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ORIGINAL RESEARCH

Improved patient-reported outcomes in patients with psoriatic arthritis treated with risankizumab: analysis of the Phase 3 trial KEEPsAKE 2

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ABSTRACT

Objectives Determine the impact of 24-week risankizumab (RZB) versus placebo (PBO) on patient-reported outcomes (PROs) in patients with psoriatic arthritis (PsA) and inadequate response to one or two biologics (Bio-IR) and/or ≥1 conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR).

Methods Patients in the Phase 3 trial, KEEPsAKE 2, were randomised (1:1) to RZB 150 mg or PBO by subcutaneous injection. PROs assessed: 36-Item Short-Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-Fatigue), Patient's Assessment of Pain by visual analogue scale (VAS), Patient's global assessment of disease activity (PtGA), EuroQoL-5 Dimension-5 Level (EQ-5D-5L) and Work Productivity and Activity Impairment—PsA (WPAI-PsA). Least squares mean change from baseline at week 24 was compared between RZB versus PBO by mixed-effects repeated regression modelling.

Results At week 24, RZB versus PBO treatment resulted in significant differences (95% CIs) in mean change from baseline in ranked secondary endpoints SF-36 physical component summary score (3.9 (2.4 to 5.3); p<0.001) and FACIT-Fatigue (2.2 (0.6 to 3.9); p=0.009) and improvements in pain (–8.1 (–12.8 to –3.5)), PtGA (–8.8 (–13.5 to –4.2)) and EQ-5D-5L index (0.08 (0.04 to 0.11)) and VAS (5.9 (1.9 to 9.8)) (all nominal p<0.01). More RZB-treated versus PBO-treated patients reported improvements from baseline at week 24 in 7 of 8 SF-36 subdomains (nominal p<0.05). At week 24, more RZB-treated versus PBO-treated patients reported improvements in 3 of 4 WPAI-PsA domains (nominal p≤0.01).

Conclusion Overall, RBZ treatment resulted in improvements in pain, fatigue, health-related quality of life and ability to perform work in Bio-IR and/or csDMARD-IR patients with PsA.

Trial registration number NCT03671148.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psoriatic arthritis (PsA) is a chronic inflammatory disease that frequently leads to impaired physical functioning, resulting in reduced health-related quality of life.

WHAT THIS STUDY ADDS

⇒ This analysis determined the impact of treatment with risankizumab versus placebo on key patient-reported outcomes in patients with PsA.
⇒ Risankizumab-treated versus placebo-treated patients reported greater improvements in pain, fatigue and health-related quality of life.
⇒ Risankizumab-treated versus placebo-treated patients also reported greater improvements in the ability to perform work.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ These results complement the achievement of primary clinical endpoints observed with treatment, with improvements perceived by patients that should be considered in treatment decision-making.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogenous, chronic inflammatory disease that is frequently characterised by different disease domains, including psoriasis, axial and peripheral arthritis, enthesitis and dactylitis. Approximately 30% of patients with psoriasis will develop PsA.[1–3] Over time, PsA leads to significantly impaired physical functioning, resulting in reduced health-related quality of life (HRQoL) in these patients.[1 4] Due to the significant physical limitations of PsA, the ability to perform daily living, work and social activities is often impaired. Indeed, overall disease activity is negatively associated with work presenteeism and productivity, and positively associated with absenteeism. Furthermore, duration of disease negatively impacts patients' ability to remain employed and, as such, 36% of working-age patients with PsA were reported to be unemployed.[1 4 5]

The impact of PsA on physical limitations is also comparable to the impact of PsA on mental health and the prevalence of depression and anxiety is substantial in these patients.[6 7]

The OMERACT PsA Working Group recommends that clinical studies consider the 'life impact' that an emerging therapy may have, outside of the pathophysiological benefits. More specifically, they recommend obtaining patient-reported information regarding pain, physical functioning, perceived disease activity, fatigue and overall QoL.[8 9] Patient-reported outcomes (PROs) are important tools for understanding a therapy's efficacy in the eyes of the patient. This is critical because perceived efficacy may significantly impact patients' willingness to receive treatment.[10 11] Risankizumab (RZB) is an interleukin (IL-23) inhibitor currently under development for the treatment of adults diagnosed with active PsA. Phase 2 and Phase 3 studies in patients with PsA have shown that RZB treatment significantly improves patient pain, physical functioning (determined by Health Assessment Questionnaire-Disability index) and disease severity, as seen by reduced Psoriasis Area and Severity Index and American College of Rheumatology scores.[12–14] This analysis aimed to characterise the impact of 24-week treatment with RZB versus placebo (PBO) on PROs in patients with active PsA who are enrolled in KEEPsAKE 2 to understand treatment benefits of RZB from the patient perspective.

PATIENTS AND METHODS

Study design

KEEPsAKE 2 (NCT03671148) is a Phase 3, randomised, PBO-controlled, double-blind, multicentre study comparing the effects of RZB with PBO after 24 weeks of treatment in patients with active PsA who have an inadequate response or intolerance to one or two biologic disease-modifying antirheumatic drugs (DMARDs) (Bio-IR) and/or to ≥1 conventional synthetic DMARD (csDMARD-IR).[14] Patients were randomised 1:1 to receive RZB 150 mg or PBO by subcutaneous injection at weeks 0, 4 and 16.

Full details on study design and patient attrition were published previously.[14]

Patients

Patients eligible for the study were ≥18 years old with a clinical diagnosis of PsA and with symptom onset at least 6 months prior to study and fulfilment of the Classification Criteria for PsA (CASPAR) at screening. Patients had active disease as defined by ≥5 tender joints (based on 68 joint counts; TJC68) and ≥5 swollen joints (based on 66 joint counts; SJC66), and active plaque psoriasis with at least one psoriatic plaque ≥2 cm in diameter or presence of nail psoriasis at baseline. Patients were permitted to be on ≤2 of the following background csDMARDs: methotrexate (MTX), sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine, iguratimod or ciclosporin A; csDMARD use had to remain stable. To be considered Bio-IR, patients must have demonstrated an inadequate response, defined as a lack of efficacy after ≥12 weeks therapy, or intolerance to one or two bDMARDs intended to treat PsA. To be considered csDMARD-IR, patients had to demonstrate an inadequate response or intolerance to a previous or current treatment with ≥1 of the following csDMARDs: MTX, sulfasalazine, leflunomide, apremilast, bucillamine, iguratimod or ciclosporin A. Patients in the csDMARD-IR only population must not have had any prior exposure to bDMARDs (ie, bDMARD-naïve) used to treat PsA to be eligible for inclusion; patients who were csDMARD-IR and Bio-IR entered the study in the Bio-IR population. Any patient with an active chronic infection, with prior exposure to IL-12 or IL-12/23 inhibitors, and who were pregnant, breastfeeding or planning to become pregnant, were excluded. Concomitant use of Janus kinase (JAK) inhibitors, biologic and biosimilar therapies, opiates (except low-potency opiates: tramadol, codeine or hydrocodone alone or in combination with acetaminophen), live vaccines and non-oral corticosteroids (except low-potency topicals) was not permitted during the study. A maximum oral dose of ≤10 mg/day of prednisone equivalent was permitted.

PRO measures

This study assessed several PROs across several different domains of HRQoL in RZB-treated versus PBO-treated patients with PsA. PROs included the 36-item Short-Form Health Survey (SF-36), the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-Fatigue), the EQ-5D-5 Level (EQ-5D-5L), Patient's Assessment of Pain by visual analogue scale (VAS), Patient's Global Assessment of disease activity (PtGA) and the PsA-specific Work Productivity and Activity Impairment (WPAI-PsA) questionnaire.

The SF-36 is a 36-item survey of patient health consisting of eight domains: physical functioning (PF), bodily pain (BP), role physical (RP), role emotional (RE), mental health (MH), social functioning (SF), vitality (VT) and general health perceptions (GH). There are also two composite scores included in the SF-36: the physical component score (PCS) and mental component score (MCS). All domains and component scores were determined on a 0–100 scale, with higher scores indicating a favourable health state.[15 16] The FACIT-Fatigue is a 13-item questionnaire that evaluates fatigue and its impact on daily living activities and physical functioning. Scores are determined by a 5-point Likert scale, with a total score range of 0–52; higher scores denote more severe fatigue.[17] The EQ-5D-5L is a general HRQoL questionnaire consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients rate these dimensions from 1 to 5 based on severity, and scores are indexed to ≤1 (the value of full health), with higher scores indicating higher health utility.[18] The EQ-5D-5L was also assessed by a horizontal 100 mm VAS ranging from 0 (worst health

patient can imagine) to 100 (best health patient can imagine) in which patients report on their health status for that day. Patient's Assessment of Pain is measured on a VAS ranging from 0 to 100 mm. For the assessment, patients report their pain levels over the last 24 hours, with higher scores indicating more severe pain.[19] PtGA was used to assess the patient's perception of overall funtionality in the context of disease activity using a VAS ranging from 0 to 100 mm, with higher scores denoting more severe impairment.[20 21] The WPAI-PsA measure is

Table 1 Baseline demographics and clinical characteristics

Demographics	Total (n=443)	Risankizumab (150 mg) (n=224)	Placebo (n=219)
Sex, n (%)			
Female	224 (55.1)	124 (55.4)	120 (54.8)
Age (years), mean±SD	52.9±12.6	53.1±12.5	52.7±12.6
White race, n (%)	428 (96.6)	218 (97.3)	210 (95.9)
Duration of PsA (years), mean±SD	8.2±8.3	8.2±8.2	8.2±8.3
Presence of dactylitis (LDI >0), n (%)	97 (22.0)	40 (17.9)	57 (26.3)
Presence of enthesitis (LEI >0), n (%)	305 (68.8)	147 (65.6)	158 (72.1)
PASI (in patients with BSA ≥3%), mean±SD	8.0±8.4	7.7±6.7	8.4±9.9
Tender joint count (68 joints), mean±SD	22.6±14.4	22.8±14.9	22.3±13.8
Swollen joint count (66 joints), mean±SD	13.3±8.9	13.0±8.7	13.6±9.0
Body surface area—psoriasis ≥3, n (%)	242 (54.6)	123 (54.9)	119 (54.3)
Number of prior csDMARDs, n (%)			
0	23 (5.2)	12 (5.4)	11 (5.0)
1	169 (38.1)	88 (39.3)	81 (37.0)
2	120 (27.1)	60 (26.8)	60 (27.4)
>3	131 (29.6)	64 (28.6)	67 (30.6)
Number of prior bDMARDs, n (%)			
0	237 (53.5)	119 (53.1)	118 (53.9)
≥1	206 (46.5)	105 (46.9)	101 (46.1)
Number of prior failed bDMARDs, n (%)			
0	269 (60.7)	137 (61.2)	132 (60.3)
1	136 (30.7)	72 (32.1)	64 (29.2)
≥2	38 (8.6)	15 (6.7)	23 (10.5)
Concomitant csDMARD at baseline, n (%)			
Any csDMARD	270 (60.9)	141 (62.9)	129 (58.9)
Any MTX	209 (47.2)	110 (49.1)	99 (45.2)
MTX alone	191 (43.1)	102 (45.5)	89 (40.6)
MTX and other csDMARD	18 (4.1)	8 (3.6)	10 (4.6)
csDMARD other than MTX	61 (13.8)	31 (13.8)	30 (13.7)
Any sulfasalazine, without MTX	18 (4.1)	9 (4.0)	9 (4.1)
Any leflunomide, without MTX	27 (6.1)	12 (5.4)	15 (6.8)
Any apremilast, without MTX	14 (3.2)	9 (4.0)	5 (2.3)
None	173 (39.1)	83 (37.1)	90 (41.1)
BMI in kg/m^2, n (%)			
BMI <25	76 (17.2)	38 (17.0)	38 (17.4)
BMI ≥25 to <30	136 (30.7)	68 (30.4)	68 (31.1)
BMI ≥30	231 (52.1)	118 (52.7)	113 (51.6)

bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis.

Table 2 Baseline PRO Scores

PRO	Risankizumab (150 mg)	Placebo
SF-36, mean±SD	n=224	n=219
Physical functioning	36.0±9.4	35.8±9.8
Role physical	37.3±9.2	37.0±9.1
Bodily pain	36.9±7.4	36.3±7.9
General health	40.0±9.7	39.4±9.4
Vitality	41.4±10.3	41.4±9.9
Social functioning	40.7±10.4	40.4±10.8
Role emotional	42.4±11.2	41.5±12.3
Mental health	43.6±11.1	44.3±10.9
PCS	35.6±8.8	35.2±9.1
MCS	45.3±11.7	45.3±11.7
FACIT-Fatigue, mean±SD	n=224 28.2±11.5	n=219 27.7±12.7
EQ-5D-5L index, mean±SD	n=224 0.64±0.23	n=219 0.63±0.22
EQ-5D-5L VAS, mean±SD	n=224 56.1±22.2	n=219 54.2±22.4
Pain VAS, mean±SD	n=224 55.0±23.5	n=219 57.0±23.1
PtGA VAS, mean±SD	n=224 56.2±21.8	n=219 56.2±23.0
WPAI (0%–100%), mean±SD		
Overall work impairment*	n=127 47.4±28.9	n=136 50.1±27.6
Activity impairment	n=224 50.5±26.6	n=219 51.6±25.7
Absenteeism*	n=127 12.4±24.1	n=136 11.8±23.5
Presenteeism*	n=123 41.3±26.0	n=131 45.1±24.2

*Reported only for patients who were employed.
EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; MCS, mental component summary; PCS, physical component summary; PRO, patient-reported outcome; PtGA, patient's global assessment of disease activity; SF-36, 36-Item Short-Form Health Survey; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.

a well-validated instrument used to assess impairment in work and daily activities.[22] There are four domains to the WPAI-PsA: overall work impairment, activity impairment, absenteeism and presenteeism. Patients assess the impact of PsA on their abilities to perform work or regular activities over the past 7 days, and scores range from 0% to 100% impairment.

Pain and PtGA were assessed at day 1 and weeks 4, 8, 12, 16 and 24. The SF-36, EQ-5D-5L, FACIT-Fatigue and WPAI were assessed at day 1 and weeks 12 and 24.

Statistical analysis

Demographics and baseline characteristics endpoints were summarised using descriptive statistics. For binary endpoints, numbers and percentages were summarised, while mean and SD were reported for continuous endpoints. Efficacy analyses, including PROs, were assessed in the full analysis set population that was defined as all randomised patients who received ≥1 dose of study drug. For all PRO endpoints investigated in this manuscript, least square mean change from baseline and 95% CIs at week 24 were compared between RZB and PBO treatment groups, using mixed-effects repeated measures regression modelling controlled for stratifying variables of current use of csDMARD (0 vs ≥1), number of prior bDMARDs (0 vs ≥1) and extent of psoriasis (≥3% body surface area (BSA) or <3% BSA) at baseline. The mixed-effects repeated measures model used longitudinal data for up to 24 weeks and excluded data from patients after initiation of rescue therapy or concomitant treatments for PsA that could meaningfully impact the assessment. The SF-36 PCS and FACIT-Fatigue were ranked secondary endpoints and were controlled for multiplicity adjustment to ensure a strong control of family-wise type I error rate at significance level alpha=0.05 (two-sided). Analysis of all other measures was not multiplicity controlled, and the nominal p values are reported. Analyses were repeated by the following subgroups of the full analysis set population: csDMARD-IR only (bDMARD-naïve) patients versus bDMARD-IR, and body mass index (BMI) scores (BMI kg/m^2: <25, ≥25 to <30, ≥30) at baseline.

Ethics

The protocol, informed consent form(s), recruitment material, and all patient materials were approved by an independent ethics committee or institutional review board at all study sites (see online supplemental table S1 for full list). All patients provided written informed consent prior to enrolment. The clinical study was conducted in accordance with the current Declaration of Helsinki and is consistent with the International Conference on Harmonisation Good Clinical Practice and Good Epidemiology Practices, and all applicable local regulatory requirements. All patient data were anonymised and complied with patient confidentiality requirements.

RESULTS

Baseline demographic and clinical characteristics

A total of 444 patients with PsA were randomised to receive RZB (n=224) or PBO (n=220), and baseline characteristics were balanced between groups (table 1). One patient was randomised but did not receive the study drug and thus was excluded from the full analysis set population.[14] As previously reported, 215 (96.0%) and 199 (90.5%) patients who received RZB or PBO, respectively, completed the week 24 study visit.[14]

The average patient age was 52.9±12.6 years, with a mean disease duration of 8.2 years, and 55% of patients

Table 3 Least squares mean change from baseline

PRO	Risankizumab (150 mg) LS mean change (95% CI)	Placebo LS mean change (95% CI)	Difference (95% CI)
FACIT-Fatigue*	n=224 4.9 (3.7 to 6.0)	n=219 2.6 (1.4 to 3.9)	2.2 (0.6 to 3.9)†
EQ-5D-5L index	n=197 0.09 (0.06 to 0.12)	n=165 0.01 (–0.02 to 0.04)	0.08 (0.04 to 0.11)‡
EQ-5D-5L VAS	n=197 7.6 (4.8 to 10.3)	n=165 1.7 (–1.2 to 4.7)	5.9 (1.9 to 9.8)†
Pain VAS	n=197 –14.7 (–17.8 to –11.5)	n=165 –6.5 (–9.9 to –3.1)	–8.1 (–12.8 to –3.5)‡
PtGA VAS	n=197 –16.5 (–19.7 to –13.3)	n=165 –7.7 (–11.1 to –4.2)	–8.8 (–13.5 to –4.2)‡

*Multiplicity-adjusted results for ranked secondary endpoints were significant (p=0.009).
†Nominal p<0.01 for risankizumab versus placebo.
‡Nominal p<0.001 for risankizumab versus placebo.
EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; LS, least squares; PRO, patient-reported outcome; PtGA, patient's global assessment of disease activity; VAS, visual analogue scale.

(n=224) were women. Over 90% (n=420) of patients reported prior csDMARD use, with approximately one-third of patients each reporting prior use of 1, 2 or ≥3 csDMARDs, respectively. Overall, 39% (n=174) of patients were Bio-IR. Overall, 61% (n=270) of patients reported concomitant csDMARD use at baseline. Concomitant MTX use was most common (n=209, 47%) compared with csDMARDs other than MTX (n=61, 14%). Over a third of patients reported no concomitant csDMARD use (n=173, 39%). More than one half (n=231, 52%) of patients had a BMI >30 (table 1).

Least squares mean change from baseline

In general, both groups demonstrated similar scores across all PROs at baseline (table 2).

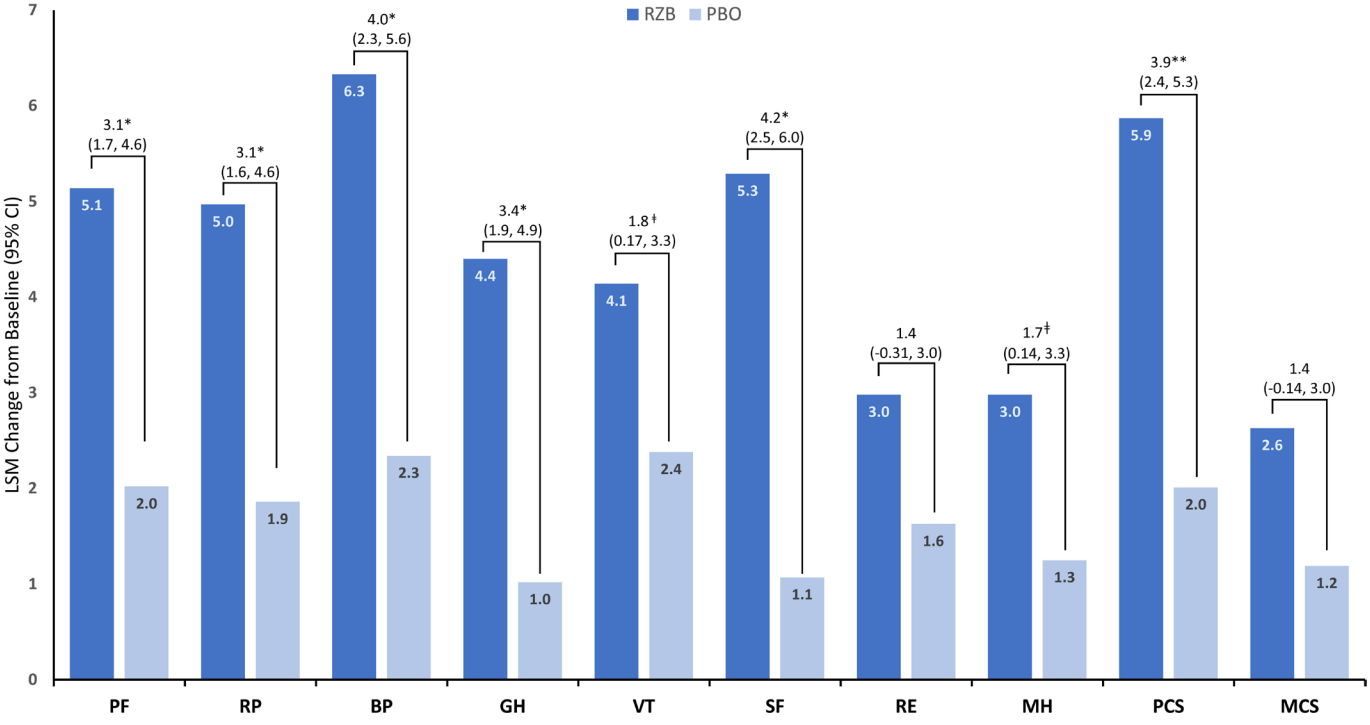

Figure 1 Least squares mean change from baseline in SF-36 Scores at 24 weeks. *Nominal p<0.001. **Multiplicity-adjusted p<0.001 for RZB versus PBO. †Nominal p≤0.01 for RZB versus PBO. ǂNominal p<0.05 for RZB versus PBO. BP, bodily pain; GH, general health; LSM, least squares mean; MCS, mental component summary; MH, mental health; PBO, placebo; PCS, physical component summary; PF, physical health; RE, role emotional; RZB, risankizumab; RP, role physical; SF, social functioning; VT, vitality.

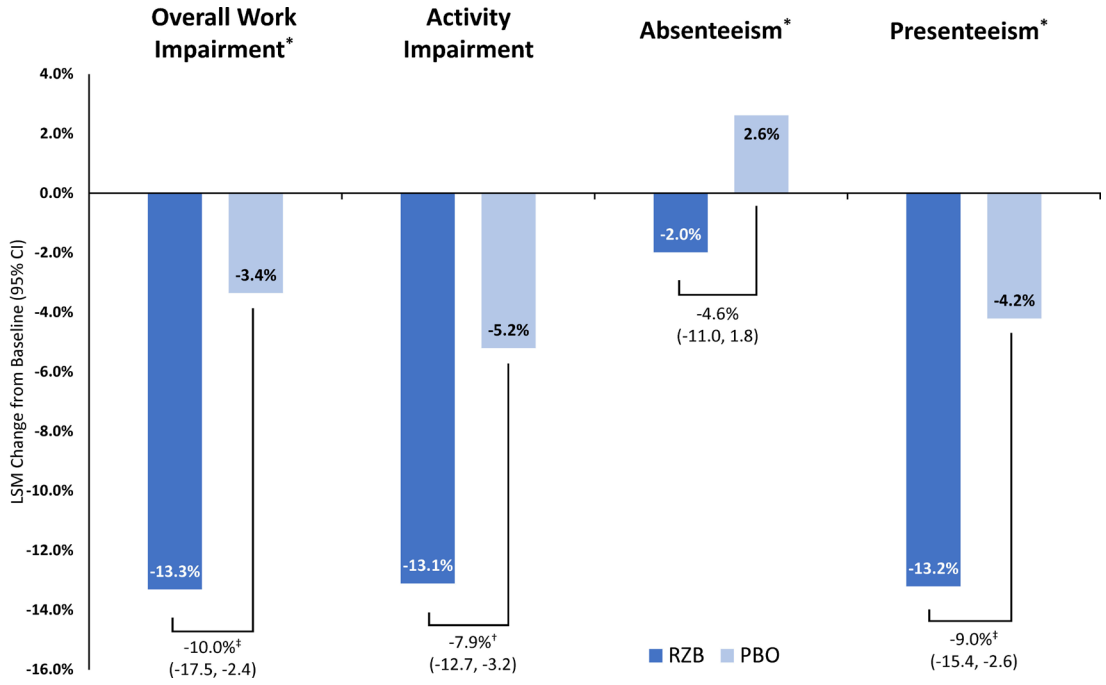

Figure 2 Least squares mean percent change from baseline in WPAI Scores at 24 weeks. *Reported only for patients who were employed. †Nominal p<0.001 for RZB versus PBO. ‡Nominal p≤0.01 for RZB versus PBO. LSM, least squares mean; PBO, placebo; RZB, risankizumab; WPAI, Work Productivity and Activity Impairment.

Fatigue, pain, general health status (EQ-5D-5L) and disease activity state

Patients receiving RZB demonstrated notable improvements, as compared with PBO, in all PROs at week 24 (table 3). Specifically, patients receiving RZB versus PBO reported a greater mean change from baseline in FACIT-Fatigue scores. This resulted in a significant difference (95% CI) between groups (2.2 (0.6 to 3.9), p=0.009). Notable differences between groups were also observed in EQ-5D-5L index and VAS scores. There was a 0.08 difference in EQ-5D-5L index scores between RZB-treated and PBO-treated groups (95% CI: 0.08 (0.04 to 0.11); nominal p<0.001). Similarly, there was a 5.9-point (95% CI: 1.9 to 9.8) difference between RZB and PBO groups in EQ-5D-5L VAS scores (nominal p<0.01). Patients receiving RZB reported greater improvement in pain (VAS) than those receiving PBO, resulting in a notable difference (95% CI) between groups (–8.1 (–12.8 to –3.5), nominal p<0.001). Similarly, greater improvements were also seen in PtGA (VAS) in RZB-treated versus PBO-treated patients, resulting in a –8.8-point difference between groups (95% CI: –13.5 to –4.2; nominal p<0.001).

SF-36 domains and component scores

Figure 1 shows the improvements in SF-36 domains and component scores in RZB-treated versus PBO-treated patients. RZB-treated patients had greater improvements, as determined by the differences between least squares mean changes from baseline, in seven of the eight SF-36 domains (PF, RP, BP, GH, VT, SF and MH; nominal p<0.05) and the multiplicity-adjusted SF-36 PCS score (p<0.001).

Visual depiction, via spydergram, of the differences between RZB-treated versus PBO-treated patients at week 24 in SF-36 domains is presented in online supplemental figure 1. The figure shows that all patients have substantial negative impacts on their HRQoL at baseline due to the nature of the disease and that RZB-treated patients report consistently higher scores at week 24 in comparison to PBO-treated patients.

Work and activity impairment

After 24 weeks of treatment, patients receiving RZB reported greater improvements in three of the four WPAI domain scores than patients receiving PBO (figure 2). There was a –10% difference (95% CI: –17.5% to –2.4%, nominal p≤0.01) in overall work impairment between treatment groups. Similar differences (95% CI) between RZB and PBO groups were also shown for activity impairment (–7.9% (–12.7% to –3.2%), nominal p<0.001) and presenteeism (–9.0% (–15.4% to –2.6%), nominal p<0.01). There was no notable difference in change from baseline in absenteeism between groups (–4.6% (–11.0 to 1.8)).

Mean change from baseline at 24 weeks by subgroup

Both csDMARD-IR (bDMARD-naïve) patients and bDMARD-IR treated with RZB versus PBO saw notable improvements in multiple PROs (table 4); results were similar to those observed in the primary analysis. Differences between RZB-treated and PBO-treated patients at week 24 were numerically higher among bDMARD-IR patients for several PROs, including fatigue, EQ-5D-5L VAS, pain, PtGA, SF-36 PCS, overall work and activity

Table 4 Least squares mean change from baseline among patients who were csDMARD-IR (bDMARD-naïve) or bDMARD-IR at 24 weeks

	csDMARD-IR (bDMARD-naïve)			bDMARD-IR		
PRO, LS mean change (95% CI)	Risankizumab (150 mg)	Placebo	Difference (95% CI)	Risankizumab (150 mg)	Placebo	Difference (95% CI)
SF-36 PCS	n=106 6.09 (4.66 to 7.52)	n=96 3.04 (1.58 to 4.50)	3.05 (1.07 to 5.03)*	n=91 5.58 (4.14 to 7.03)	n=70 0.51 (–1.08 to 2.10)	5.07 (2.93 to 7.21)†
SF-36 MCS	n=106 3.7 (2.2 to 5.3)	n=96 2.2 (0.6 to 3.8)	1.5 (–0.7 to 3.7)	n=91 1.6 (0.03 to 3.2)	n=70 0.1 (–1.6 to 1.9)	1.45 (–0.87 to 3.77)
FACIT-Fatigue	n=106 5.8 (4.2 to 7.4)	n=96 4.1 (2.4 to 5.8)	1.7 (–0.6 to 4.0)	n=91 4.1 (2.4 to 5.8)	n=70 1.0 (–0.8 to 2.9)	3.1 (0.6 to 5.6)*
EQ-5D-5L index	n=106 0.08 (0.04 to 0.11)	n=95 0.04 (0.00 to 0.07)	0.04 (–0.01 to 0.09)	n=91 0.10 (0.07 to 0.14)	n=70 –0.02 (–0.07 to 0.02)	0.13 (0.07 to 0.18)†
EQ-5D-5L VAS	n=106 6.4 (2.6 to 10.1)	n=95 5.9 (2.0 to 9.8)	0.4 (–4.9 to 5.7)	n=91 9.1 (5.1 to 13.1)	n=70 –3.8 (–8.2 to 0.7)	12.9 (6.9 to 18.8)†
Pain VAS	n=106 –16.6 (–21.1 to –12.0)	n=95 –9.6 (–14.3 to –4.9)	–7.0 (–13.4 to –0.6)*	n=91 –13.1 (–17.6 to –8.6)	n=70 –3.1 (–8.1 to 1.9)	–10.0 (–16.7 to –3.2)*
PtGA VAS	n=106 –19.1 (–23.5 to –14.8)	n=95 –12.9 (–17.4 to –8.4)	–6.2 (–12.4 to –0.1)*	n=91 –13.8 (–18.6 to –9.0)	n=70 –1.1 (–6.5 to 4.2)	–12.7 (–19.8 to –5.5)†
WPAI (0% to 100%)						
Overall work impairment‡	n=54 –12.9 (–19.9 to –6.0)	n=48 –6.2 (–13.4 to 1.1)	–6.8 (–16.5 to 3.0)	n=43 –15.4 (–23.8 to –7.1)	n=39 –0.9 (–9.6 to 7.8)	–14.5 (–26.5 to –2.5)*
Activity impairment	n=106 –13.7 (–18.4 to –8.9)	n=95 –7.6 (–12.6 to –2.7)	–6.0 (–12.7 to 0.6)	n=91 –12.6 (–17.2 to –8.1)	n=70 –2.1 (–7.1 to 3.0)	–10.6 (–17.3 to –3.8)*
Absenteeism‡	n=54 –2.2 (–7.4 to 3.0)	n=48 1.2 (–4.4 to 6.7)	–3.4 (–10.8 to 4.1)	n=43 –2.4 (–10.3 to 5.4)	n=39 3.2 (–5.1 to 11.4)	–5.6 (–16.9 to 5.8)
Presenteeism‡	n=52 –12.1 (–18.0 to –6.2)	n=46 –6.7 (–12.9 to –0.5)	–5.4 (–13.7 to 2.9)	n=41 –15.7 (–22.7 to –8.8)	n=36 –1.4 (–8.8 to 5.9)	–14.3 (–24.4 to –4.3)†

*Nominal p<0.05 for risankizumab versus placebo.
†Nominal p<0.001 for risankizumab versus placebo.
‡Reported only for patients who were employed.
bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; IR, inadequate responder; LS, least squares; MCS, mental component summary; PCS, physical component summary; PRO, patient-reported outcome; PtGA, patient's global assessment of disease activity; SF-36, 36-Item Short-Form Health Survey; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.

impairment and presenteeism compared with patients with csDMARD-IR.

Additionally, RZB-treated versus PBO-treated patients had a trend towards greater improvements from baseline at week 24 regardless of BMI score at baseline (table 5).

DISCUSSION

It is recommended to assess the impact of PsA and treatment benefits from the patient's perspective regarding pain, physical functioning, perceived disease activity, fatigue and overall QoL.[8 9] Results from KEEPsAKE 2, a study in patients with PsA who have inadequate response or intolerance to bDMARDs and/or csDMARDs, demonstrated that RZB greatly improved PROs at week 24 as compared with PBO across several HRQoL domains as recognised by the GRAPPA-OMERACT working group to measure the impact of disease on patients with PsA.[23] At baseline, patients had substantially reduced HRQoL as assessed by SF-36 domain scores. Patients who received RZB experienced notable improvements in fatigue and general health status as assessed by both EQ-5D-5L index and VAS scores. Patient-reported pain and overall perception of disease activity were also reduced at week 24 in RZB-treated versus PBO-treated patients. Patients treated with RZB reported notable improvements in seven of the eight SF-36 domains and SF-36 PCS scores. Improvements in WPAI overall work impairment, activity impairment and presenteeism were also reported. A majority of patients were on background csDMARD; however, there was still a major effect on PROs with the addition of RZB in comparison to PBO. Similar results were observed when patients were stratified by prior bDMARD exposure status and BMI scores at baseline. Differences between RZB-treated versus PBO-treated patients were higher among bDMARD-IR versus csDMARD-IR (bDMARD-naïve) patients, suggesting a further benefit of RZB treatment to those patients.

It is important to contextualise the findings of this study against other drug classes indicated for the treatment of PsA. A wide variety of therapies are approved

Table 5 Least squares mean change from baseline at 24 weeks among patients with varying BMI levels at baseline

	BMI <25 kg/m^2		25≤BMI<30 kg/m^2		BMI ≥30 kg/m^2	
PRO, LS mean change (95% CI)	Risankizumab (150 mg)	Placebo	Risankizumab (150 mg)	Placebo	Risankizumab (150 mg)	Placebo
SF-36 PCS	n=33 5.41 (2.96 to 7.87)	n=30 –0.44 (–2.98 to 2.11)	n=63 5.58 (3.88 to 7.29)	n=54 2.55 (0.73 to 4.38)	n=101 6.18 (4.69 to 7.67)	n=82 2.64 (1.05 to 4.24)
SF-36 MCS	n=33 3.4 (0.6 to 6.2)	n=30 0.3 (–2.7 to 3.2)	n=63 2.5 (0.5 to 4.4)	n=54 1.4 (–0.7 to 3.5)	n=101 2.6 (1.0 to 4.1)	n=82 1.3 (–0.4 to 2.9)
FACIT–Fatigue	n=33 3.8 (1.1 to 6.6)	n=30 –0.2 (–3.0 to 2.7)	n=63 4.1 (2.1 to 6.1)	n=54 3.0 (0.9 to 5.2)	n=101 5.7 (4.0 to 7.4)	n=82 3.1 (1.3 to 4.9)
EQ–5D–5 L index	n=33 0.09 (0.04 to 0.15)	n=30 0.02 (–0.04 to 0.08)	n=63 0.07 (0.02 to 0.11)	n=53 –0.00 (–0.05 to 0.04)	n=101 0.10 (0.07 to 0.14)	n=82 0.02 (–0.02 to 0.06)
EQ–5D–5 L VAS	n=33 7.7 (1.3 to 14.1)	n=30 –3.2 (–9.9 to 3.6)	n=63 5.1 (–0.0 to 10.3)	n=53 3.9 (–1.7 to 9.4)	n=101 8.9 (5.1 to 12.7)	n=82 1.8 (–2.3 to 5.9)
Pain VAS	n=33 –13.0 (–20.6 to –5.4)	n=29 –0.1 (–8.1 to 7.9)	n=63 –10.5 (–16.5 to –4.6)	n=54 –9.7 (–16.1 to –3.3)	n=101 –17.6 (–22.0 to –13.2)	n=82 –6.2 (–10.9 to –1.5)
PtGA VAS	n=33 –19.6 (–26.6 to –12.6)	n=29 –3.8 (–11.3 to 3.6)	n=63 –11.4 (–17.3 to –5.4)	n=54 –13.0 (–19.4 to –6.5)	n=101 –18.6 (–23.0 to –14.1)	n=82 –5.7 (–10.5 to –0.9)
WPAI (0% to 100%)						
Overall work impairment	n=19 –17.0 (–27.6 to –6.4)	n=16 –1.9 (–13.6 to 9.7)	n=25 –9.7 (–19.5 to 0.2)	n=28 –1.3 (–10.6 to 8.1)	n=53 –14.5 (–22.5 to –6.6)	n=43 –4.4 (–13.0 to 4.1)
Activity impairment	n=33 –14.9 (–22.0 to –7.8)	n=30 –1.9 (–9.3 to 5.6)	n=63 –11.5 (–17.7 to –5.2)	n=53 –5.8 (–12.6 to 0.9)	n=101 –13.8 (–18.5 to –9.2)	n=82 –6.5 (–11.5 to –1.5)
Absenteeism*	n=19 –0.4 (–9.2 to 8.5)	n=16 5.5 (–4.3 to 15.2)	n=25 1.0 (–5.5 to 7.6)	n=28 2.9 (–3.4 to 9.2)	n=53 –3.3 (–10.2 to 3.7)	n=43 0.8 (–6.8 to 8.5)
Presenteeism*	n=19 –18.7 (–27.3 to –10.1)	n=15 –8.0 (–17.7 to 1.7)	n=25 –10.1 (–18.8 to –1.3)	n=27 –1.5 (–10.0 to 7.0)	n=49 –13.8 (–20.2 to –7.3)	n=40 –4.4 (–11.1 to 2.4)

*Reported only for patients who were employed.
bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; IR, inadequate responder; MCS, mental component summary; PCS, physical component summary; PRO, patient-reported outcome; PtGA, patient's global assessment of disease activity; SF-36, 36-Item Short-Form Health Survey; VAS, visual analogue scale.

to treat PsA, such as csDMARDs (eg, MTX), bDMARDs (eg, tumour necrosis factor (TNF), IL-17, IL-12/23 and IL-23 inhibitors) and targeted synthetic DMARDs (eg, apremilast and JAK inhibitors).[24] Understanding the benefits of these treatments from a patient's perspective is critical, as perceived efficacy may significantly impact a patient's willingness to receive treatment.[10 11] The results presented in this study with RZB are comparable to PRO improvements observed for RZB in previous studies in patients with PsA, as well as for other treatments for PsA. Previously, RZB significantly reduced pain at 24 weeks compared with the PBO treatment group in a Phase 2 trial. The results are comparable to the current study as the difference in mean change on the pain VAS was significant for RZB-treated versus PBO-treated patients. In Phase 3 trials, ustekinumab, an IL-12/23 inhibitor, improved SF-36 PCS and other measures of patients' HRQoL in patients with PsA who were MTX-naïve, MTX-experienced, or TNF-inhibitor experienced.[25] After 24 weeks of treatment on the TNF inhibitor etanercept, patients' SF-36 PCS and MCS and all eight domain scores were significantly improved versus PBO.[26] Comparably, scores on SF-36 PCS and seven of eight domain scores were also greater in the RZB treatment group than the PBO group in this study after 24 weeks of treatment. In a study with the IL-17A inhibitor ixekizumab, patients reported significant improvement relative to PBO in the joint pain VAS, PtGA and EQ-5D-5L through week 24,[27] comparable to the results of this study for RZB.

Achieving and maintaining improvements in work productivity is noteworthy because approximately one-third of respondents in a multinational survey[28] reported that they missed work because of PsA, and approximately one-third reported that their PsA impacted their ability to work full-time.[1 4 5] In the current study, patients treated with RZB versus PBO reported greater reductions in impairments in work productivity, absenteeism and presenteeism. Patients treated with RZB versus PBO also reported greater reductions in daily activity impairment.

This study has strengths and limitations. Strengths included the blinded and randomised study design that allows for less biased reporting from each patient and mitigates biases due to differences between treatment groups. This study used multiple PROs to reflect and capture the multiple burdens experienced by patients with PsA, although the skin domain was not specifically assessed. A skin PRO such as the Dermatology Quality of Life Index was not included and should be considered

for inclusion in future clinical trials assessing the impact of RZB on patients with PsA. At the time of the study development, GRAPPA-OMERACT had only provisionally included the Psoriatic Arthritis Impact of Disease questionnaire and therefore this PRO was also not assessed in the current trial despite wide clinical usage. Additional limitations included the collection of PRO data at fixed visits, sometimes weeks apart and with no day-to-day data. Prolonged recall of symptoms may introduce recall bias, which could affect patient perceptions of efficacy. In addition, most PROs presented here were not multiplicity controlled; thus, some significance values are nominal. Completing several PROs may result in response fatigue, thereby introducing bias. Results were limited to 24 weeks and should be confirmed long-term.

CONCLUSION

In patients with active PsA who were Bio-IR and/or csDMARD-IR, RZB treatment resulted in greater improvements in physical functioning, fatigue, pain, HRQoL and ability to perform work compared with PBO. These results complement the reductions in disease severity observed with treatment, with improvements perceived by patients that need to be taken into consideration in treatment decisions.

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Data availability statement Data are available upon reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (eg, 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. This 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 (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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