results were maintained or further improved from week 24 to 52 for both limited and extensive SJC patients (**Figure 1**)

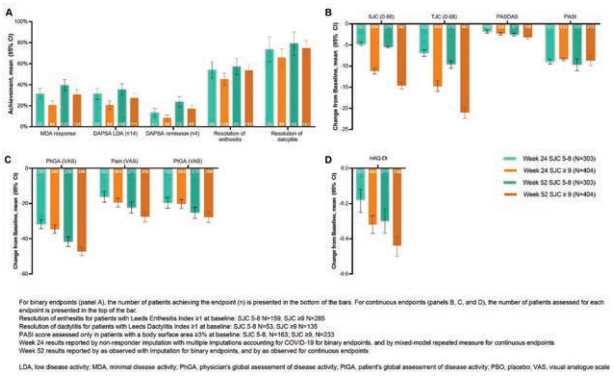
Conclusion: RZB is efficacious in reducing signs and symptoms of PsA in patients, regardless of patterns of joint involvement. More patients in the limited joint involvement group achieved stringent treatment targets such as MDA and DAPSA remission at both weeks 24 and 52.

Table 1. Baseline Disease Characteristics

	SJC 5-8 (N=303)	SJC ≥9 (N=404)
SJC66	6.5 (1.1)	16.8 (8.3)
TJC68	13.4 (9.4)	27.5 (14.5)
DAPSA	31.5 (11.3)[a]	57.3 (21.4)
PASDAS[b]	5.8 (0.9)	6.8 (1.1)
LEI[c]	2.3 (1.3)	3.1 (1.5)
LDI[d]	54.1 (60.8)	110.3 (128.3)
PASI[e]	10.5 (9.6)	9.5 (9.0)
HAQ-DI	1.0 (0.6)[a]	1.3 (0.6)
PhGA (VAS)[f]	58.3 (18.0)	64.5 (16.6)
PtGA (VAS)	54.1 (22.2)[a]	59.8 (21.2)
Pain (VAS)	51.6 (23.0)	60.0 (22.1)

All parameters are mean (SD)[a]N = 302[b]SJC 5-8, N=148; SJC ≥9, N=220[c]For pts with LEI >0 at BL; SJC 5-8, N=159; SJC ≥9, N=285[d]For pts with LDI >0 at BL; SJC 5-8, N=53; SJC ≥9, N=135[e]For pts with BSA ≥3% at BL; SJC 5-8, N=163; SJC ≥9, N=233[f]SJC 5-8, N=290; SJC ≥9, N=395LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PASDAS, PsA Disease Activity Score; VAS, visual analogue scale.

Figure. Efficacy Endpoints at Weeks 24 and 52 in Patients With Limited and Extensive Joint Involvement



For binary endpoints (panel A), the number of patients achieving the endpoint (n) is presented in the bottom of the bars. For continuous endpoints (panels B, C, and D), the number of patients assessed for each endpoint is presented in the top of the bar.
Resolution of enthesitis for patients with Leeds Enthesitis Index ≥1 at baseline: SJC 5-8 N=159, SJC ≥9 N=285
Resolution of dactylitis for patients with Leeds Dactylitis Index ≥1 at baseline: SJC 5-8 N=53, SJC ≥9 N=135
PASI score assessed only in patients with a body surface area ≥3% at baseline: SJC 5-8, N=163, SJC ≥9, N=233
Week 24 results reported by non-responder imputation with multiple imputations accounting for COVID-19 for binary endpoints, and by mixed-model repeated measure for continuous endpoints
Week 52 results reported by as observed with imputation for binary endpoints, and by as observed for continuous endpoints

LDA, low disease activity; MDA, minimal disease activity; PhGA, physician's global assessment of disease activity; PtGA, patient's global assessment of disease activity; PBO, placebo; VAS, visual analogue scale

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POS1544

LONG-TERM SAFETY AND EFFICACY OF TOFACITINIB IN PATIENTS WITH PSORIATIC ARTHRITIS BY PRIOR BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUG EXPOSURE

Keywords: Targeted synthetic drugs, Psoriatic arthritis, bDMARD

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Background: Patients (pts) with psoriatic arthritis (PsA) exposed to tumour necrosis factor inhibitors (TNFi) may have attenuated response or higher adverse event (AE) risk with subsequent treatment. Tofacitinib efficacy/safety in PsA pts was shown in 3 Phase (P)3 trials and 1 long-term extension (LTE) trial.

Objectives: Assess long-term safety/efficacy of tofacitinib in TNFi-inadequate responder (IR) and biologic disease-modifying antirheumatic drug (bDMARD)-naïve PsA pts.

Methods: Pooled data from P3 trials (NCT01877668/NCT01882439/NCT03486457) of PsA pts receiving ≥1 tofacitinib dose and 1 LTE trial (NCT01976364) of PsA pts receiving tofacitinib 5 mg BID (dose switching allowed after 1 month) were stratified by TNFi-IR or bDMARD-naïve status at P3 trial baseline (BL). Safety assessed in P3/LTE trials. Efficacy assessed in LTE trial only to Month (M)36 (longitudinal models, data as observed): MDA and HAQ-DI (≥0.35 improvement) response rates and change from BL (Δ) in PASDAS. Data reported as all tofacitinib (pts receiving ≥1 tofacitinib dose) or constant tofacitinib 5 mg BID (pts assigned to tofacitinib 5 mg BID in P3/LTE trials or placebo→tofacitinib 5 mg BID in P3 trials and maintained this dose).

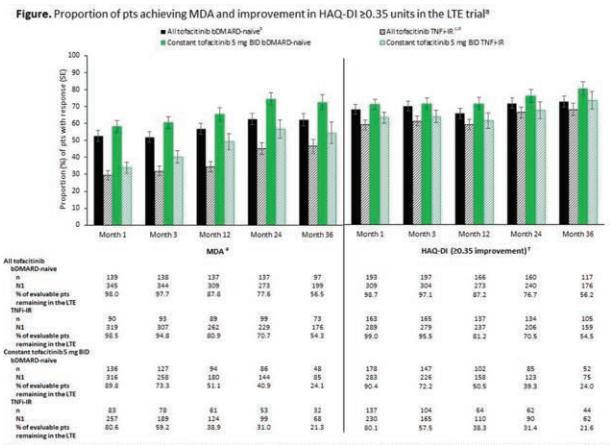
Results: 408 TNFi-IR (incl. 29 TNFi-exposed with unknown IR status) and 562 bDMARD-naïve pts from P3/LTE trials were assessed. Differences in P3 trial BL characteristics in TNFi-IR vs bDMARD-naïve pts included longer disease duration (all tofacitinib, mean: 8.9 vs 5.6 years), higher HAQ-DI scores (mean: 1.2 vs 0.9) and a higher proportion (%) of pts aged ≥65 years (9.6 vs 7.7) and from North America (27.5 vs 8.0). Treatment-emergent AE (TEAE) incidence rates were higher in TNFi-IR vs bDMARD-naïve pts; serious AE (SAE), serious infection (SI) and herpes zoster (HZ; all tofacitinib) incidence rates were numerically higher in TNFi-IR vs bDMARD-naïve pts (confidence intervals [CIs] overlapped; Table 1). Deaths, malignancies excl. non-melanoma skin cancer (NMSC), NMSC, major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) events were observed (Table 1). Tofacitinib response/improvements were sustained to M36 in pts remaining in LTE trial, regardless of prior treatment. At all time points, TNFi-IR vs bDMARD-naïve pts had lower MDA response rates and slightly lower HAQ-DI response rates (Figure 1) and ΔPASDAS (all tofacitinib/constant tofacitinib 5 mg BID: M1 -2.3/-2.5 vs -2.9/-3.0; M6 -2.5/-2.8 vs -3.0/-3.1; M12 -2.7/-2.9 vs -3.0/-3.2; M24 -2.9/-3.1 vs -3.2/-3.4; M36 -3.0/-3.2 vs -3.1/-3.4).

Table 1. Safety in P3/LTE trials[a]

	All tofacitinib		Constant tofacitinib 5 mg BID	
	TNFi-IR[b] N=408 899 PY	bDMARD-naïve[c] N=562 1255 PY	TNFi-IR N=217 282 PY	bDMARD-naïve N=325 422 PY
n Incidence rate (95% CI)				
TEAE	373 181.8 (163.8, 201.2)	457 117.8 (107.3, 129.1)	180 219.6 (188.7, 254.2)	240 161.2 (141.5, 183.0)
SAE	67 8.2 (6.4, 10.5)	71 6.0 (4.7, 7.6)	25 9.5 (6.1, 14.0)	23 5.6 (3.6, 8.4)
Death	1 0.1 (0.0, 0.6)	1 0.1 (0.0, 0.4)	1 0.4 (0.0, 2.0)	1 0.2 (0.0, 1.3)
SI	13 1.5 (0.8, 2.5)	11 0.9 (0.4, 1.6)	5 1.8 (0.6, 4.1)	5 1.2 (0.4, 2.8)
HZ	19 2.2 (1.3, 3.4)	19 1.6 (0.9, 2.4)	4 1.5 (0.4, 3.7)	6 1.4 (0.5, 3.1)
Malignancies excl. NMSC[d]	3 0.3 (0.1, 1.0)	12 1.0 (0.5, 1.7)	2 0.7 (0.1, 2.5)	5 1.2 (0.4, 2.8)
NMSC[d]	7 0.8 (0.3, 1.6)	9 0.7 (0.3, 1.4)	4 1.4 (0.4, 3.6)	2 0.5 (0.1, 1.7)
MACE[d]	2 0.2 (0.0, 0.8)	4 0.3 (0.1, 0.8)	0 0.0 (0.0, 1.3)	3 0.7 (0.2, 2.1)
VTE	0 0.0 (0.0, 0.4)	2 0.2 (0.0, 0.6)	0 0.0 (0.0, 1.3)	0 0.0 (0.0, 0.9)

[a]Concomitant csDMARD required at start of P3 trials; allowed but not required in LTE trialMedian exposure (range), days: [b]988 (1, 1544); [c]744 (1, 1715)[d]Adjudicatedn, number of pts with events; PY, pt-years

Figure. Proportion of pts achieving MDA and improvement in HAQ-DI ≥0.35 units in the LTE trial[a]



	MDA[e]					HAQ-DI (≥0.35 improvement)[f]				
All tofacitinib bDMARD-naïve										
n	139	138	137	137	97	193	197	166	160	117
N1	345	344	309	273	199	309	304	273	240	176
% of evaluable pts remaining in the LTE	98.0	97.7	87.8	77.6	56.5	98.7	97.1	87.2	76.7	56.2
TNFi-IR										
n	90	93	89	99	73	163	165	137	134	105
N1	319	307	262	229	176	289	279	237	206	159
% of evaluable pts remaining in the LTE	98.5	94.8	80.9	70.7	54.3	99.0	95.5	81.2	70.5	54.5
Constant tofacitinib 5 mg BID bDMARD-naïve										
n	136	127	94	86	48	178	147	102	85	52
N1	316	258	180	144	85	283	226	158	123	75
% of evaluable pts remaining in the LTE	89.8	73.3	51.1	40.9	24.1	90.4	72.2	50.5	39.3	24.0
TNFi-IR										
n	83	78	61	53	32	137	104	64	62	44
N1	257	189	124	99	68	230	165	110	90	62
% of evaluable pts remaining in the LTE	80.6	59.2	38.9	31.0	21.3	80.1	57.5	38.3	31.4	21.6

Analysis was assessed by generalised linear models with repeated measures and mixed effects using a logistic regression model, fitted to include treatment group, prior DMARD or bDMARD use, sex and region, and a two-way interaction between prior DMARD or bDMARD use and visit, as covariates.
Data were as observed.
[a]Pts enrolled into the LTE trial had completed or discontinued NCT03778658/NCT03829709 for reasons other than an AE related to the trial drug. Pts received tofacitinib 5 mg BID and could adjust the dose to tofacitinib 10 mg BID after 1 month for efficacy reasons; dose adjustments from tofacitinib 10 mg BID to tofacitinib 5 mg BID could occur thereafter for safety reasons. Concomitant csDMARD was allowed but not required. 'All tofacitinib' groups in the efficacy analyses included pts receiving tofacitinib 5 or 10 mg BID in the LTE trial (in the safety analyses, pts exposed to either tofacitinib dosage in the P3 trials were included as well). 'Constant tofacitinib' groups included pts who initiated and maintained the tofacitinib 5 mg BID dose in the LTE trial (in the safety analyses, pts randomised to tofacitinib 5 mg BID or received tofacitinib 5 mg BID following placebo, and maintained this dose were also included)
[b]Most common reasons for discontinuation were AE(s) (8.2%), no longer willing to participate in the trial (6.6%) and insufficient clinical response (2.6%)
[c]Most common reasons for discontinuation were insufficient clinical response (8.0%), AE(s) (3.0%) and no longer willing to participate in the trials (6.2%)
[d]1 pt was previously exposed to TNFi although IR status was unknown (pts from NCT03486847 were excluded from the efficacy analyses)
[e]All tofacitinib bDMARD-naïve, N=392; all tofacitinib TNFi-IR, N=324; constant tofacitinib 5 mg BID bDMARD-naïve, N=352; constant tofacitinib 5 mg BID TNFi-IR, N=319
[f]All tofacitinib bDMARD-naïve, N=313; all tofacitinib TNFi-IR, N=292; constant tofacitinib 5 mg BID bDMARD-naïve, N=313; constant tofacitinib 5 mg BID TNFi-IR, N=287
BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; MDA, minimal disease activity; N, number of evaluable pts at BL LTE trial; N1, number of evaluable pts at each visit; n, number of pts with response; SE, standard error

Conclusion: For pts remaining in LTE trial, tofacitinib efficacy was greater in bDMARD-naïve vs TNFi-IR pts; response was maintained over time in both groups. Incidence rates were higher for TEAEs and numerically higher for SAE, SI and HZ (all tofacitinib) in TNFi-IR vs bDMARD-naïve pts. Results consistent with other advanced PsA treatments. Limitations included small event numbers, as observed data and BL characteristic differences.

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POS1545

MODULATION OF SERUM BIOMARKERS IN PATIENTS WITH PSA TREATED WITH RISANKIZUMAB IN THE PHASE 3 KEEPSAKE 2 STUDY

Keywords: Psoriatic arthritis, Biomarkers, Clinical trials

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Background: Risankizumab (RZB) is a selective interleukin (IL) 23 p19 subunit monoclonal antibody that inhibits IL-23. RZB 150 mg has shown greater improvements in key clinical domains such as skin, joints, enthesitis, and dactylitis compared with placebo (PBO) in patients with active psoriatic arthritis (PsA) in the global phase 3 trials KEEPsAKE 1 (NCT03675308) and KEEPsAKE 2 (NCT03671148) [1,2].

Objectives: To elucidate the mode of action of RZB in patients with PsA by assessing the dynamics of circulating protein biomarkers in the KEEPsAKE 2 study.

Methods: Serum samples from patients who participated in the optional biomarker exploratory analysis in the KEEPsAKE 2 study (PBO, n=189; RZB 150 mg, n=183) were used for this analysis. A commercially available multiplexed Proximity Extension Assay platform was used to assess the levels of 92 inflammation-related protein biomarkers (BMs) and a validated immunoassay was used to evaluate beta-defensin 2 (BD-2) in serum samples collected at baseline, week 4, and week 24. Changes from baseline in protein levels were expressed as log2 fold change. A repeated measure mixed linear model was used to determine BMs modulated by RZB. Correlations between relative BM levels and disease activity measures were derived using Pearson's correlation; Psoriasis Area and Severity Index (PASI) was transformed as log10 (x+1) before the analysis.

Results: Key demographics and baseline characteristics for the subset of patients included in the biomarker evaluation were comparable between PBO and RZB and were consistent with those reported in the total population for the clinical study. At baseline, the relative levels of 10 BMs (chemokine ligand 20 [CCL20], IL-17A, IL-17C, IL-24, IL-6, S100 calcium-binding protein A12 [S100A12], oncostatin M [OSM], vascular endothelial growth factor A [VEGF-A], C-X-C motif chemokine ligand 1 [CXCL1] and colony stimulating factor 1 [CSF-1]) positively correlated with at least 1 baseline disease activity measure. IL-6 was significantly and positively correlated with the inflammation marker high sensitivity C-reactive protein [hsCRP]) and musculoskeletal endpoint (Psoriatic Arthritis Disease Activity Score [PASDAS]). CCL20, IL-17A, IL-17C, and BD-2 (BMs known to contribute to psoriasis) were correlated with baseline PASI. RZB treatment significantly decreased IL-17A, IL-17C, IL-6, and BD-2 compared with PBO treatment at week 4 (the earliest time-point when samples were available), with further decreases continuing through week 24 (**Figure 1**). In patients with PsA treated with RZB the decrease in IL-6 correlated with PASDAS improvement, while the decrease in BD-2 correlated with PASI improvement.

Conclusion: IL-23, a cytokine that is important in the generation, maintenance, and proliferation of Th17 cells, serves as a major contributor to the pathophysiology of PsA [3]. Treatment with the IL-23 inhibitor RZB downregulated biomarkers associated with musculoskeletal and skin-related disease activity, and resulted in a favorable clinical response for patients with active PsA. Further investigation is needed to assess the possible relationship between changes in IL-23–related biomarkers at week 4 and long-term clinical response.

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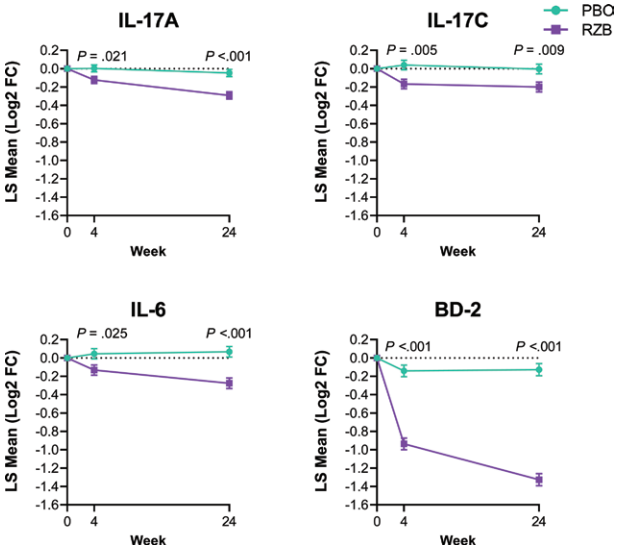

Figure 1. Biomarkers decreased following treatment with RZB compared with PBO. Nominal *P* values compare RZB and PBO at weeks 4 and 24. FC, fold change; IL, interleukin; LS, least squares; PBO, placebo; RZB, risankizumab.

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