Long-Term Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 244-Week Results From the KEEPsAKE 2 Trial

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OBJECTIVE

To report the long-term efficacy and safety of risankizumab in patients with PsA having an inadequate response or intolerance to biological therapies and/or csDMARDs

CONCLUSIONS

Long-term treatment with risankizumab demonstrates durable efficacy through 244 weeks for adult patients with active PsA and an inadequate response to biological therapies and/or cDMARD(s)

The safety profile of risankizumab remains consistent with previous studies, with no new safety risks identified

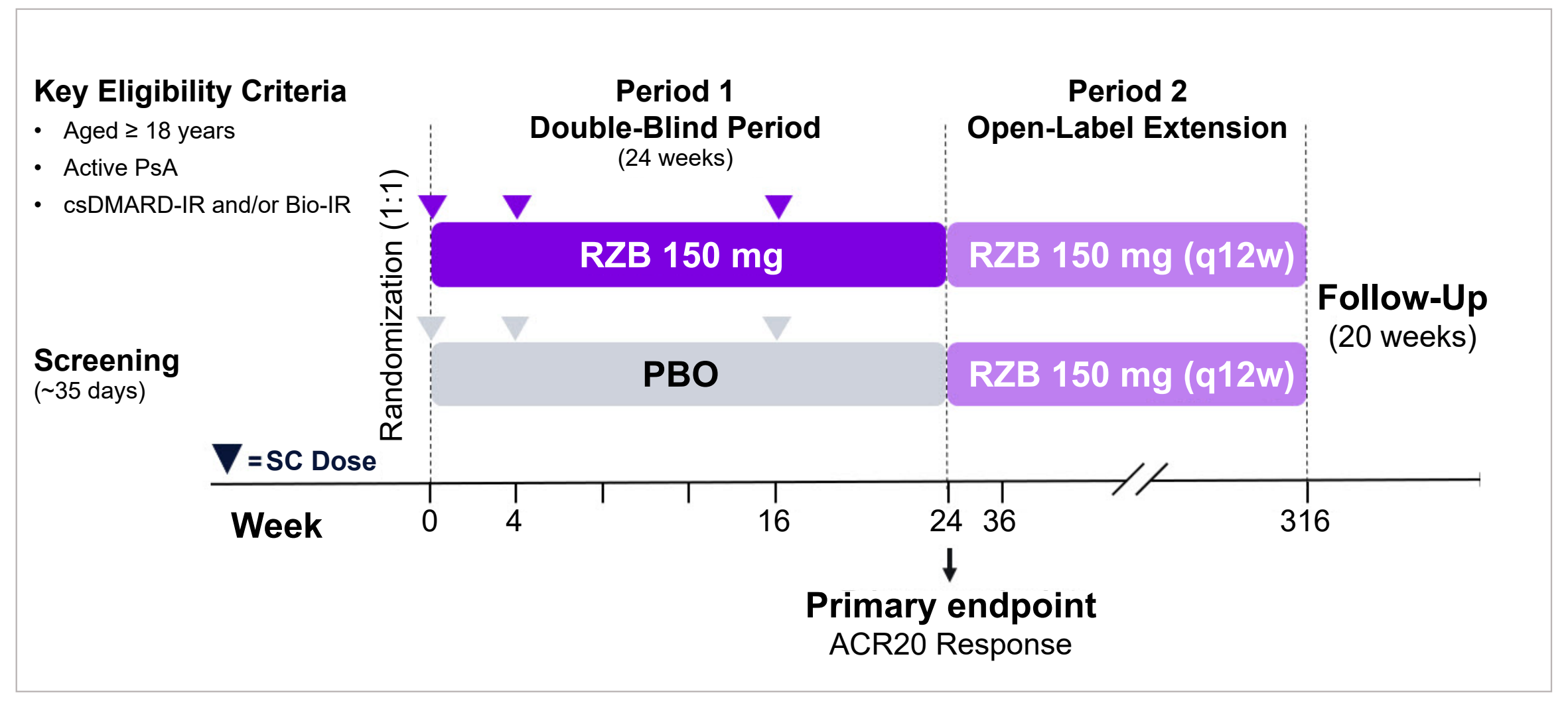
INTRODUCTION

- Risankizumab (RZB) is a humanized IgG1 monoclonal antibody that targets the p19 subunit of interleukin-23 with high affinity and specificity and is approved for the treatment of adult patients with psoriatic arthritis (PsA)
- KEEPsAKE 2 (NCT03671148) is a global, multicenter, ongoing phase 3 clinical trial to assess the efficacy and safety of RZB compared with placebo (PBO) in adults with active PsA who have previously shown inadequate response or intolerance to 1 or 2 biological therapies (Bio-IR) and/or at least 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR)
- At week 24 of the KEEPsAKE 2 trial, more patients randomized to RZB vs PBO achieved the primary endpoint of ACR20; continuous treatment with RZB 150 mg showed efficacy across disease domains, with associated improvements in patient quality of life[1]
- Here, we report the long-term efficacy and safety results of the KEEPsAKE 2 trial through week 244

METHODS

- Following a 24-week double-blind, PBO-controlled, parallel-group treatment period (period 1), patients continued into an open-label extension treatment period from week 24 through week 316 (period 2)
- In period 1, patients were randomized 1:1 to receive subcutaneous RZB 150 mg or PBO at weeks 0, 4, and 16
- Starting at week 28, all patients received open-label RZB 150 mg every 12 weeks thereafter
- Safety and efficacy were assessed in all randomized patients who received ≥ 1 dose of RZB
- Data are reported as observed (AO); missing data for binary endpoints were imputed using nonresponder imputation (NRI), with exception for data missing due to COVID-19 (NRI-C) or geopolitical conflict, which are imputed by multiple imputation (NRI-MI); results for continuous endpoints are reported by mixed-effect model repeated measurement (MMRM)

Figure 1. KEEPsAKE 2 Study Design


Key Eligibility Criteria

- Aged ≥ 18 years
- Active PsA
- csDMARD-IR and/or Bio-IR

Screening
(~35 days)

▼ = SC Dose

Randomization (1:1)

Period 1
Double-Blind Period
(24 weeks)

Period 2
Open-Label Extension

RZB 150 mg → RZB 150 mg (q12w)

PBO → RZB 150 mg (q12w)

Follow-Up
(20 weeks)

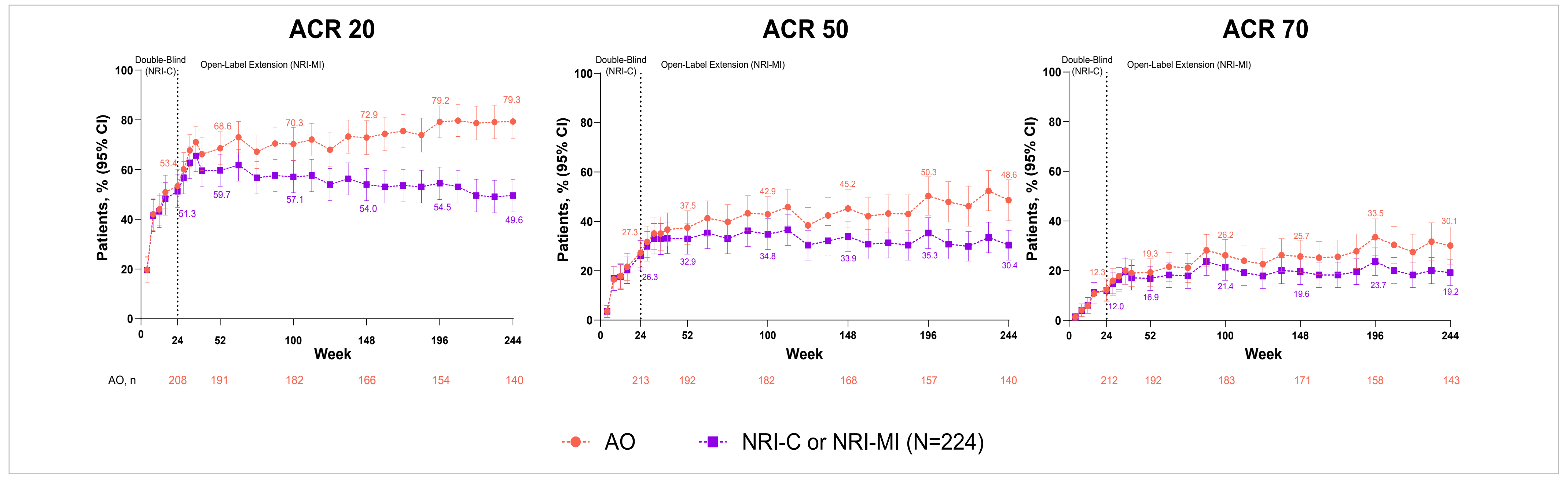
Primary endpoint
ACR20 Response

ACR20, ≥ 20% improvement in American College of Rheumatology; Bio-IR, biological therapy-inadequate response; csDMARD-IR, conventional synthetic disease-modifying antirheumatic drug-inadequate response; PBO, placebo; PsA, psoriatic arthritis; RZB, risankizumab; SC, subcutaneous.

RESULTS

- Patients treated with RZB demonstrated durable and long-term improvement in key signs and symptoms of PsA, including achievement of ACR20, ACR50, and ACR70 (**Figure 2**), and MDA (**Figure 4**) through 244 weeks
- Among patients with baseline psoriasis (≥ 3% BSA), enthesitis (LEI > 1), or dactylitis (LDI > 1), RZB treatment led to the achievement of PASI90, resolution of enthesitis (LEI = 0), and resolution of dactylitis (LDI = 0), respectively, by a majority of patients through 244 weeks (**Figure 3,4)**
- The overall rates of TEAEs (165.8 E/100 PY), serious TEAEs (9.7 E/100 PY) and AEs leading to discontinuation of study drug (1.5 E/100 PY) remained consistent with those reported in the 24-week PBO-controlled period 1 (**Table 1**)

Figure 2. Achievement of ACR Responses in Patients Originally Randomized to RZB



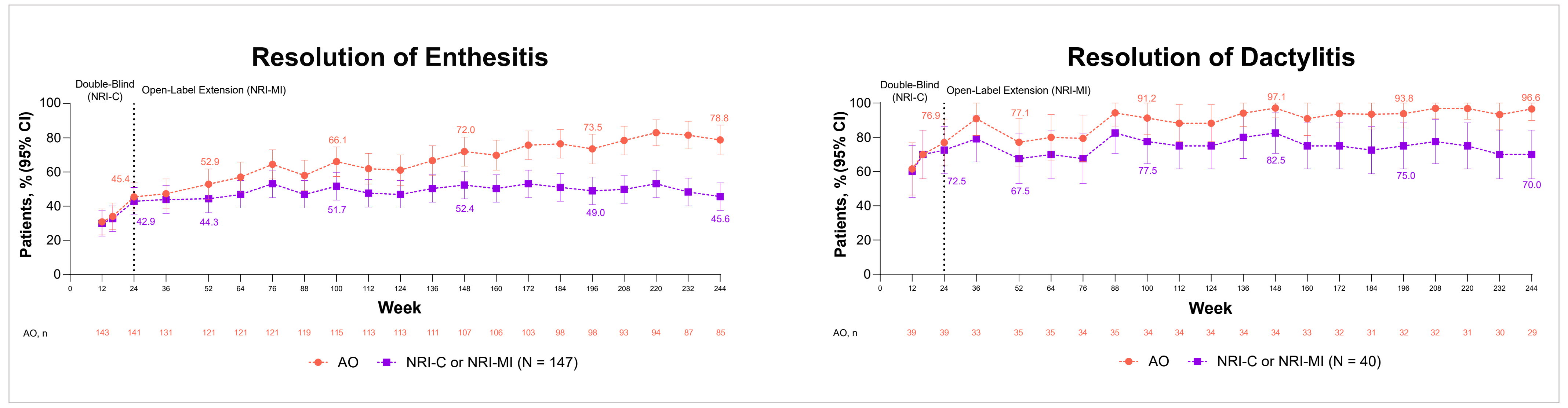
ACR20/50/70, ≥ 20/50/70% improvement in American College of Rheumatology score; AO, as observed; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRI-MI, missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict which are imputed by multiple imputations; RZB, risankizumab.

Table 1. Safety Profile Through Week 244

Parameter	RZB Week 24[a], N = 224 PY = 104.3 Events (E/100 PY)	PBO Week 24[a], N = 219 PY = 101.3 Events (E/100 PY)	All RZB[b] Week 244, N = 419 PY = 1646.7 Events (E/100 PY)
TEAE	286 (274.2)	292 (288.3)	2730 (165.8)
Serious TEAE	14 (13.4)	15 (14.8)	160 (9.7)
TEAE leading to discontinuation of study drug	2 (1.9)	6 (5.9)	24 (1.5)
Adjudicated MACE[c,d]	1 (1.0)	0	7 (0.4)
Serious infection	3 (2.9)	5 (4.9)	23 (1.4)
Opportunistic infections excluding TB/herpes zoster	0	0	2 (0.1)
Active TB	0	0	0
Herpes zoster[e]	0	1 (1.0)	7 (0.4)
Malignant tumors	1 (1.0)	3 (3.0)	27 (1.6)
NMSC[f]	1 (1.0)	3 (3.0)	20 (1.2)
Excluding NMSC[g]	0	0	7 (0.4)
Serious hypersensitivity[h]	0	0	1 (< 0.1)
All deaths (including non-treatment emergent)[i]	0	0	4 (0.2)

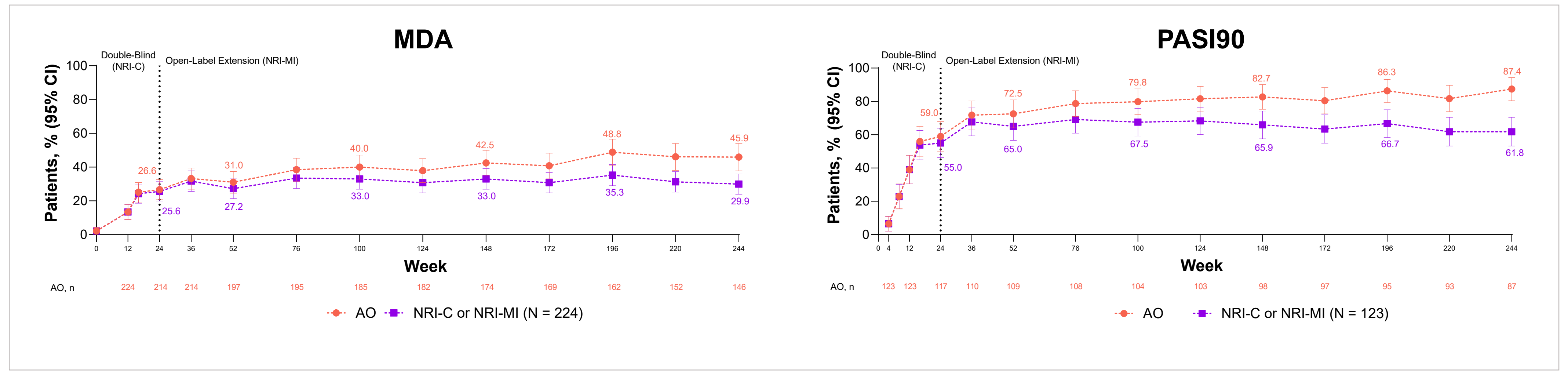
E/100 PY; events per 100 patient-years; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-years; RZB, risankizumab; TB, tuberculosis; TEAE, treatment-emergent adverse events.
TEAE were defined as any adverse event with an onset date that was on or after the first dose of risankizumab and up to 140 days after the last dose of risankizumab if the patient discontinued the study drug prematurely.
[a] 24-week data from KEEPsAKE 2 was previously published in Östör A, et. al. *Ann Rheum Dis*. 2022;81:351–58.
[b] Reported for all randomized patients who received at least one dosage of RZB through week 244.
[c] There were 7 adjudicated MACE occurrences: 1 death from acute myocardial infarction (< 0.1 E/PY), 3 nonfatal myocardial infarctions (0.2 E/PY), and 3 nonfatal strokes (0.2 E/PY).
[d] The incidence rate of MACE for patients with PsA is 0.46 E/100 PY, as derived from population-based epidemiological studies and published in Li L, et al. *J Clin Rheumatol*. 2015;21:405-410.
[e] The incidence rate of herpes zoster for patients with PsA is about 1.0 E/100 PY, as derived from population-based epidemiological studies and published in Yun H, et al. *Arthritis Rheumatol*. 2016;68:2328-2337.
[f] The incidence rate of NMSC for patients with PsA is 0.61 E/100 PY, as derived from population-based epidemiological studies and published in Vaengebjerg S, et al. *JAMA Dermatol*. 2020; 156:421-429.
[g] The incidence rate of malignant tumors (excluding NMSC) for patients with PsA is 0.48 E/100 PY, as derived from population-based epidemiological studies and published in Vaengebjerg, et al. *JAMA Dermatol*. 2020; 156:421-429.
[h] Event of idiopathic thrombocytopenic purpura assessed as no reasonable possible relationship to study treatment, per investigator. Patient remained on study drug.
[i] There were a total of 4 deaths, 3 of which were treatment emergent: 1 death was unspecified; 1 death was due to complications from metastatic adenocarcinoma; 1 death was due to complications from stage IV hepatic cancer, and 1 death occurred on day 616 (83 days after last dose;

Figure 3. Resolution of Enthesitis and Dactylitis in Patients Originally Randomized to RZB



AO, as observed; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRI-MI, missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict; PBO, placebo; RZB, risankizumab.
Resolution of enthesitis defined as Leeds Enthesitis Index (LEI) = 0 and reported among patients with LEI > 0 at baseline (RZB, n = 147; PBO/RZB, n = 158).
Resolution of dactylitis defined as Leeds Dactylitis Index (LDI) = 0 and reported among patients with LDI > 0 at baseline (RZB, n = 40; PBO/RZB, n = 57).

Figure 4. Achievement of MDA and PASI90 in Patients Originally Randomized to RZB



AO, as observed; MDA, minimal disease activity; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRI-MI, missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict, which are imputed by multiple imputations; PASI 90, ≥ 90% reduction in Psoriasis Area and Severity Index; RZB, risankizumab.

Table 2. Additional Efficacy Endpoints Through Week 244

Endpoint	Week 52 RZB	Week 52 PBO to RZB	Week 148 RZB	Week 148 PBO to RZB	Week 244 RZB	Week 244 PBO to RZB
Change from baseline in TJC, mean (95% CI)[a]	-16.2 [N = 195] (-17.9, -14.5)	-15.1 [N = 183] (-16.8, -13.3)	-16.60 [N = 224] (-17.85, -15.35)	-15.31 [N = 215] (-16.62, -13.51)	-17.75 [N = 224] (-19.15, -16.36)	-16.42 [N = 215] (-17.90, -14.93)
Change from baseline in SJC, mean (95% CI)[a]	-11.1 [N = 195] (-12.3, -10.0)	-10.5 [N = 183] (-11.7, -9.4)	-10.84 [N = 224] (-11.45, -10.23)	-10.89 [N = 215] (-11.53, -10.25)	-11.41 [N = 224] (-12.23, -10.60)	-11.11 [N = 215] (-11.98, -10.25)
Change from baseline in patient's assessment of pain (VAS), mean (95% CI)[a]	-20.3 [N = 193] (-23.9, -16.7)	-21.7 [N = 183] (-25.7, -17.7)	-20.78 [N = 224] (-24.18, -17.39)	-20.35 [N = 215] (-23.92, -16.79)	-21.32 [N = 224] (-24.82, -17.81)	-21.88 [N = 215] (-25.61, -18.14)
PASI100, % (n/N)[b]	61.5 (67/109)	60.4 (61/101)	61.0 (75/123)	52.1 (62/119)	50.4 (62/123)	46.2 (55/119)
Achievement of BASDAI 50, % (n/N)[c]	35.6 (16/45)	45.5 (15/33)	33.3 (16/48)	23.1 (9/39)	22.9 (11/48)	23.1 (9/39)
Change from baseline in BASDAI[d]	-2.33 [N = 45] (-2.99, -1.66)	-2.21 [N = 33] (-3.13, -1.28)	-2.48 [N = 48] (-3.20, -1.76)	-2.06 [N = 36] (-2.89, -1.23)	-2.29 [N = 48] (-3.05, -1.53)	-2.14 [N = 36] (-3.02, -1.26)
Change from baseline in HAQ-DI, mean (95% CI)	-0.26 [N = 224] (-0.32, -0.20)	-0.34 [N = 215] (-0.41, -0.28)	-0.24 [N = 224] (-0.32, -0.16)	-0.27 [N = 215] (-0.36, -0.19)	-0.26 [N = 224] (-0.34, -0.18)	-0.30 [N = 215] (-0.38, -0.21)
Change from baseline in SF-36 PCS score, mean (95% CI)	6.28 [N = 223] (5.22, 7.33)	7.30 [N = 213] (6.21, 8.39)	6.09 [N = 223] (4.83, 7.36)	5.60 [N = 213] (4.27, 6.92)	6.98 [N = 223] (5.61, 8.34)	6.89 [N = 213] (5.44, 8.33)
Change from baseline in FACIT-Fatigue score, mean (95% CI)	5.7 [N = 223] (4.5, 6.9)	7.0 [N = 213] (5.8, 8.2)	6.0 [N = 223] (4.6, 7.5)	5.1 [N = 213] (3.6, 6.6)	6.6 [N = 223] (5.1, 8.1)	6.5 [N = 213] (5.0, 8.1)

AO, as observed; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50, ≥ 50% reduction in Bath Ankylosing Spondylitis Disease Activity Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire; HAQ-DI, Health Assessment Questionnaire-Disability Index; MMRM, Mixed-Effect Model Repeated Measurement; NRI-MI, missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict, which are imputed by multiple imputations; PASI100, 100% reduction in Psoriasis Area and Severity Index; PBO, placebo; RZB, risankizumab; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale.
All changes are least-square mean changes from baseline. Results for continuous endpoints are reported by MMRM.
[a] Results for these continuous endpoints are reported AO at week 52, and by MMRM at week 148 and week 244.
[b] Reported for patients with ≥ 3% of body surface area (BSA) affected by psoriasis at baseline (RZB, n = 123; PBO/RZB, n = 119), AO at week 52, and by NRI-MI at week 148 and week 244.
[c] Reported for patients with axial spondylitis at baseline, AO at week 52, and by NRI-MI at week 148 and week 244.
[d] Reported for patients with axial spondylitis at baseline, AO at week 52, and by MMRM at week 148 and week 244.

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