SUPPLEMENTAL MATERIAL

Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from the KEEPsAKE 1 study

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Supplementary Table S1 Eligibility criteria

Consent	
1	Patient must be functionally able to read and understand a written informed consent form, study-related instructions, and study questionnaires
2	Patients must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. The use of Legally Authorized Representatives (LARs) is prohibited for this protocol
3	Employees of the sponsor and/or study sites and their family members may not be enrolled in this study
Demographics and Laboratory Assessments	
4	Adult male or female, at least 18 years old (patients must also meet the legal age of majority per local law)
5	Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: • Serum aspartate transaminase (AST) < 2 × upper limit of normal (ULN); • Serum alanine transaminase (ALT) < 2 × ULN; • Serum total bilirubin ≤ 2.0 mg/dL; except for patients with isolated elevation of indirect bilirubin relating to Gilbert syndrome; • Total white blood cell (WBC) count > 3,000/μL; • Absolute neutrophil count (ANC) > 1,500/μL; • Platelet count > 100,000/μL; • Hemoglobin > 8.0 g/dL
6	Patient is willing and able to comply with procedures required in this protocol
Disease Activity	
7	Patient has a clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) at Screening Visit
8	Patient has active disease defined as ≥ 5 tender joints (based on 68 joint counts) and ≥ 5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline
9	Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥ 2 cm diameter or nail changes consistent with psoriasis at the Screening Visit
10	Presence of either at Screening:

	• ≥ 1 erosion on radiograph as determined by central imaging review or; • hs-CRP ≥ 3.0 mg/L
Patient History	
11	To be considered csDMARD-IR: • Patient must have demonstrated an inadequate response (lack of efficacy after minimum 12-week duration of therapy) to previous or current treatment with at least 1 of the following csDMARD at maximally tolerated dose: MTX, sulfasalazine (SSZ), leflunomide (LEF), apremilast, bucillamine and iguratimod, or ciclosporin A ○ MTX-IR is defined as an inadequate response (lack of efficacy after minimum 12 weeks duration of therapy) at the following doses ranges: ≥ 15 mg/week, or ≥ 10 mg/week in patients who are intolerant of MTX at doses ≥ 12.5 mg/week after complete titration (for patients in some countries, such as China, Korea, Malaysia, Singapore, Hong Kong, Taiwan, and Japan inadequate response to MTX is defined as ≥ 7.5 mg/week or as required per local authorities) • Alternatively, patient must have an intolerance to or contraindication for csDMARDs as determined by the investigator
12	No evidence of hepatitis B (HBV), hepatitis C (HCV) infection, human immunodeficiency virus (HIV) infection, or TB defined as: • HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for patients who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] patients where mandated by local requirements) • HCV: HCV RNA detectable in any patient with anti-HCV antibody (HCV Ab) • HIV: Confirmed positive anti-HIV antibody (HIV Ab) test. Ineligibility due to a positive HIV test should be documented in the CRF as a screen failure due to criterion 16 to keep this test result private • TB: Patients with a positive QuantiFERON® TB /PPD test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, patients are not required to be treated with prophylactic anti-TB therapy prior to or during the study if the patient is considered low risk for reactivation per the investigator judgment
13	No active systemic infection during the last 2 weeks prior to Baseline Visit (exception: common cold), as assessed by the investigator
14	No documented active or suspected malignancy or history of any malignancy within the last 5 years except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix
15	No history of organ transplantation requiring continued immunosuppression
16	No major surgery performed within 12 weeks prior to randomization or planned during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation)
17	No history of clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the opinion of the Investigator would compromise the safety or interfere with the patient's participation in this study,

	including a positive HIV test, or would make the patient an unsuitable candidate to receive study drug or would put the patient at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care
18	No active skin disease other than psoriasis which could interfere with the assessment of psoriasis
19	No history of extra-articular manifestations of PsA (e.g., PsO, uveitis, or inflammatory bowel disease [IBD]) that is not clinically stable for at least 30 days prior to Screening
20	No prior joint surgery at joints to be assessed within this study in the 8 weeks prior to the Baseline Visit or treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the 8 weeks prior to the Baseline Visit
21	No history of fibromyalgia, any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus.) • Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made • Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly
22	No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months
23	No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class
Contraception	
24	A negative serum pregnancy test is required at the Screening Visit for all female patients of childbearing potential. In addition, a negative urine pregnancy test is required at Baseline prior to the first dose of study drug for all female patients of childbearing potential. Patients with a borderline serum pregnancy test at Screening must have a negative serum pregnancy test ≥ 3 days later to document continued lack of a positive result
25	If female, patient must be of non-childbearing potential OR a female of childbearing potential practicing at least 1 protocol-specified method of birth control, that is effective from Study Day 1 through at least 140 days (20 weeks) after the last dose of study drug (local practices may require 2 methods of birth control)
26	Female patient may not be pregnant, breastfeeding, or considering becoming pregnant during the study and for at least 140 days (20 weeks) after the last dose of study drug
Concomitant Medications	
27	Patients are not required to be receiving csDMARD therapy to participate in the clinical trial. However, patients on current treatment with concomitant csDMARDs at study entry must be on ≤ 2 of only the following csDMARDs for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit at the following doses: • MTX (≤ 25 mg/week);

	• SSZ (≤ 3000 mg/day); • LEF (≤ 20 mg/day); • apremilast (≤ 60 mg/day); • hydroxychloroquine (HCQ) (≤ 400 mg/day); • bucillamine (≤ 300 mg/day); • iguratimod (≤ 50 mg/day) • ciclosporin A (≤ 5 mg/kg/day) No other csDMARDs are permitted. The combination of MTX and LEF is exclusionary. Where mandated by local requirements only, treatment with at least one of the following medications is required: non-biologic csDMARDs, NSAIDs, acetaminophen low potency opioids (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen), or oral corticosteroids at dose equivalent to prednisone ≤ 10 mg/day
28	Patients who need to discontinue or modify dose or dosing interval of their csDMARD therapy prior to the Baseline Visit in order to comply with Eligibility Criterion 27 must follow the procedure specified below: • LEF must be discontinued ≥ 8 weeks prior to baseline if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine or activated charcoal or as per local label); • Discontinuation or modification of all other csDMARDS must occur ≥ 4 weeks prior to Baseline or at least five times the mean terminal elimination half-life of the drug before undergoing the Baseline Visit, whichever is longer
29	Patients are permitted to take stable doses of NSAIDs, acetaminophen/paracetamol, low potency opiates (tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen), oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids for stable medical conditions. However, these medications must have been at a stable dose for ≥ 1 week prior to the Baseline Visit without an anticipated dose adjustment during study duration
30	Patients must have discontinued all opiates (except for tramadol, codeine, or hydrocodone, alone or in combination with acetaminophen) for ≥ 1 week prior to the first dose of study drug
31	No prior exposure to any biologic immunomodulation agents including risankizumab

32	No use of the following concomitant psoriasis treatments within the specified timeframe prior to Baseline Visit:
	• Oral retinoids within 4 weeks;
	• Fumarates within 1 week;
	• Psoralens and Ultraviolet A (PUVA) within 4 weeks;
	• Ultraviolet A (UVA) and Ultraviolet B (UVB) within 2 weeks;
	• Topical treatments, including medicated shampoos, within 2 weeks, with the exception of the following:
	  ○ Bland (without beta or alpha hydroxy acids) emollients
	  ○ Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only.
	  ○ Topical anti-itch treatment with no expected effect on psoriatic skin lesions

33	Patient must not have received any live vaccine within 6 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 140 days (20 weeks) after the last dose of study drug

34	Patient must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study.

Supplementary Table S2 Efficacy results at week 52 (as observed)

Parameter	RZB 150 mg (*N* = 483)	PBO to RZB 150 mg (*N* = 481)
Resolution of enthesitis,[a] *n/N* (%) (95% CI)	244/393 (62.1) (57.3, 66.9)	257/396 (64.9) (60.2, 69.6)
Resolution of dactylitis,[b] *n/N* (%) (95% CI)	143/171 (83.6) (78.1, 89.2)	148/181 (81.8) (76.1, 87.4)
Change from baseline in mNAPSI score,[c] mean (95% CI)	−13.64 (−15.28, −11.99)	−10.91 (−12.50, −9.33)
Change from baseline in PGA-F score,[c] mean (95% CI)	−1.2 (−1.4, −1.1)	− 1.1 (−1.2, −0.9)
PGA-F clear or minimal with ≥ 2 grades of improvement,[c] *n/N* (%) (95% CI)	105/181 (58.0) (50.8, 65.2)	86/176 (48.9) (41.5, 56.2)
MDA achievement, *n/N* (%) (95% CI)	183/444 (41.2) (36.6, 45.8)	132/440 (30.0) (25.7, 45.8)
Change from baseline in HAQ-DI, mean (95% CI)	−0.43 (−0.48, −0.37)	−0.32 (−0.38, −0.27)
≥ 0.35 change from baseline in HAQ-DI,[d] *n/N* (%) (95% CI)	238/381 (62.5) (57.6, 67.3)	191/379 (50.4) (45.4, 55.4)
Change from baseline in pain VAS score,[e] mean (95% CI)	−27.5 (−30.1, −24.9)	−23.1 (−25.8, −20.5)

Based on full analysis set.
Data as observed at all visits up to the cut-off date (19 April 2021).

[a]Defined as LEI = 0 among patients with LEI >0 at baseline. Pooled from KEEPsAKE 1 and KEEPsAKE 2.

[b]Defined as LDI = 0 among patients with LDI >0 at baseline. Pooled from KEEPsAKE 1 and KEEPsAKE 2.

[c]Among patients with nail psoriasis at baseline (RZB, *N* = 309; PBO, *N* = 338).

[d]Among patients with baseline HAQ-DI ≥0.35 at baseline.

[e]Among patients with baseline pain VAS score (RZB, *N* = 440; PBO, *N* = 435).

AO: as observed; 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; PBO, placebo; PGA-F: Physician Global Assessment of Fingernail Psoriasis; RZB: Risankizumab; VAS: visual analog scale.

Supplementary Table S3 Enthesitis and dactylitis over time (as observed)

	Week 24 (Period 1)		Week 52 (Period 1 and 2)	
Parameter	**RZB 150 mg**	**PBO**	**RZB 150 mg**	**PBO to RZB 150 mg**
Change from baseline in LEI,[a] mean (95% CI)	−1.8*** (−2.0, −1.6)	−1.2 (−1.4, −1.0)	−2.0 (−2.2, −1.8)	−1.7 (−1.9, −1.6)
Change from baseline in LDI,[b] mean (95% CI)	−74.1 (−82.9, −65.3)	−68.4 (−77.2, −59.5)	−91.7 (−113.0, −70.4)	−76.4 (−96.5, −56.2)

Based on full analysis set.
Week 24, least squares mean change; week 52, mean change.
*** $P < 0.001$.
[a]Among patients with LEI>0 at baseline (RZB, $N = 297$; PBO, $N = 290$).
[b]Among patients with LDI>0 at baseline (RZB, $N = 148$; PBO, $N = 147$).
LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; PBO: placebo; RZB: risankizumab.

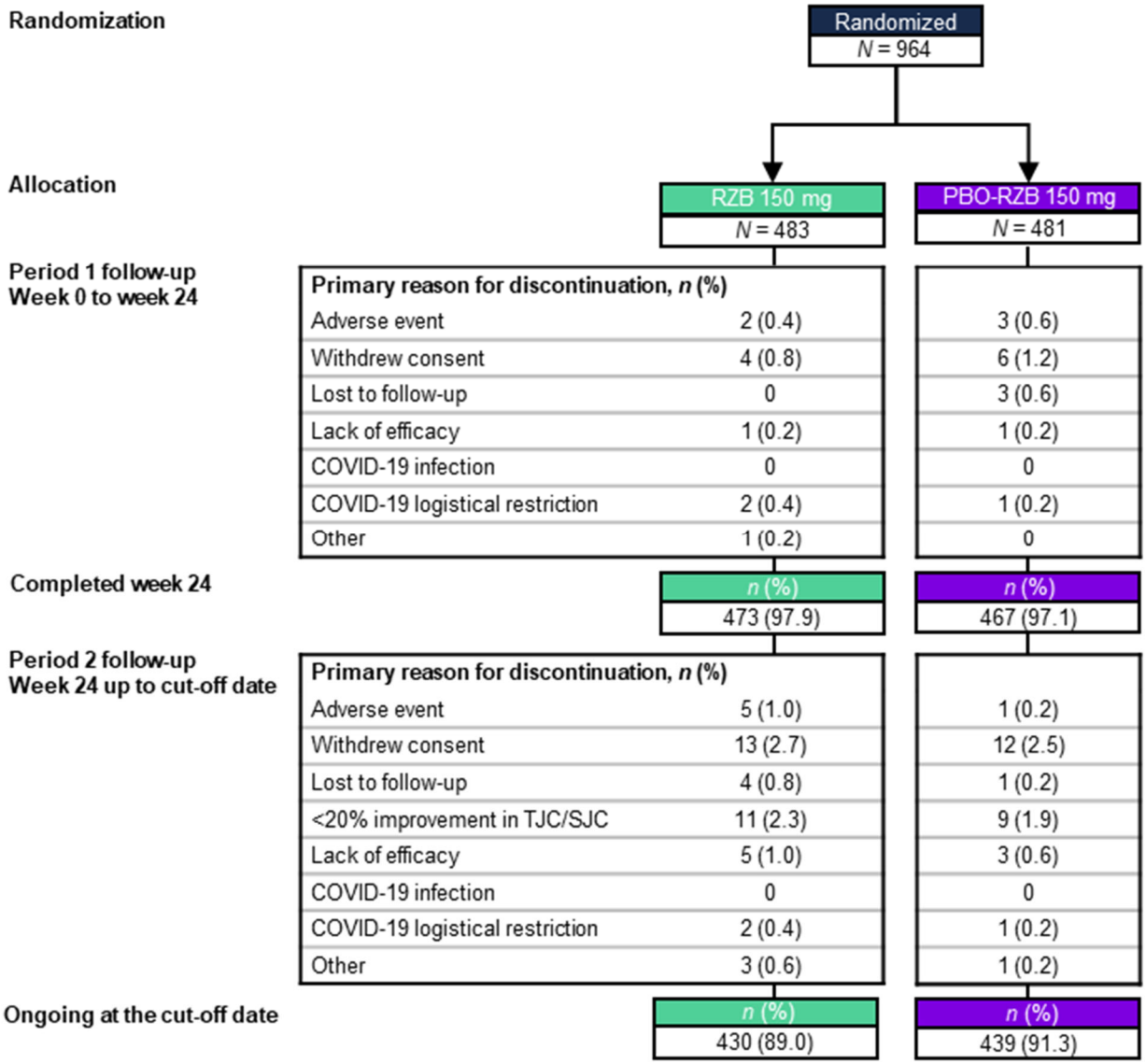
Supplementary Table S4 Post-baseline grades for select liver function tests

	PBO → RZB		RZB	Any RZB[c]
***n*/PYs (*n*/100 PYs)**	**Weeks 0–24 (PBO)**	**Week 24 to data cutoff[a]**	**Week 0 to data cutoff[b]**	**Week 0 to data cutoff**
ALT				
Grade 1	98/198.0 (49.5)	97/333.4 (29.1)	141/523.5 (26.9)	238/857.0 (27.8)
Grade 2	9/220.9 (4.1)	7/361.6 (1.9)	8/585.3 (1.4)	15/946.9 (1.6)
Grade 3	4/221.2 (1.8)	1/365.6 (0.3)	12/583.0 (2.1)	13[d]/948.5 (1.4)
Grade 4	0/222.3 (0)	0/365.6 (0)	0/591.3 (0)	0/956.9 (0)
AST				
Grade 1	63/209.4 (30.1)	74/336.8 (22.0)	119/531.9 (22.4)	193/868.7 (22.2)
Grade 2	4/221.3 (1.8)	4/363.8 (1.1)	5/587.0 (0.9)	9/950.7 (0.9)
Grade 3	2/221.8 (0.9)	3/365.4 (0.8)	8/587.0 (1.4)	11[d]/952.4 (1.2)
Grade 4	0/222.3 (0)	0/365.6 (0)	0/591.3 (0)	0/956.9 (0)
Bilirubin				
Grade 1	12/219.7 (5.5)	9/362.3 (2.5)	24/578.5 (4.1)	33/940.8 (3.5)
Grade 2	4/221.4 (1.8)	1/365.5 (0.3)	3/590.3 (0.5)	4/955.8 (0.4)
Grade 3	0/222.3 (0)	0/365.6 (0)	0/591.3 (0)	0/956.9 (0)
Grade 4	0/222.3 (0)	0/365.6 (0)	0/591.3 (0)	0/956.9 (0)

Toxicity grading scale is based on Common Terminology Criteria version 4.03.
ALT and AST: Grade 1: 1.0 to <3.0 × ULN; Grade 2: 3.0 to <5.0 × ULN; Grade 3: 5.0 to <20 × ULN; Grade 4: >20 × ULN.
Bilirubin: Grade 1: 1.0 to <1.5 × ULN; Grade 2: 1.5 to <3.0 × ULN; Grade 3: 3.0 to <10.0 ULN; Grade 4: >10.0 × ULN.
n/100 PYs is defined as number of patients with at least one event (maximum grade and worse than baseline) per 100 PYs.

Post-baseline grade must be more extreme (worse) than the baseline grade to be included in the numerator. If a patient did not have a baseline value, then the patient would be counted in the numerator if the patient had one or more post-baseline values and met the specific criteria.
[a]Patients received PBO through week 24; only elevations after starting RZB treatment at week 24 through the long-term data cut-off date (19 April 2021) are reported.
[b]Includes patients receiving RZB treatment from week 0 to the long-term data cut-off date (19 April 2021).
[c]Any RZB 150 mg includes all patients who received RZB 150 mg, including those who started on RZB 150 mg at randomization and those who switched from PBO to RZB 150 mg at week 24.
[d]Grade 3 transaminase elevations were observed in 16 unique patients: three patients had a medical history of hepatic steatosis, chronic pancreatitis and/or cytolysis syndrome; five patients experienced elevations after initiation of isoniazid with levels returning to baseline after discontinuation of isoniazid; one patient observed elevations after initiation of fenofibrate with levels returning to baseline after discontinuation of fenofibrate; two patients with grade 2 and/or 3 baseline transaminase levels experienced transient elevations; four patients taking concomitant methotrexate experienced elevations that all returned to baseline or were trending toward baseline values as of the data cut-off date; one patient experienced elevated transaminases while hospitalized for SAE of septicemia and experienced sudden death 14 days after resolution of septicemia.
ALT: alanine aminotransferase AST: aspartate aminotransferase, PBO: placebo; PYs: patient years; RZB: risankizumab; SAE: serious adverse events; ULN: upper limit of the normal range.

Supplementary Fig. S1 Patient Disposition



PBO: placebo; RZB: risankizumab; SJC: swollen joint count; TJC: tender joint count.