Long-Term Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 196-Week Results From the KEEPsAKE 2 Trial

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OBJECTIVE

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

CONCLUSIONS

Long-term treatment with risankizumab provides a durable efficacy response through 196 weeks for adult patients with active PsA and an inadequate response to biological therapies and/or cDMARD(s)

Risankizumab is generally well tolerated with no new safety signals

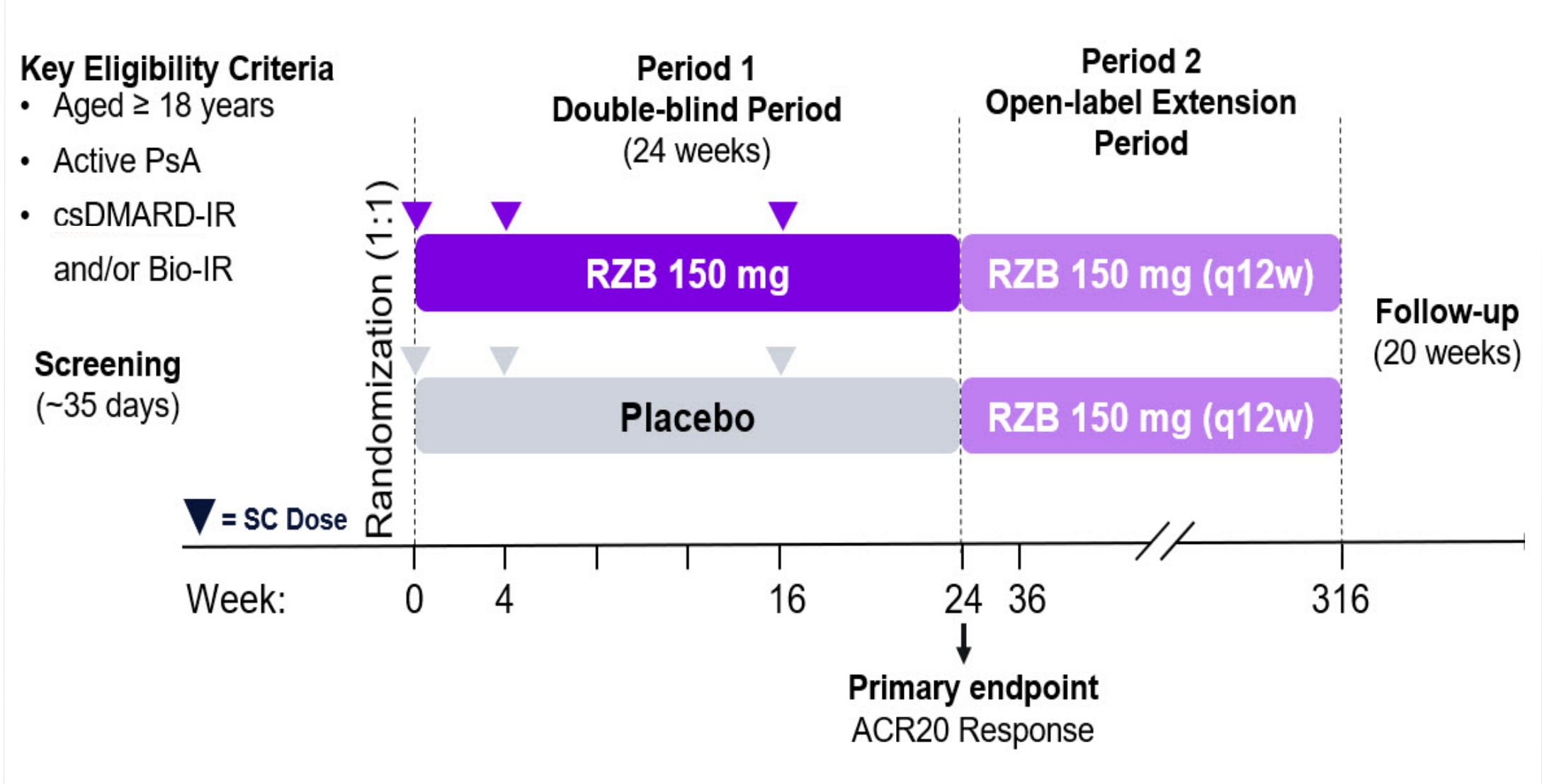
INTRODUCTION

- Risankizumab (RZB), a humanized immunoglobulin G1 monoclonal antibody that inhibits interleukin-23 by targeting its p19 subunit with high affinity and specificity, is approved for the treatment of adult patients with PsA
- KEEPsAKE 2 (NCT03671148) is an ongoing, global, phase 3, multicenter clinical trial to evaluate the efficacy and safety of RZB vs placebo (PBO) in adults with active PsA who have a history of inadequate response or intolerance to 1 or 2 biological therapies (Bio-IR) and/or ≥1 conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR) therapy
- More patients randomized to RZB compared to PBO in the KEEPsAKE 2 trial achieved the primary endpoint of ACR20 at week 24, and the trial has demonstrated efficacy of treatment with continuous RZB 150 mg across several disease domains, with associated improvements in quality of life, patient functioning, and pain[1]
- Here, we report the efficacy and safety results from the KEEPsAKE 2 trial through week 196

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 until week 316
- Data are reported as observed (AO); missing data for categorical endpoints were imputed using non-responder imputation (NRI), with exception for data missing due to COVID-19 or geopolitical conflict, which are imputed by multiple imputations; results for continuous endpoints were reported by mixed-effect model repeated measurement (MMRM)

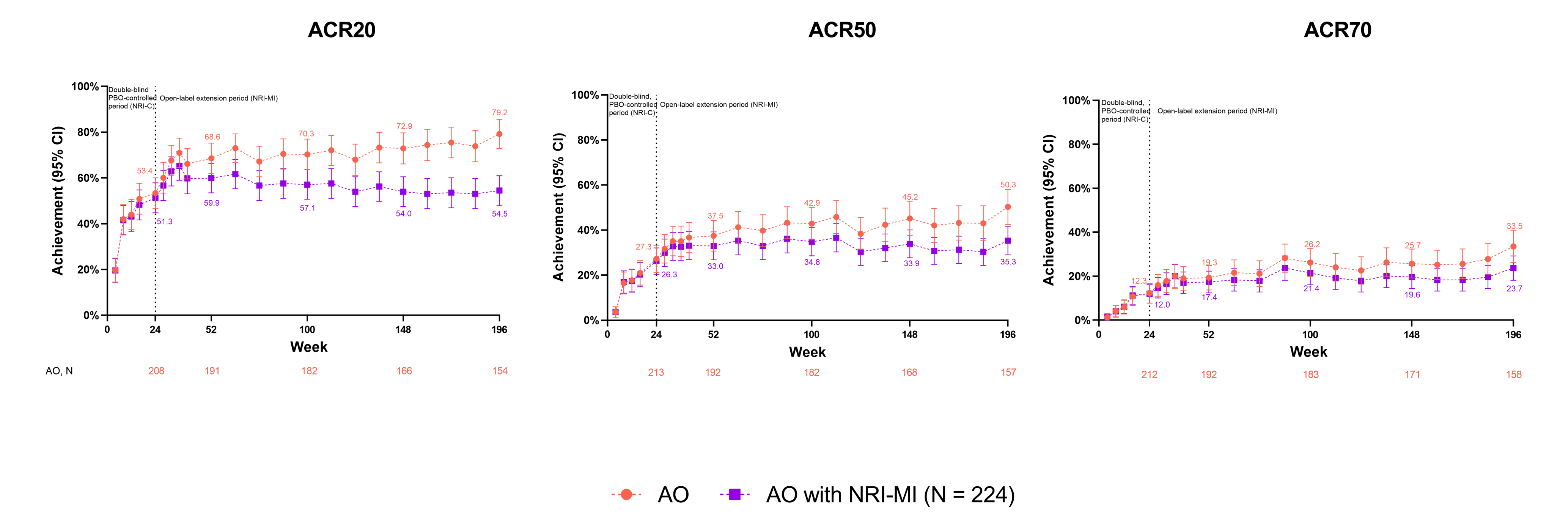
Figure 1. Study Design



RESULTS

- Patients treated with RZB demonstrated durable, long-term improvement in key signs and symptoms of PsA including achievement of ACR20, ACR50, ACR70, PASI90, MDA, resolution of enthesitis and dactylitis through 196 weeks
- The overall rates of TEAEs (170.7 E/100PYs), serious TEAEs (9.8 E/100PYs) and AEs leading to discontinuation of study drug (1.4 E/100PYs) remained stable and comparable to those reported in placebo-controlled period 1

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



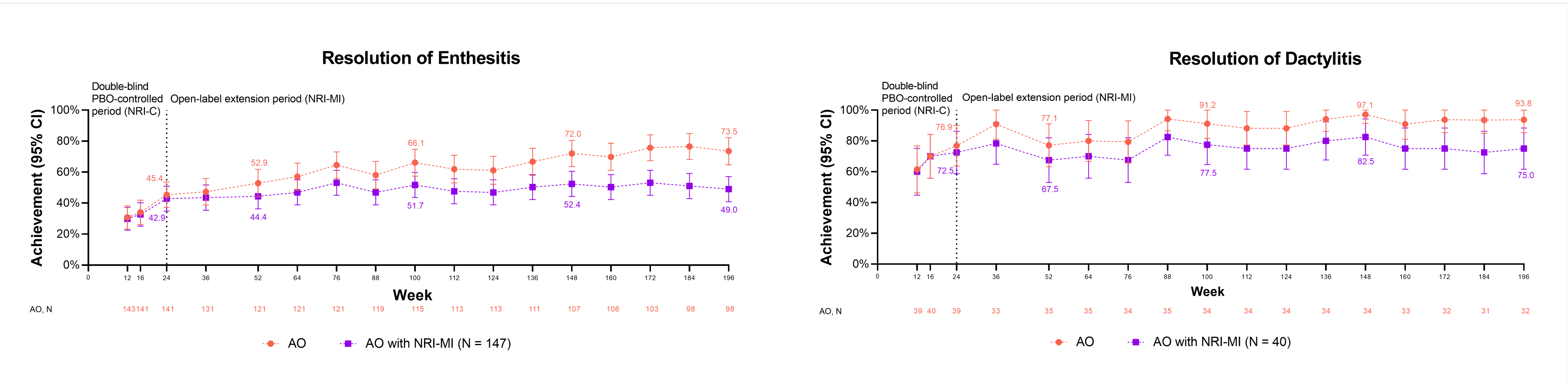
ACR20/50/70, ≥ 20/50/70% improvement in American College of Rheumatology score; AO with NRI-MI, as observed (AO) with missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict which are imputed by multiple imputations; NRI-C, non-responder imputation incorporating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

Table 1. Safety Profile Through Week 196

Parameter, E (Events/100PY)	RZB Week 24[a] (N = 224) PY = 104.3	PBO Week 24[a] (N = 219) PY = 101.3	All RZB Week 196 (N = 419) PY = 1382.8
TEAE	286 (274.2)	292 (288.3)	2361 (170.7)
Serious TEAE	14 (13.4)	15 (14.8)	136 (9.8)
TEAE leading to discontinuation of study drug	2 (1.9)	6 (5.9)	19 (1.4)
COVID-19-related TEAE	1 (1.0)	0	153 (11.1)
Adjudicated MACE	1 (1.0)	0	7 (0.5)
Cardiovascular death - sudden cardiac death	0	0	0
Cardiovascular death - heart failure	0	0	0
Cardiovascular death - acute myocardial infarction	0	0	1 (<0.1)
Non-fatal myocardial infarction	0	0	3 (0.2)
Non-fatal stroke	1 (1.0)	0	3 (0.2)
Serious infection	3 (2.9)	5 (4.9)	20 (1.4)
Opportunistic infections excluding TB/herpes zoster	0	0	2 (0.1)
Active TB	0	0	0
Herpes zoster	0	1 (1.0)	5 (0.4)
Malignant tumors	1 (1.0)	3 (3.0)	23 (1.7)
NMSC	1 (1.0)	3 (3.0)	18 (1.3)
Excluding NMSC	0	0	5 (0.4)
Serious hypersensitivity	0	0	1 (<0.1)[b]
Adjudicated anaphylactic reaction	0	0	0
All Deaths (including non-treatment emergent)	0	0	4 (0.3)[c]

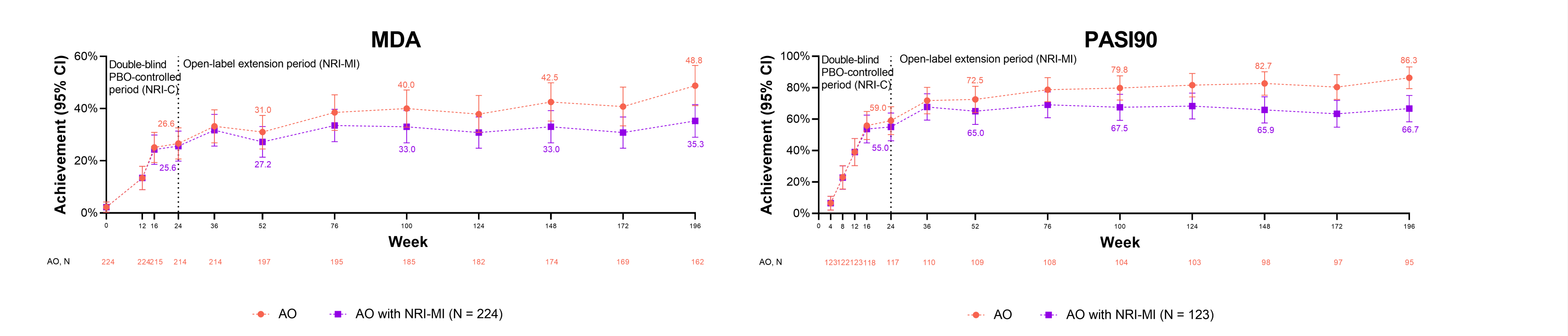
MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; PY, patient-years; RZB, risankizumab; TB, tuberculosis; TEAE, treatment-emergent adverse events.
TEAE were defined as any AE with an onset date that was on or after the first dose of risankizumab and up to 140 days after the last 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]Event of idiopathic thrombocytopenic purpura assessed as NRP per investigator. Patient remained on study drug.
[c]There were total of 4 deaths, 3 of which were treatment emergent. 1 death was unspecified and deemed due to general disorders and administration site conditions; 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; non-treatment-emergent) due to cardiac arrest.

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



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).
AO with NRI-MI, as observed (AO) with missing data imputed as non-responders except those missing due to COVID-19 or geopolitical conflict; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.

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



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

Table 2. Additional Efficacy Endpoints Through Week 196

	Week 52		Week 148		Week 196	
	RZB	**PBO to RZB**	**RZB**	**PBO to RZB**	**RZB**	**PBO to RZB**
ACR20, % (n)	58.5 (131)	55.7 (122)	54.0 (121)	46.6 (102)	54.5 (122)	50.2 (110)
ACR50, % (n)	32.1 (72)	32.0 (70)	33.9 (76)	28.8 (63)	35.3 (79)	37.0 (81)
ACR70, % (n)	16.5 (37)	21.0 (46)	19.6 (44)	16.4 (36)	23.7 (53)	22.8 (50)
MDA, % (n)	27.2 (61)	33.8 (74)	33.0 (74)	28.3 (62)	35.3 (79)	37.4 (82)
Change from baseline in TJC*	-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, -14.00)	-17.55 [N = 224] (-18.68, -16.41)	-16.81 [N = 215] (-18.00, -15.62)
Change from baseline in SJC*	-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)	-11.44 [N = 224] (-11.87, -11.02)	-11.57 [N = 215] (-12.02, -11.13)
Change from baseline in patient's assessment of pain (VAS)*	-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)	-24.50 [N = 224] (-27.82, -21.18)	-23.58 [N = 215] (-27.07, -20.09)
Resolution of enthesitis, % (n/N)⁺	43.5 (64/147)	52.5 (83/158)	53.1 (78/147)	47.5 (75/158)	49.0 (72/147)	50.0 (79/158)
Resolution of dactylitis, % (n/N)⁻	67.5 (27/40)	70.2 (40/57)	82.5 (33/40)	61.4 (35/57)	75.0 (30/40)	59.6 (34/57)
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)	-0.34 [N = 215] -0.43, -0.25)
PASI90, % (n/N)^	64.2 (79/123)	59.7 (71/119)	65.9 (81/123)	58.8 (70/119)	66.7 (82/223)	56.3 (67/119)
PASI100, % (n/N)^	54.5 (67/123)	51.3 (61/119)	61.0 (75/123)	52.1 (62/119)	59.3 (73/123)	51.3 (61/119)
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)	6.46 [N = 223] (5.17, 7.75)	6.16 [N = 213] (4.81, 7.51)
Change from baseline in FACIT-Fatigue score, mean (95% CI)	5.7 [N = 223] (4.6, 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)	6.0 [N = 223] (4.6, 7.4)	6.6 [N = 213] (5.1, 8.0)

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; PASI 90, ≥90% reduction in Psoriasis Area and Severity Index; PASI 100, 100% reduction in Psoriasis Area and Severity Index; PBO, placebo; RZB, risankizumab; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary.
All changes are least square mean changes from baseline; Results for binary endpoints are based on as-observed (AO) data with missing data imputed as non-responder imputation (NRI) at week 52, and as AO with non-responder imputation incorporating multiple imputations (NRI-MI) if there are missing data due to COVID-19 or geopolitical conflict, at week 148 and week 196; results for continuous endpoints are reported by mixed-effect model repeated measurement (MMRM).
*Results for these binary endpoints are reported by AO at week 52 and by AO with NRI-MI at week 148 and week 196.
⁺Defined as Leeds Enthesitis Index (LEI) = 0 and reported among patients with LEI >0 at baseline (RZB, N = 147; PBO/RZB, N = 158).
⁻Defined as Leeds Dactylitis Index (LDI) = 0 and reported among patients with LDI >0 at baseline (RZB, N = 40; PBO/RZB, N = 57).
^Reported for patients with ≥ 3% of body surface area (BSA) affected by psoriasis at baseline (RZB, N = 123; PBO/RZB, N = 119), as AO with imputation at week 52 and AO with NRI-MI at week 148 and week 196.

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1. Östör A, et. al. *Ann Rheum Dis*. 2022;81:351-8.

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