Rheumatol Ther (2024) 11:633–648
https://doi.org/10.1007/s40744-024-00657-2

ORIGINAL RESEARCH

Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 100-Week Results from the KEEPsAKE 2 Randomized Clinical Trial

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Received: November 28, 2023 / Accepted: February 14, 2024 / Published online: March 18, 2024

ABSTRACT

Introduction: Long-term therapeutic options providing durable response and tolerability are needed for psoriatic arthritis (PsA). The ongoing KEEPsAKE 2 trial is evaluating risankizumab treatment in patients with active PsA who previously had inadequate response/intolerance to ≥ 1 conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR) and/or 1–2 biologic DMARDs (bDMARD-IR). Herein, we report results through 100 weeks of treatment.

Methods: KEEPsAKE 2 is a global phase 3 trial. Patients with active PsA were randomized 1:1 to double-blind subcutaneous risankizumab 150 mg or placebo (weeks 0, 4, and 16). At week 24, all patients received open-label risankizumab every 12 weeks until end of study. Efficacy endpoints included achieving ≥ 20% improvement in PsA symptoms using American College of Rheumatology criteria (ACR20), attaining minimal disease activity (MDA; meeting ≥ 5/7 criteria of low disease activity and extent), and improving in other measures.

Results: At the cutoff date, 345/443 (77.9%) patients were ongoing in the study. ACR20 was

Prior Presentation: The 100-week analyses of the KEEPsAKE 2 study were previously presented at ACR Convergence 2022, November 10–14, Philadelphia, PA, and the 31st EADV Congress, September 7–10, 2022, Milan, Italy, and online.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-024-00657-2.

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achieved in 57.1% and 52.5% of the continuous risankizumab and placebo/risankizumab cohorts, respectively, at week 100 and in 60.0% and 55.8%, respectively, at week 52. In week 52 responders, maintenance of ACR20 at week 100 was achieved in 74.8% (continuous risankizumab) and 78.7% (placebo/risankizumab) of patients. In the continuous risankizumab and placebo/risankizumab cohorts, respectively, MDA was achieved by 33.0% and 33.3% of patients at week 100 and by 27.2% and 33.8% at week 52. Among MDA responders at week 52, maintenance of MDA response was achieved by 83.6% and 73.0% of the continuous risankizumab and placebo/risankizumab cohorts, respectively. Risankizumab was well tolerated through week 100.

Conclusions: Risankizumab demonstrated durable efficacy and tolerability through 100 weeks; most patients who achieved ACR20 and MDA responses at week 52 maintained this achievement through week 100. There were no new safety signals in patients who had csDMARD-IR and bDMARD-IR.

Trial Registration: ClinicalTrials.gov NCT03671148.

PLAIN LANGUAGE SUMMARY

Risankizumab, a biologic disease-modifying antirheumatic drug, helps control the body's immune system to reduce symptoms of psoriatic arthritis (a disease that inflames the joints of people who have the skin condition psoriasis). The ongoing KEEPsAKE 2 study is evaluating how well risankizumab works and how safe it is for treating adult patients with active psoriatic arthritis who previously experienced inadequate response to one or more specific types of disease-modifying anti-arthritis drugs. Patients were randomly assigned to receive either risankizumab or an inactive drug; after 24 weeks, all patients received risankizumab. At study week 100, 57% of patients who were assigned to receive continuous risankizumab since the start of the study experienced a 20% or more improvement in a measure of psoriatic arthritis symptoms using criteria established by the American College of Rheumatology (ACR20); a similar proportion of patients achieved a 20% improvement at both weeks 24 and 52. Similarly, 56% and 53% of patients who switched from inactive drug to risankizumab achieved ACR20 at weeks 52 and 100 (more than before switching to risankizumab at week 24). Minimal disease activity (MDA) was evaluated by assessing joint and skin symptoms, affected body surface area, pain, and physical function. At week 100, 33% of patients achieved MDA (both groups), which was similar to week 52. Most patients who achieved ACR20 or MDA at week 52 maintained responses at week 100. Improvements with risankizumab were seen in several other measures of treatment outcomes through week 100. Risankizumab was generally safe through 100 weeks.

Keywords: bDMARD-IR; csDMARD-IR; IL-23; KEEPsAKE 2; Long-term treatment; Psoriatic arthritis; Risankizumab

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Key Summary Points

Why carry out this study?

Patients with psoriatic arthritis require safe and effective long-term treatment.

We report the 100-week efficacy and safety results of the ongoing KEEPsAKE 2 study for adults with active psoriatic arthritis treated with risankizumab.

What was learned from the study?

Patients enrolled in the KEEPsAKE 2 study had previous inadequate response/intolerance to one or more conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR) and/or one or two biologic DMARDs (bDMARD-IR).

At week 100, risankizumab treatment demonstrated durable improvement in the signs and symptoms of psoriatic arthritis and was generally well tolerated with a long-term stable safety profile in patients with csDMARD-IR and/or bDMARD-IR.

INTRODUCTION

The systemic, chronic, inflammatory disease psoriatic arthritis (PsA) can affect joints, synovium, entheses, tendons, nails, and bones [1]. Progression can cause irreversible damage to joints leading to disability and reduced health-related quality of life, with higher burden of disease associated with increased total healthcare costs [2, 3].

There are several established treatment options for patients with PsA, including nonsteroidal anti-inflammatory drugs, glucocorticoid injections, and systemic therapies with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [4]. Unfortunately, some patients have PsA that is inadequately controlled with or intolerant to csDMARDs (csDMARD-IR) [4]; for these patients, biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted therapies are available, such as inhibitors of tumor necrosis factor, interleukin (IL)-17, IL-12/23, Janus kinase, and phosphodiesterase 4 [4].

Despite the diverse range of treatments for PsA, only one-third to one-half of people with PsA successfully achieve sustained minimal disease activity (MDA); patients with PsA without sustained MDA have higher risk of joint damage [5, 6], resulting in a continued need for long-term effective treatment options.

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that specifically inhibits IL-23 by binding to its p19 subunit [7–9]. The efficacy and safety of risankizumab continues to be evaluated in two ongoing, global, phase 3, multicenter, randomized clinical trials, KEEPsAKE 1 (NCT03675308) and KEEPsAKE 2 (NCT03671148), in adults with active PsA.

The KEEPsAKE 1 and KEEPsAKE 2 trials are being conducted in parallel; KEEPsAKE 1 enrolled patients with csDMARD-IR, and KEEPsAKE 2 enrolled patients with csDMARD-IR and/or patients with inadequate response or intolerance to bDMARDs (bDMARD-IR) [10, 11]. In the first 24-week placebo-controlled study period for both trials, risankizumab 150 mg was well tolerated and significantly improved key PsA disease outcomes compared with placebo in patients with csDMARD-IR and/or bDMARD-IR [10, 11]. Patients who had initially been randomized to receive placebo in both the KEEPsAKE 1 and KEEPsAKE 2 studies were switched at week 24 to receive risankizumab 150 mg, and at the 52-week analysis, risankizumab demonstrated robust, durable efficacy for patients with csDMARD-IR and/or bDMARD-IR; risankizumab continued to be well tolerated through each of the studies [12, 13].

Herein, we report updated data on the efficacy, safety, and tolerability of risankizumab through 100 weeks of treatment in the ongoing KEEPsAKE 2 trial.

METHODS

Study Design and Population

The study design, including inclusion and exclusion criteria, has been previously reported for KEEPsAKE 2, an ongoing, multicenter, double-blind, phase 3 trial [11, 13]. The week 100 data cutoff date was March 21, 2022. In brief, eligible patients were adults with active PsA who had demonstrated csDMARD-IR (one or more therapies) or bDMARD-IR (one or two therapies). The bDMARD-IR population was evaluated separately because achieving disease control in these patients may be difficult as their disease can be treatment refractory.

The KEEPsAKE 2 trial had two study periods. Period 1 was a 24-week, double-blind, placebo-controlled, parallel-group treatment period, and period 2 was an open-label period starting from week 24. In period 1, patients were randomized 1:1 to receive either placebo or risankizumab 150 mg at weeks 0, 4, and 16. In period 2, patients who were initially randomized to the placebo group received a blinded dose of risankizumab 150 mg at week 24, and patients who were initially randomized to risankizumab received a blinded dose of placebo. From week 28 onward, patients received open-label risankizumab 150 mg every 12 weeks. Since all patients received risankizumab during the open-label period, patients who were initially randomized to risankizumab are referred to as the "continuous risankizumab" cohort and those patients randomized to placebo and switched to risankizumab are referred to as the "placebo/risankizumab" cohort. As prespecified in the study protocol, patients with $< 20\%$ improvement in tender or swollen joint count for two consecutive visits on or after week 36 (since week 32 was the first visit that could be assessed) compared with baseline were discontinued from risankizumab.

Ethical Approval

The independent ethics committee or institutional review board at each study site (see Supplemental Table S1) approved the study protocol, informed consent forms, and recruitment materials before patient enrollment. The studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. All patients provided written informed consent at screening.

Efficacy Assessments

All efficacy analyses were conducted with data from all patients who received at least one dose of risankizumab. Efficacy assessments included measures of the signs and symptoms of PsA, specifically, the proportion of patients achieving $\geq 20\%$, $\geq 50\%$, and $\geq 70\%$ improvement from baseline in American College of Rheumatology criteria (ACR20, ACR50, and ACR70); resolution of enthesitis (Leeds Enthesitis Index [LEI] = 0, among patients with LEI > 0 at baseline); resolution of dactylitis (Leeds Dactylitis Index [LDI] = 0, among patients with LDI > 0 at baseline); and status of MDA (defined as fulfilling five of the following seven criteria: a tender joint count ≤ 1, a swollen joint count ≤ 1, Psoriasis Area and Severity Index [PASI] score ≤ 1 or affected body surface area $\leq 3\%$, patient's assessment of pain score measured using a visual analog score [VAS] ≤ 15 mm on a 100-mm scale, patient's global assessment of disease activity VAS ≤ 20 mm, Health Assessment Questionnaire–Disability Index [HAQ-DI] score ≤ 0.5, or LEI score ≤ 1). Skin clearance was assessed as achieving $\geq 90\%$ reduction in PASI (PASI 90) in patients with an affected body surface area $\geq 3\%$ at baseline.

Patient-reported outcomes included change from baseline in HAQ-DI scores, which measures physical function (lower scores indicate less disability), the proportion of patients achieving clinically meaningful improvement in HAQ-DI scores (≥ 0.35 decrease from baseline) in patients with ≥ 0.35 HAQ-DI scores at baseline, change from baseline in the 36-Item Short Form Health Survey Physical Component Summary score (SF-36 PCS; higher scores show less physical impairment), pain measured using a 100-mm VAS (score range 0–100; higher scores

indicating more pain), and the Functional Assessment of Chronic Illness Therapy–Fatigue Questionnaire score (FACIT-Fatigue; higher scores show less fatigue). All efficacy outcomes were assessed through week 100.

Safety Assessments

Safety was evaluated throughout the study as treatment-emergent adverse events (TEAEs; coded using the Medical Dictionary for Regulatory Activities version 24.1) and laboratory tests. TEAEs were defined as adverse events with an onset date on or after the first dose of study drug and up to 140 days after the last dose if the patient discontinued the study drug prematurely. Safety results are reported for all patients who received at least one dose of risankizumab 150 mg.

Safety data are described through the data cutoff dates for weeks 24 and 100 and are reported using exposure-adjusted event rates (events [E]/100 patient-years [PYs]). Laboratory abnormalities were classified by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

For efficacy endpoints, data through week 24 were reported using nonresponder imputation (NRI) with missing data due to COVID-19 handled by multiple imputation. Patients with data missing because of reasons other than COVID-19 or after intercurrent events (i.e., initiation of rescue medication or concomitant medications that could meaningfully impact efficacy assessment) were imputed as nonresponders and a mixed-effect model for repeated measures considering intercurrent events. Long-term analysis (weeks 24–100) used NRI with multiple imputation for missing data due to COVID-19 for categorical variables and mixed-effect model for repeated measures for continuous variables based on as observed data; all other missing data were treated as nonresponders. For all timepoints, continuous efficacy endpoints were analyzed using a mixed-effect model for repeated measures. All efficacy data were additionally evaluated using an as observed approach with no imputation of missing values. TEAEs were summarized using E/100 PYs.

RESULTS

Patient Disposition and Characteristics

At the start of study period 1443 patients were randomized and received ≥ 1 dose of study drug; of these patients, 414 (93.5%) entered the open-label study period 2. At the 100-week data cutoff date, there were 181/224 (80.8%) patients in the continuous risankizumab cohort and 164/219 (74.9%) patients in the placebo/risankizumab cohort continuing in the study. The most common reason for discontinuation of study participation in both treatment groups during period 2 was withdrawal of consent in 22/443 (5.0%) patients. Overall, the most common reason for discontinuation of study drug in period 2 (irrespective of whether they remained enrolled in the study) was not achieving a $\geq 20\%$ improvement in tender joint count or swollen joint count compared with baseline at two consecutive visits on or after week 36 (29/443 [6.5%]), per the protocol requirements for discontinuation.

Patient demographics and characteristics at baseline have been previously reported and were similar between treatment groups; the patients' median age was 53 (range 23–84) years, 55.1% of patients were female, and 46.5% of patients were bDMARD-IR [11].

Efficacy

As previously reported, the primary endpoint of the KEEPsAKE 2 study was met, with significantly more patients achieving ACR20 with risankizumab at week 24 compared with those patients receiving placebo (51.3% vs. 26.5%; $p < 0.001$); all secondary endpoints vs. placebo were also met ($p < 0.05$) [11].

Joint- and Skin-Related Endpoints

At week 100, the proportion of patients achieving ACR20 was 57.1% in the continuous risankizumab cohort and 52.5% in the placebo/risankizumab cohort, demonstrating a durable response from week 52 (60.0% and 55.8%, respectively) (Table 1; Fig. 1a). Additionally, 34.8% and 33.8% patients achieved ACR50 (Table 1; Fig. 1b), and 21.4% and 17.4% patients achieved ACR70 at week 100 (Table 1; Fig. 1c) in the continuous risankizumab and placebo/risankizumab cohorts, which were similar to the rates observed at week 52 (ACR50, 33.2% and 32.0%; ACR70, 17.1% and 21.0%) (Table 1; Fig. 1b, c). The high, durable responses in ACR20, ACR50, and ACR70 for both treatment cohorts over time through week 100 were also demonstrated when data were evaluated as observed with no imputation of missing values (Supplemental Fig. S1).

In patients who achieved an ACR20 response at week 52, 74.8% and 78.7% maintained this level of response at week 100 in the continuous risankizumab and placebo/risankizumab cohorts, respectively (Supplemental Table S2). Maintenance of response was also observed at week 100 for ACR50 in 72.2% and 68.6% of week 52 ACR50 responders and for ACR70 in 81.1% and 63.0% of week 52 ACR70 responders (Supplemental Table S2). Maintenance of response at week 100 for ACR20, ACR50, and ACR70 in week 52 responders was consistent with the as observed data (Supplemental Table S2).

Among patients with enthesitis (LEI $>$ 0) at baseline, resolution of enthesitis at week 100 had occurred in 51.7% (76/147) of those in the continuous risankizumab cohort and 53.2% (84/158) in the placebo/risankizumab cohort; the week 100 response rates for both cohorts were similar to resolution of enthesitis at week 52 (43.5% [64/147] and 52.5% [83/158], respectively) (Table 1). Similarly, among patients with dactylitis (LDI $>$ 0) at baseline, 77.5% (31/40) and 68.4% (39/57) of the continuous risankizumab and placebo/risankizumab cohorts achieved resolution of dactylitis at week 100 compared with 67.5% (27/40) and 71.5% (41/57) at week 52 (Table 1). Rates of resolution of enthesitis and dactylitis in both cohorts over time through week 100 were similar when data were evaluated as observed (Supplemental Table S3).

The proportion of patients who had a body surface area of psoriasis $\geq$ 3% at baseline who achieved PASI 90 at week 100 was 67.5% (83/123) of patients in the continuous risankizumab cohort and 61.3% (73/119) of patients in the placebo/risankizumab cohort; these response rates were similar at week 52 in both cohorts (65.0% [80/123] and 59.7% [71/119], respectively) (Table 1; Fig. 2) and were similar when data were evaluated as observed (Supplemental Fig. S2). Maintenance of PASI 90 response at week 100 was achieved in 84.8% and 84.5% of patients who had PASI 90 response at week 52 in the continuous risankizumab and placebo/risankizumab cohorts and were similar in the as observed dataset (Supplemental Table S2).

The benefits of risankizumab treatment were evident at week 100 in the subgroup of patients with bDMARD-IR, which typically represents a more difficult-to-treat population. Responses in the bDMARD-IR subgroup were generally consistent across joint- and skin-related efficacy endpoints through week 100 (Supplemental Table S4), with ACR20 achieved by 49.1% and 43.6% of patients with bDMARD-IR in the continuous risankizumab cohort and the placebo/risankizumab cohort, respectively.

Patient-Reported Outcomes

Patients reported less disability at week 100 than at baseline, as shown by the HAQ-DI scores. The change from baseline at week 100 in HAQ-DI scores was − 0.26 in the continuous risankizumab cohort and − 0.31 in the placebo/risankizumab cohort; these scores were sustained from week 52 (− 0.26 and − 0.34, respectively) (Table 1). Clinically meaningful improvements in HAQ-DI ($\geq$ 0.35 decrease from baseline) scores at week 100 were achieved in 39.8% and 46.5%, which were similar to week 52 (43.4% and 48.7% of patients in the continuous risankizumab cohort and the placebo/risankizumab cohort, respectively) (Table 1).

Similarly, patients reported less physical impairment at week 100 compared with baseline on the SF-36 PCS scores. The change from

Table 1 Efficacy results through week 100

Parameter	Week 24 (period 1)[a]		Week 52 (period 1 and 2)		Week 100 (period 1 and 2)	
	RZB ***n* = 224**	**PBO** ***n* = 219**	**Continuous RZB** ***n* = 224**	**PBO/RZB** ***n* = 219**	**Continuous RZB** ***n* = 224**	**PBO/RZB** ***n* = 219**
ACR20, *n* (%)	115 (51.3)***,†	58 (26.5)	135 (60.0)	122 (55.8)	128 (57.1)	115 (52.5)
(95% CI)	(44.8, 57.9)	(20.7, 32.4)	(53.6, 66.5)	(49.2, 62.4)	(50.7, 63.6)	(45.9, 59.1)
ACR50, *n* (%)	59 (26.3)***	20 (9.3)	74 (33.2)	70 (32.0)	78 (34.8)	74 (33.8)
(95% CI)	(20.3, 32.3)	(5.4, 13.2)	(27.0, 39.4)	(25.8, 38.1)	(28.6, 41.1)	(27.5, 40.1)
ACR70, *n* (%)	27 (12.0)*	13 (5.9)	38 (17.1)	46 (21.0)	48 (21.4)	38 (17.4)
(95% CI)	(7.7, 16.3)	(2.7, 9.0)	(12.1, 22.1)	(15.6, 26.4)	(16.1, 26.8)	(12.3, 22.4)
Resolution of enthesitis,[b,c] *n/N* (%)	63/147 (42.9)**	48/158 (30.4)	64/147 (43.5)	83/158 (52.5)	76/147 (51.7)	84/158 (53.2)
(95% CI)	(34.9, 50.9)	(23.2, 37.6)	(35.5, 51.6)	(44.7, 60.3)	(43.6, 59.8)	(45.4, 60.9)
Resolution of dactylitis,[c,d] *n/N* (%)	29/40 (72.5)***	24/57 (42.1)	27/40 (67.5)	41/57 (71.5)	31/40 (77.5)	39/57 (68.4)
(95% CI)	(58.7, 86.3)	(29.3, 54.9)	(53.0, 82.0)	(59.7, 82.0)	(64.6, 90.4)	(56.4, 80.5)
PASI 90,[e] *n/N* (%)	68/123 (55.0)***,†	12/119 (10.2)	80/123 (65.0)	71/119 (59.7)	83/123 (67.5)	73/119 (61.3)
(95% CI)	(46.2, 63.9)	(4.7, 15.6)	(56.6, 73.4)	(50.9, 68.5)	(59.2, 75.8)	(52.6, 70.1)
Change from baseline in HAQ-DI, mean	− 0.22***	− 0.05	− 0.26	− 0.34	− 0.26	− 0.31
(95% CI)	(− 0.28, − 0.15)	(− 0.12, 0.02)	(− 0.32, − 0.19)	(− 0.41, − 0.28)	(− 0.33, − 0.19)	(− 0.38, − 0.24)
Clinically meaningful improvement from baseline in HAQ-DI,[f] *n/N* (%)	78/196 (39.9)***	44/187 (23.6)	85/196 (43.4)	91/187 (48.7)	78/196 (39.8)	87/187 (46.5)
(95% CI)	(33.0, 46.8)	(17.5, 29.7)	(36.5, 50.3)	(41.5, 55.8)	(32.9, 46.6)	(39.4, 53.7)
Change from baseline in SF-36 PCS, mean	5.9***,†	2.0	6.3	7.3	6.4	6.5
(95% CI)	(4.9, 6.9)	(0.9, 3.1)	(5.2, 7.3)	(6.2, 8.4)	(5.3, 7.6)	(5.2, 7.7)
Change from baseline in patient's assessment of pain (VAS),[g] mean	− 14.7***	− 6.5	− 18.8	− 19.6	− 20.8	− 20.4
(95% CI)	(− 17.8, − 11.5)	(− 9.9, − 3.1)	(− 21.9, − 15.8)	(− 22.7, − 16.5)	(− 23.9, − 17.7)	(− 23.7, − 17.2)

Table 1 continued

Parameter	Week 24 (period 1)[a]		Week 52 (period 1 and 2)		Week 100 (period 1 and 2)	
	RZB *n* = 224	PBO *n* = 219	Continuous RZB *n* = 224	PBO/RZB *n* = 219	Continuous RZB *n* = 224	PBO/RZB *n* = 219
Change from baseline in FACIT-Fatigue, mean (95% CI)	4.9**,† (3.7, 6.0)	2.6 (1.4, 3.9)	5.7 (4.6, 6.9)	7.0 (5.8, 8.2)	5.4 (4.1, 6.7)	6.3 (5.0, 7.7)
MDA, *n* (%) (95% CI)	57 (25.6)***,† (19.9, 31.4)	25 (11.4) (7.2, 15.6)	61 (27.2) (21.4, 33.1)	74 (33.8) (27.5, 40.1)	74 (33.0) (26.9, 39.2)	73 (33.3) (27.1, 39.6)

The continuous RZB cohort was randomized to RZB 150 mg (period 1) and remained on RZB (period 2). The PBO/RZB cohort was randomized to placebo (period 1) and switched to RZB 150 mg (period 2). All changes are least squares mean changes from baseline. Results are based on the full analysis set, and NRI-C (week 24) or NRI-MI (weeks 52 and 100) were used for binary/categorical endpoints; MMRM was used for continuous variables based on as observed data

ACR20/50/70 ≥ 20%/≥ 50%/≥ 70% improvement in American College of Rheumatology criteria, *CI* confidence interval, *FACIT-Fatigue* Functional Assessment of Chronic Illness Therapy–Fatigue, *HAQ-DI* Health Assessment Questionnaire–Disability Index, *MDA* minimal disease activity, *MMRM* mixed-effect model for repeated measures, *NRI-C* nonresponder imputation incorporating multiple imputation where (1) missing data due to COVID-19 were handled by multiple imputation and (2) patients with data missing because of reasons other than COVID-19 or after intercurrent events (i.e., initiation of rescue medication or concomitant medications that could meaningfully impact efficacy assessment) were imputed as nonresponders and a mixed-effect model for repeated measures considering intercurrent events, *NRI-MI* nonresponder imputation incorporating multiple imputation for patients with missing data due to COVID-19, *PASI 90* ≥ 90% reduction in Psoriasis Area Severity Index, *PBO* placebo, *RZB* risankizumab, *SF-36 PCS* 36-item Short Form Health Survey Physical Component Summary, *VAS* Visual Analog Scale

*Nominal $p < 0.05$. **Nominal $p < 0.01$. ***Nominal $p < 0.001$. †Statistically significant under overall type I error control

[a]Results for 24 weeks previously reported [11]

[b]Defined as Leeds Enthesitis Index = 0

[c]Among patients with enthesitis or dactylitis at baseline (enthesitis at baseline: RZB, *n* = 147; PBO, *n* = 158; dactylitis at baseline: RZB, *n* = 40; PBO, *n* = 57)

[d]Defined as Leeds Dactylitis Index = 0

[e]Among patients with ≥ 3% body surface area affected by psoriasis at baseline (baseline: RZB, *n* = 123; PBO, *n* = 119)

[f]Improvement defined as HAQ-DI ≥ 0.35 decrease from baseline in patients with baseline HAQ-DI ≥ 0.35 (baseline: RZB, *n* = 224; PBO, *n* = 219)

[g]Improvement defined as decrease from baseline ≥ 10 mm in pain among patients with baseline pain VAS score (baseline: RZB, *n* = 224; PBO, *n* = 219)

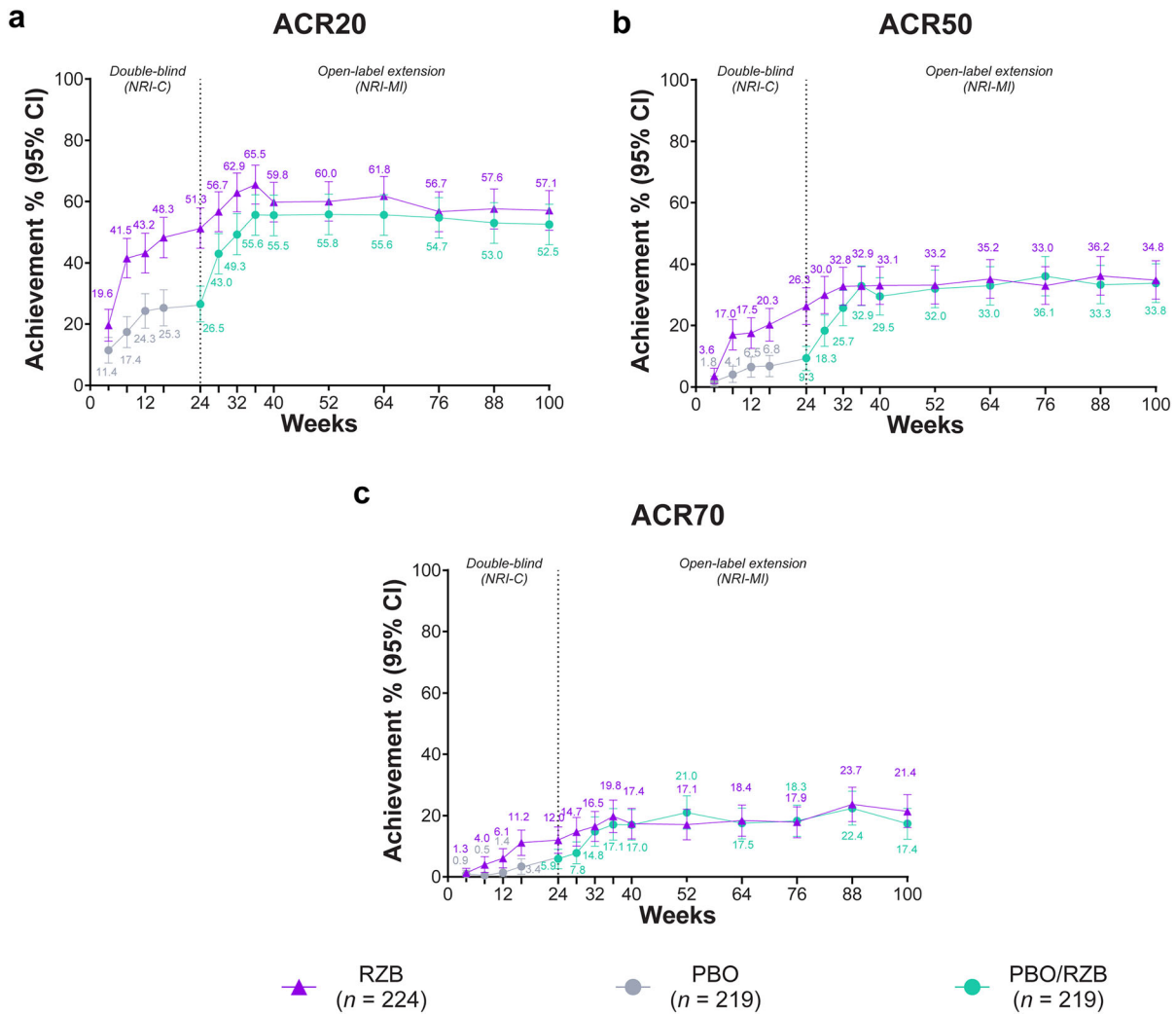

Fig. 1 ACR responses over time for risankizumab 150 mg and placebo over the 24-week, double-blind treatment period and for open-label continuous risankizumab and placebo/risankizumab cohorts from weeks 24 through 100 for **a** ACR20, **b** ACR50, and **c** ACR70 (full analysis set). Results are based on the full analysis set, and NRI-C (week 24) or NRI-MI (weeks 52 and 100) was used for binary/categorical endpoints. *ACR20/50/70* ≥ 20%/≥ 50%/≥ 70% improvement in American College of Rheumatology criteria, *CI* confidence interval, *NRI-C* nonresponder imputation incorporating multiple imputation where (1) missing data due to COVID-19 were handled by multiple imputation and (2) patients with data missing because of reasons other than COVID-19 or after intercurrent events (i.e., initiation of rescue medication or concomitant medications that could meaningfully impact efficacy assessment) were imputed as nonresponders and a mixed-effect model for repeated measures considering intercurrent events, *NRI-MI* nonresponder imputation incorporating multiple imputation for patients with missing data due to COVID-19, *PBO* placebo, *RZB* risankizumab

baseline to week 100 in SF-36 PCS scores was 6.4 and 6.5 in the continuous risankizumab and placebo/risankizumab cohorts, respectively, which were similar to week 52 (6.3 and 7.3) (Table 1).

Maintenance of response at week 100 in clinically meaningful improvements in patient's assessment of pain, defined as a decrease from baseline assessment of pain of ≥ 10 mm in pain VAS, was observed in 77.7%

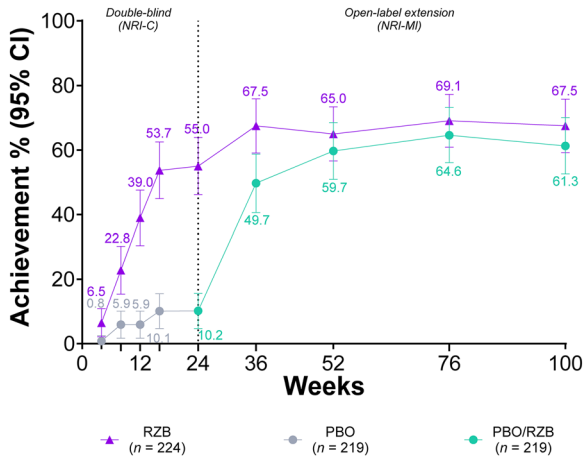

Fig. 2 PASI 90 response over time in patients with ≥ 3% body surface area affected by psoriasis at baseline receiving risankizumab 150 mg or placebo over the 24-week, double-blind treatment period and receiving open-label risankizumab 150 mg from weeks 24 through 100 (full analysis set). Results are based on the full analysis set, and NRI-C (week 24) or NRI-MI (weeks 52 and 100) was used for binary/categorical endpoints. *CI* confidence interval, *NRI-C* nonresponder imputation incorporating multiple imputation where (1) missing data due to COVID-19 were handled by multiple imputation and (2) patients with data missing because of reasons other than COVID-19 or after intercurrent events (i.e., initiation of rescue medication or concomitant medications that could meaningfully impact efficacy assessment) were imputed as nonresponders, and a mixed-effect model for repeated measures considering intercurrent events, *NRI-MI* nonresponder imputation incorporating multiple imputation for patients with missing data due to COVID-19, *PASI 90* ≥ 90% reduction in Psoriasis Area and Severity Index, *PBO* placebo, *RZB* risankizumab

and 78.2% of week 52 responders (Supplemental Table S2). Patient-reported pain was lower at week 100 compared with baseline assessments, with 20.8-mm and 20.4-mm reductions in the continuous risankizumab and placebo/risankizumab cohorts, respectively, which were similar to the reductions reported at week 52 (18.8 mm and 19.6 mm) (Table 1).

Patients continued to report less fatigue at week 100 compared with baseline. The change from baseline to week 100 in FACIT-Fatigue scores was 5.4 in the continuous risankizumab cohort and 6.3 in the placebo/risankizumab cohort, which were both consistent with week 52 (5.7 and 7.0, respectively) (Table 1).

The findings in HAQ-DI, SF-36 PCS, pain VAS, and FACIT-Fatigue were similar for both treatment cohorts over time through week 100 when data were evaluated as observed (Supplemental Table S3). The benefits of risankizumab treatment for patient-reported outcomes (HAQ-DI, SF-36 PCS, and FACIT-Fatigue) were still evident at week 100 in the subgroup of patients with bDMARD-IR, which typically represents a more difficult-to-treat population, and exhibited similar patterns of responses as the overall treatment cohorts (Supplemental Table S4).

Minimal Disease Activity

At week 100, the proportion of patients achieving MDA was 33.0% and 33.3% in the continuous risankizumab and placebo/risankizumab cohorts, respectively, which was similar to week 52 with 27.2% of patients in the continuous risankizumab cohort and 33.8% of patients in the placebo/risankizumab cohort achieving MDA (Table 1). When data were evaluated as observed, the overall trend in achieving MDA over time through week 100 was similar in both cohorts (Supplemental Table S3). Maintenance of MDA response at week 100 was achieved by 83.6% and 73.0% of week 52 responders in the continuous risankizumab and placebo/risankizumab cohorts, respectively, and the trend in maintenance of response for MDA was similar when data were evaluated as observed (Supplemental Table S2).

For patients in the bDMARD-IR subgroup, a lower proportion achieved MDA at week 100 (continuous risankizumab, 22.6%; placebo/risankizumab, 27.7%) compared with the overall treatment cohorts (Supplemental Table S4).

Safety

Overall, long-term safety data were available for 419 patients who received risankizumab (either continuous risankizumab or placebo/risankizumab cohorts at week 24), representing 810.1 PYs of exposure; with the additional PYs, rates remained stable and the long-term safety data at week 100 were generally consistent with

weeks 24 and 52 [11, 13]. The rate for any TEAEs in patients receiving risankizumab was 180.5 E/100 PYs after at least 100 weeks of exposure (Table 2).

The most common TEAEs (defined as ≥ 4.0 E/100 PYs) were COVID-19 infections (8.1 E/100 PYs), upper respiratory tract infections (5.2 E/100 PYs), psoriatic arthropathy (4.9 E/100 PYs), nasopharyngitis (4.2 E/100 PYs), and hypertension (4.2 E/100 PYs).

Serious TEAEs occurred at a rate of 9.9 E/100 PYs, and COVID-19-related TEAEs occurred at a rate of 8.9 E/100 PYs (Table 2). A total of 13 serious infections (1.6 E/100 PYs) were reported, with COVID-19 infection or COVID-19 pneumonia accounting for two of these 13 events. There were two events (0.2 E/100 PYs) of opportunistic infection (one event of clostridial sepsis and one event of oral fungal infection) and four events (0.5 E/100 PYs) of herpes zoster (Table 2), none of which required a study drug dose modification; of these, two opportunistic infections (one event of clostridial sepsis and one of herpes zoster) were new events since the

Table 2 Summary of safety during risankizumab treatment through week 100

Events (E/100 PYs)	Week 24		Long-term[a]	
	RZB 150 mg *n* = 224, PYs = 104.3		Any RZB[b] 150 mg *n* = 419, PYs = 810.1	
Any TEAE	286	(274.2)	1462	(180.5)
Serious TEAE	14	(13.4)	80	(9.9)
TEAE leading to discontinuation of study drug	2	(1.9)	10	(1.2)
COVID-19-related TEAE	1	(1.0)	72	(8.9)
MACE	1	(1.0)	4	(0.5)
Serious infections	3	(2.9)	13	(1.6)
Opportunistic infections				
Infections excluding TB and herpes zoster	0		2	(0.2)
Active TB	0		0	
Herpes zoster	0		4	(0.5)
Malignant tumors				
NMSC	1	(1.0)	13	(1.6)
Malignancies excluding NMSC	0		2	(0.2)
All deaths[c]	0		1	(0.1)

E events, *MACE* major adverse cardiovascular events, *NMSC* nonmelanoma skin cancer, *PYs* patient-years, *RZB* risankizumab, *TB* tuberculosis, *TEAE* treatment-emergent adverse event

TEAEs were defined as an adverse event with an onset date that is on or after the first dose of RZB and up to 140 days after the last dose of RZB if patient discontinued study drug prematurely

[a]Safety reported through data cutoff date (March 21, 2022), which includes data though week 100

[b]Any RZB includes the continuous RZB cohort, which was randomized to RZB 150 mg (period 1) and remained on RZB (period 2), and the PBO/RZB cohort, which was randomized to placebo (period 1) and switched to RZB 150 mg (period 2)

[c]In the long-term safety analysis set, one death was reported. The cause of death was cardiac arrest in a female patient aged 55 years with several cardiovascular risk factors including obesity, hypercholesterolemia, hypertension, smoking, and family history of cardiovascular disease who died on study day 616 (83 days after the last dose of RZB 150 mg)

52-week data cutoff date. There were no cases of active tuberculosis.

TEAEs leading to discontinuation of risankizumab occurred at a rate of 1.2 E/100 PYs (Table 2). Psoriatic arthropathy was the most common TEAE leading to discontinuation of study drug with four reported events (0.5 E/100 PYs).

Overall, four adjudicated major adverse cardiovascular events were reported (0.5 E/100 PYs) through the week 100 data cutoff date (Table 2); three of these events were reported at the 52-week cutoff date (two nonfatal myocardial infarctions and one nonfatal stroke) [13]. One major adverse cardiovascular event occurred since the week 52 cutoff date, which was a death due to cardiac arrest in a female patient aged 55 years with several cardiovascular risk factors including obesity, hypercholesterolemia, hypertension, and smoking. The patient died 83 days after the last dose of risankizumab, and the event was assessed as having no reasonable possibility of being associated with risankizumab by the investigator.

A total of 15 malignant tumors were reported (1.9 E/100 PYs) (Table 2); of these, four events of nonmelanoma skin cancer were newly reported since week 52. There were no new cases of grade ≥ 3 (i.e., > 5 times the upper limit of normal [ULN]) elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin between week 52 and week 100. No liver function tests met the criteria for biochemical Hy's Law (total bilirubin $> 2 \times$ ULN and ALT or AST $\geq 3 \times$ ULN).

DISCUSSION

Risankizumab demonstrated robust and durable efficacy across multiple disease domains through 100 weeks of treatment in adults with active PsA who previously had inadequate response to csDMARD or bDMARD in the ongoing KEEPsAKE 2 study. The proportion of patients with improvements from baseline in clinical signs and symptoms of PsA at week 100 was generally similar to the proportion of patients achieving improvements at weeks 24 and 52, including improvement in joint symptoms (ACR20/50/70), resolution of enthesitis and dactylitis, and improvement in skin clearance (PASI 90). Furthermore, most patients who achieved ACR20/50/70 and/or PASI 90 at week 52 maintained their responses at week 100. Additionally, improvements from baseline in patient-reported outcomes were generally similar at week 100 compared with weeks 24 and 52, reflecting reduced disability (HAQ-DI), physical impairment (SF-36 PCS), assessment of pain (VAS), and fatigue (FACIT-Fatigue). Most patients who had achieved a clinically meaningful reduction in pain VAS at week 52 maintained response at week 100. Similarly, MDA status at week 100 was achieved by 33.0% of patients in both treatment cohorts, which was similar to the proportion of patients who achieved MDA at week 52. The majority of patients who achieved MDA at week 52 maintained MDA response at week 100. A status of MDA provides an overview of the patient's general PsA extent and activity and is a composite measure of multiple disease domains including joints, skin, and health-related quality of life, which has been recommended by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis/Outcome Measures in Rheumatology Group for patient assessment [14].

The KEEPsAKE 2 study enrolled patients with previous bDMARD-IR or csDMARD-IR, and there were clinically meaningful improvements from baseline in the signs and symptoms of PsA in both groups; the efficacy of risankizumab was similar from week 52 to 100, and week 52 responders demonstrated maintenance of response through week 100. Patients who have failed a prior bDMARD therapy tend to experience lower treatment effectiveness on subsequent bDMARD treatments [15, 16], suggesting that the patients with bDMARD-IR PsA may have PsA that is harder to treat than PsA in bDMARD-naive patients, which is not unexpected in patients with chronic conditions who have experienced inadequate response or intolerance to treatments. Nevertheless, responses across all joint and skin endpoints were generally consistent from weeks 52 to 100 in patients with previous bDMARD-IR.

Risankizumab was generally well tolerated for long-term use in the KEEPsAKE 2 study, with no new safety signals identified through week 100, and a safety profile that was similar to both KEEPsAKE studies at weeks 24 and 52 [10–13], with the exception of treatment-emergent COVID-19 infections which increased from 1.0 E/100 PYs at week 24 to 8.9 E/100 PYs at week 100. Notably, this study was conducted during the COVID-19 pandemic. The week 24 data cutoff date in June 2020 [11] occurred 3 months after the pandemic was declared by the World Health Organization in March 2020 [17], leading to a period of lockdowns and social restrictions in many countries. By the week 100 cutoff date in March 2022, COVID-19 restrictions had eased in some countries and more contagious variants had emerged (Delta variant first detected in October 2020, and Omicron variant first detected in November 2021) [18]. The change in COVID-19 E/100 PYs between week 24 and week 100 mirror the changes observed in the average global rates of COVID-19 during the same period with 20.2 cases per million people in June 2020 increasing to 1157.7 cases per million people at the peak of Omicron variant infections in January 2022. No cases of active tuberculosis were reported, while cases of opportunistic infections including herpes zoster remained stable from weeks 52 to 100. Reports of major adverse cardiovascular events were also stable from weeks 52 to 100 [18]. One treatment-emergent death occurred between weeks 52 and 100 as a result of cardiac arrest in a patient with multiple cardiovascular risk factors including obesity, history of smoking, hypertension, hypercholesterolemia, and family history of cardiovascular disease, which was assessed by the investigators as not related to risankizumab. In a previous study, a higher incidence of nonmelanoma skin cancer was observed among patients with psoriasis (129 E/10,000 PYs) compared with the general population (78 E/10,000 PYs) [19]. In our study, there were only four new cases of nonmelanoma skin cancer between week 52 and week 100.

The progressive nature of PsA, with the possibility of permanent damage to joints [2] and the intolerance or failure of current therapies for some patients [4], highlights the continued need for treatments with sustained long-term efficacy and safety outcomes. In the ongoing KEEPsAKE 2 trial, risankizumab has demonstrated durable efficacy and tolerability through week 100 in patients with PsA that have previously demonstrated csDMARD-IR (one or more therapies) or bDMARD-IR (one or two therapies).

There are some potential limitations of the study. As is typical with randomized controlled trials, the patient population was relatively homogenous, which potentially limits the generalizability of the study results. During the double-blind, placebo-controlled period of the study (period 1), the COVID-19 pandemic caused logistical issues in most countries, which resulted in more missing data than had been anticipated. The missing data were addressed in the data analysis by adjusting the multiple imputation method. No patients missed the week 100 visit as a result of the COVID-19 pandemic. In addition, there was bias towards responders because patients who experienced $< 20\%$ improvement from baseline in tender/swollen joint count for two consecutive visits on or after week 36 were discontinued from treatment. However, patients with missing efficacy results were imputed as nonresponders.

CONCLUSIONS

Results from the KEEPsAKE 2 trial showed treatment with risankizumab through week 100 provided durable improvement in the signs and symptoms of PsA and maintenance of response at week 100 in patients who achieved ACR20/50/70, PASI, clinically meaningful reduction in pain VAS, and MDA at week 52 in adults with active disease with csDMARD-IR and/or bDMARD-IR. Risankizumab has demonstrated an acceptable, stable, long-term safety profile and was generally well tolerated. The KEEPsAKE 2 study remains ongoing for continued efficacy and safety analysis.

ACKNOWLEDGEMENTS

AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study

Medical Writing and Editorial Assistance. Medical writing support was provided by Abegale Templar, PhD, and Ray Beck, Jr, PhD, of JB Ashtin and Trisha Rettig, PhD, of AbbVie, and funded by AbbVie.

Author Contributions. AÖ, FVandenB, KP, CA, RB, JA, KC, VS, RL, LD, AMS, MMC, BP, and AK: had access to the data and participated in interpreting the data and drafting, reviewing, and approving this manuscript for publication. No honoraria or payments were made for authorship. In addition, AÖ and AMS: participated in the design/conception of this study. FVandenB, KP, CA, RB, JA, AS, and AK: were involved in data acquisition. KC: provided statistical analyses of study data.

Funding. AbbVie funded this study and participated in the study design, study research, data collection, analysis, and interpretation of data, reviewing, and approval of this manuscript. The Rapid Service Fee of this manuscript was funded by AbbVie.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized individual and trial-level data (analysis data sets), as well as other information (e.g., 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. These 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 USA and Europe and after acceptance of this manuscript for publication. These 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://vivli.org/ourmember/abbvie/ then select "Home."

Declarations

Conflict of Interest. Andrew Östör has received speaker or consulting fees and/or research grants from AbbVie, Bristol Myers Squibb, Janssen, Lilly, Novartis, Pfizer, and UCB. Filip Van den Bosch has received speaker and/or consulting fees from AbbVie, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and UCB. Kim Papp has received research funds from AbbVie, Aceleryn, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Coherus, Dermavant, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Novartis, Ortho Dermatologics, Pfizer, Sanofi Genzyme, Sun Pharma, and UCB. He is a consultant for AbbVie, Aceleryn, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Coherus, Dermavant, Forward Pharma, Galderma, Incyte, Janssen, LEO Pharma, Lilly, Meiji Seika Pharma, Merck, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Sandoz, Sanofi Genzyme, Sun Pharma, Takeda, and UCB. He is a speaker for AbbVie, Amgen, Arcutis, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Incyte, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi Genzyme, Sun Pharma, and UCB. He is a committee member for PSOLAR (Psoriasis Longitudinal Assessment and Registry) and PURE (registry of patients with moderate-to-severe chronic plaque psoriasis in Latin America and Canada). Cecilia Asnal has received honoraria or fees for serving on advisory boards or as a speaker, as well as research support from AbbVie, Amgen, Genentech, Janssen, Lilly, Pfizer, Roche, and R-Pharm. Ricardo Blanco has received grants or research support from AbbVie, Merck, and Roche. He has received consultation fees or honoraria for serving as a speaker for AbbVie, Bristol Myers Squibb, Janssen, Lilly, Merck, Pfizer and Roche. Jacob Aelion has received grants or research support from AbbVie, Amgen, AstraZeneca, Bristol Myers

Squibb, Galapagos/Gilead, Genentech, GlaxoSmithKline, Lilly, Mallinckrodt, Nektar Therapeutics, Nichi-Iko, Novartis, Pfizer, Regeneron, Roche, Sanofi, Selecta Biosciences, and UCB. Kyle Carter, Vassilis Stakias, Ralph Lippe, Leonidas Drogaris, Ahmed M. Soliman, Michael M. Chen, and Byron Padilla are full-time employees of AbbVie and may hold AbbVie stock or stock options or AbbVie patents. Alan Kivitz has received consulting fees from Horizon, Frescenius Kabi, Pfizer, GlaxoSmithKline, Janssen, Selecta, Genzyme, Gilead, Synact, Takeda, and Grunenthal; has received honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from GlaxoSmithKline, Eli Lilly, Pfizer, AbbVie, Amgen, and UCB; has served on boards or advisory boards for Horizon, Janssen, Chemocentryx, Princeton Biopartners, UCB, and Novartis; and has stock or stock options in Pfizer, GSK, Gilead, Novartis, and Amgen.

Ethical Approval. The independent ethics committee or institutional review board (see Supplemental Table S1) at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrollment. The studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. All patients provided written informed consent at screening.

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