10.2)	14.8 (10.2 to 19.4)	<0.001*
Change in mNAPSI at week 24,‡ mean (95% CI)	−9.8 (−11.0, −8.6)	−5.6 (−6.7, −4.4)	−4.2 (−5.7 to −2.7)	<0.001*
Change in PGA-F at week 24,‡ mean (95% CI)	−0.8 (−1.0, −0.7)	−0.4 (−0.5, −0.3)	−0.4 (−0.6 to −0.3)	<0.001*
Resolution of enthesitis at week 24,§ n (%)	215 (48.4)	156 (34.8)	13.9 (7.6 to 20.2)	<0.001*
Resolution of dactylitis at week 24,¶ n (%)	128 (68.1)	104 (51.0)	16.9 (7.5 to 26.4)	<0.001*
Change in PsA-mTSS at week 24, mean (95% CI)	0.23 (0.02, 0.44)	0.32 (0.11, 0.53)	−0.09 (−0.4 to 0.2)	0.50
Change in SF-36 PCS at week 24, mean (95% CI)	6.5 (5.8, 7.2)	3.2 (2.5, 3.9)	3.3 (2.4 to 4.2)	<0.001
Change in FACIT-Fatigue, at week 24, mean (95% CI)	6.5 (5.6, 7.3)	3.9 (3.1, 4.7)	2.6 (1.5 to 3.7)	<0.001
Non-ranked secondary endpoints				
ACR50 at week 24, n (%)	162 (33.4)	54 (11.3)	22.2 (17.3 to 27.2)	<0.001
ACR70 at week 24, n (%)	74 (15.3)	23 (4.7)	10.5 (6.9 to 14.2)	<0.001

All changes are from baseline. Results for binary endpoints are based on non-responder imputation incorporating multiple imputation if there were missing data due to COVID-19 or non-responder imputation if there were no missing data due to COVID-19. Results for continuous endpoints are based on mixed models for repeated measures, except for PsA-mTSS, which was based on the analysis of covariance model.
*Statistically significant under overall type I error control.
†Among patients with ≥3% body surface area affected by psoriasis at baseline (RZB, n=273; PBO, n=272).
‡Among patients with nail psoriasis at baseline (RZB, n=309; PBO, n=338).
§Defined as LEI=0 among patients with LEI >0 at baseline. Prespecified analysis of pooled data from the KEEPsAKE 1 and KEEPsAKE 2 trials (RZB, n=444; PBO, n=448).
¶Defined as LDI=0 among patients with LDI>0 at baseline. Prespecified analysis of pooled data from the KEEPsAKE 1 and KEEPsAKE 2 trials (RZB, n=188; PBO, n=204).
ACR 20/50/70, ≥20/50/70% improvement in American College of Rheumatology score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; mNAPSI, modified Nail Psoriasis Severity Index; PASI 90, ≥90% reduction in Psoriasis Area and Severity Index; PBO, placebo; PGA-F, Physician's Global Assessment of Fingernail Psoriasis; PsA-mTSS, psoriatic arthritis-modified Total Sharp Score; RZB, risankizumab; SF-36 PCS, 36-Item Short-Form Health Survey Physical Component Summary.

Efficacy assessments

A significantly greater proportion of patients treated with risankizumab versus placebo achieved the primary endpoint of ACR20 at week 24 (57.3% vs 33.5%; p<0.001; table 2) and the secondary endpoint of ACR20 at week 16 (56.3% vs 33.4%; p<0.001; table 2). ACR component results at week 24 are shown in online supplemental table S2. Higher ACR20 response rates were observed at week 24 in patients treated with risankizumab versus placebo in all prespecified subgroups defined by demographics (eg, age, sex, race, body mass index), baseline disease characteristics (eg, duration of PsA, presence of enthesitis, presence of dactylitis) and use of prior or concomitant therapy as analysed using the Cochran-Mantel-Haenszel test. Specifically, higher ACR20 response rates were observed in patients treated with risankizumab versus placebo, regardless of whether patients received concomitant csDMARDs (57.9% vs 35.9%) or risankizumab as monotherapy (55.5% vs 26.2%; online supplemental table S3).

Rapid improvements in PsA signs and symptoms were observed in patients treated with risankizumab. After a single dose, a greater proportion of patients in the risankizumab group achieved ACR20 at week 4 than did patients in the placebo group; this result persisted through week 24 (figure 2A). Similar outcomes were observed for ACR50 and ACR70, as greater proportions of patients treated with risankizumab versus placebo achieved these endpoints at week 24 (nominal p value <0.001 for both; table 2); greater improvement was observed for patients receiving risankizumab compared with placebo by week 4 for ACR50 (figure 2B) and week 8 for ACR70 (figure 2C).

Among patients with enthesitis and/or dactylitis at baseline in the KEEPsAKE 1 and KEEPsAKE 2 studies (prespecified pooled analyses), greater proportions of patients treated with risankizumab versus placebo achieved resolution of their enthesitis or dactylitis (p<0.001 for both). Unpooled results from KEEPsAKE 1 for these endpoints were consistent with the pooled results, demonstrating greater improvement with risankizumab versus placebo (resolution of enthesitis, 51.2% vs 37.2%; nominal p<0.001; resolution of dactylitis, 66.9% vs 54.4%; nominal p=0.034). Changes from baseline in PsA-mTSS were not different between patients treated with risankizumab versus placebo (table 2). The proportion of patients demonstrating no radiographic progression (change from baseline of PsA-mTSS <0 or PsA-mTSS <0.5) is provided in online supplemental table S4.

Among patients with ≥3% body surface area affected by psoriasis at baseline, a significantly greater proportion of patients treated with risankizumab versus placebo achieved PASI 90 (52.3% vs 9.9%; p<0.001; table 2); differences were observed starting at week 8 and persisted through week 24 (figure 3). Significantly greater improvements in nail outcomes (mNAPSI and PGA-F) were observed for patients treated with risankizumab versus placebo among patients with psoriatic nail disease at baseline (p<0.001 for both; table 2).

Patients treated with risankizumab demonstrated improved physical function as evidenced by a significantly greater decrease from baseline in HAQ-DI (p<0.001; table 2). In a prespecified analysis of patients with HAQ-DI ≥0.35 at baseline, a greater percentage of patients achieved the minimal clinically important difference in HAQ-DI (improvement ≥0.35 from baseline)[10] at week 24 in the risankizumab group (50.3%) compared with the placebo group (27.9%; nominal p≤0.001). In addition, greater improvements from baseline were observed for both SF-36 PCS and FACIT-Fatigue

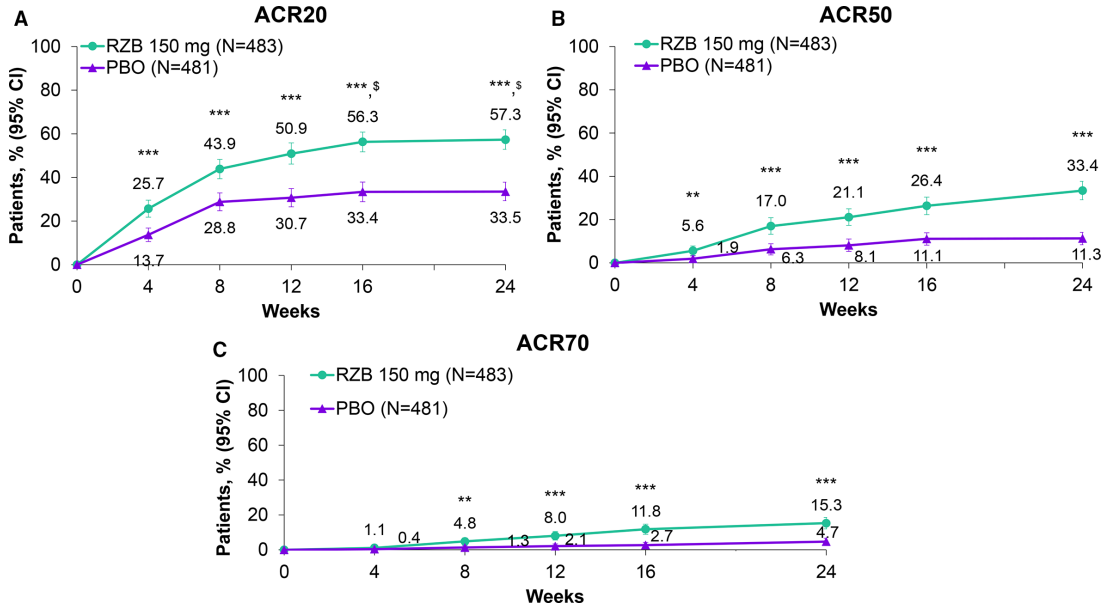

Figure 2 ACR responses over time. (A) ACR20, (B) ACR50 and (C) ACR70 response rates for risankizumab 150 mg and placebo over the 24-week, double-blind treatment period. ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology score; PBO, placebo; RZB, risankizumab. ***P≤0.001 versus PBO. $Statistically significant under overall type I error control. **P≤0.01.

in the risankizumab group compared with the placebo group (nominal p<0.001 for both).

Significantly greater proportions of patients treated with risankizumab versus placebo achieved MDA, a comprehensive measure of disease activity, at week 24 (25.0% vs 10.2%; p<0.001; table 2). Post hoc analyses of DAPSA outcomes (REM and LDA+REM, ≥50% and ≥85% score reductions) are reported in online supplemental table S5.

Safety

Treatment-emergent adverse events (TEAEs) were reported at similar frequencies in the risankizumab and placebo groups (40.4% and 38.7%, respectively; table 3). Most TEAEs were mild or moderate. Serious AE rates were comparable between groups. One death was reported for an 81-year-old male patient with dementia in the risankizumab group; the patient was hospitalised for pneumonia (week 8), subsequently developed urosepsis and died during week 13. One patient in the risankizumab group and two in the placebo group experienced COVID-19-related TEAEs. TEAEs leading to study drug discontinuation were rare (0.8% of patients in either group). TEAEs reported for ≥2% of patients in either group included nasopharyngitis, upper respiratory infection, increased alanine transaminase, increased aspartate transaminase and headache; all were reported at similar frequencies for patients in both groups (table 4).

Rates of AEs of safety interest were low and generally comparable between groups (table 3). However, injection site reactions were more frequently reported for patients in the risankizumab group; none of the reactions were serious, and no anaphylactic reactions were reported. Serious infections were reported for five patients in the risankizumab group and six patients in the placebo group.

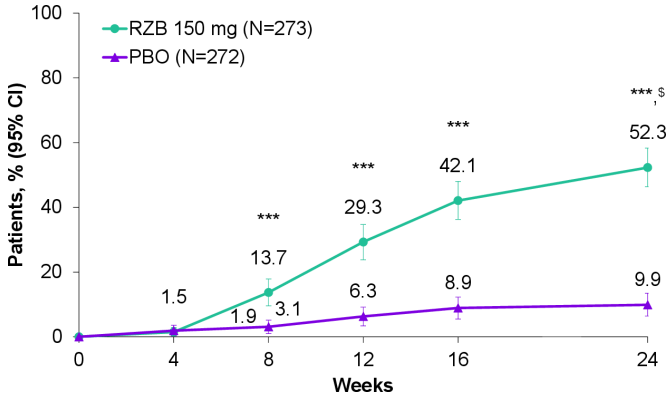

Figure 3 PASI 90 response over time. Among patients with ≥3% body surface area affected by psoriasis at baseline. PASI 90, ≥90% reduction in Psoriasis Area and Severity Index; PBO, placebo; RZB, risankizumab. ***P≤0.001 versus PBO. $Statistically significant under overall type I error control.

Table 3 Safety summary

Patients, n (%)	RZB 150 mg N=483	Placebo N=481
TEAE	195 (40.4)	186 (38.7)
COVID-19-related TEAE	1 (0.2)	2 (0.4)
Serious AE*	12 (2.5)	18 (3.7)
Severe TEAE*	10 (2.1)	9 (1.9)
TEAE leading to discontinuation of study drug	4 (0.8)	4 (0.8)
Death	1 (0.2)†	0
Serious infections‡	5 (1.0)	6 (1.2)
Active tuberculosis	0	0
Herpes zoster§	2 (0.4)	1 (0.2)
Any other opportunistic infections	0	0
Malignancy	0	2 (0.4)
Anaphylactic reactions	0	0
Injection site reactions¶	3 (0.6)	0
MACE	0	0

*Except for pneumonia, which was reported for two patients (0.4%) in the placebo group, no serious AE or severe TEAE was reported for >1 patient in either group.
†One death (urosepsis) in an 81-year-old male patient.
‡RZB: urosepsis (one patient, resulting in death), cellulitis (one patient), gastroenteritis (one patient), COVID-19 pneumonia (one patient) and viral upper respiratory tract infection leading to pneumonia (one patient); placebo: pneumonia (two patients), oral bacterial infection (one patient), dysentery (one patient), appendicitis (one patient) and cellulitis (one patient).
§All non-serious, resolved with oral antiviral agents and did not result in discontinuation of the study drug.
¶All non-serious and did not result in discontinuation of the study drug.
AE, adverse event; MACE, major adverse cardiovascular event; RZB, risankizumab; TEAE, treatment-emergent AE.

Table 4 Frequently reported TEAEs

Patients, n (%)	RZB 150 mg N=483	Placebo N=481
TEAEs reported for ≥2% of patients in either group		
Nasopharyngitis	16 (3.3)	14 (2.9)
Upper respiratory tract infection	12 (2.5)	20 (4.2)
Increased ALT	13 (2.7)	10 (2.1)
Increased AST	10 (2.1)	7 (1.5)
Headache	10 (2.1)	8 (1.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; RZB, risankizumab; TEAE, treatment-emergent adverse events.

Herpes zoster was reported for two patients receiving risankizumab and one patient receiving placebo; all were non-serious, resolved with oral antiviral treatment and did not result in treatment discontinuation. No active tuberculosis or other opportunistic infections were reported. No malignancies were reported for patients receiving risankizumab; one event each of breast cancer and non-small-cell lung cancer was observed in the placebo group.

Mean changes in haematology and clinical chemistry (except liver function tests) were small, not clinically meaningful and comparable between the risankizumab and placebo groups. Grade 3 transaminase elevations (based on Common Terminology Criteria for Adverse Events version 4.03) were reported for <2% of patients in either group (nine patients receiving risankizumab and four patients receiving placebo). Grade 3 transaminase elevations in the nine patients receiving risankizumab were transient and were not accompanied by elevations in bilirubin. Grade 3 transaminase elevations in eight of the nine patients either (1) coincided with initiation of isoniazid or fenofibrate or (2) occurred in patients with underlying medical conditions of hepatic steatosis or hepatic cytolysis syndrome. The remaining patient had grade 1 and grade 2 transaminase levels at screening and baseline and experienced a single grade 3 elevation on study day 57. Subsequent transaminase levels for this patient were at or below baseline levels while the patient continued to receive risankizumab.

DISCUSSION

Currently available csDMARDs demonstrate variable efficacy in treating the diverse clinical manifestations of PsA, and additional therapeutic agents are needed to address the range of rheumatological and dermatological signs and symptoms of disease. At week 24 of the phase 3 KEEPsAKE 1 study, risankizumab 150 mg significantly improved clinical manifestations of PsA in patients who had an inadequate response or were intolerant to one or more csDMARDs, as evidenced by the achievement of the primary efficacy endpoint (ACR20) and secondary endpoints evaluating physical function, skin and nail psoriasis and resolution of enthesitis and dactylitis.

Evidence of improved joint symptoms (ACR20/50/70) was observed at early time points and increased over time through week 24. Risankizumab was effective, regardless of concomitant csDMARD therapy, as similar efficacy rates were observed in patients treated with risankizumab as monotherapy or in combination with one or more csDMARDs. Risankizumab treatment also markedly reduced hsCRP levels. Across KEEPsAKE 1 and KEEPsAKE 2, significantly greater proportions of patients treated with risankizumab versus placebo achieved resolution of dactylitis and enthesitis. There was no difference in change from baseline in PsA-mTSS between groups at week 24.

Risankizumab treatment led to the achievement of PASI 90 in over 50% of patients with ≥3% of body surface area affected by psoriasis at baseline. Many patients with PsA have psoriatic nail disease, which is associated with substantial disease burden and negatively impacts quality of life.[11–13] Risankizumab treatment resulted in significant improvements from baseline in nail psoriasis (mNAPSI and PGA-F) among patients with psoriatic nail disease at baseline.

Significantly greater improvements in HAQ-DI and greater improvements in SF-36 PCS and FACIT-Fatigue scores demonstrate the benefits of risankizumab treatment on physical function. Together, these findings support the potential for risankizumab treatment to reduce the substantial patient burden of PsA.

By week 24, 25% of patients treated with risankizumab versus 10% in the placebo group had achieved MDA, a comprehensive measure of PsA activity and a recommended target for PsA treatment when using a treat-to-target approach,[14] further demonstrating the efficacy of risankizumab to treat the varied manifestations of PsA.

Risankizumab was generally well tolerated over 24 weeks of treatment. Notably, rates of opportunistic infection (ie, herpes zoster) were low with no reported cases of candidiasis or active tuberculosis. This safety profile is consistent with safety findings in previous studies of risankizumab in patients with psoriasis,[15 16] and no new safety concerns were identified.

Several therapeutics targeting the IL-23/IL-17 pathway are approved to treat PsA.[17] Risankizumab's mechanism of action, specifically targeting the p19 subunit of IL-23, has been previously established,[18 19] and the KEEPsAKE 1 study results further support this mechanism of action for the treatment of PsA. The demonstrated efficacy and consistent safety profile of risankizumab, along with a 3-month dosing interval, further support the value of risankizumab as a treatment option for patients with PsA.

This study is being conducted during the COVID-19 pandemic. COVID-19-related logistical restrictions have been well managed, and completion of the double-blind period was not affected. Few patients had missing data due to COVID-19, and missing data did not impact efficacy conclusions. Further, there were no serious COVID-19-related safety issues. This study is currently limited by the availability of short-term data; the ongoing extension study will evaluate the maintenance of efficacy and long-term safety. The generalisability of these results may be limited by enrichment of the study population by requiring ≥5 tender and ≥5 swollen joints and at least one erosion based on centrally read radiograph or hsCRP ≥3.0 mg/L.

In summary, results from the 24-week double-blind portion of the KEEPsAKE 1 trial demonstrate that risankizumab is well tolerated and effective for treating diverse clinical manifestations of PsA in patients who have had an inadequate response or intolerance to csDMARD therapy. Risankizumab may provide an additional therapeutic option for patients in whom standard therapies are inadequate.

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