



Ixekizumab With Tirzepatide Achieved Greater Disease Control Than Ixekizumab Alone in Adults With Psoriatic Arthritis and Overweight or Obesity: Results From a Randomized Clinical Trial

Joseph F. Merola, MD, MMSc, FAAD, FACR,¹ Philip Mease, MD,²  Alan Kivitz, MD, MACR,³ Naveed Sattar, FMedSci,⁴ Laura C. Coates, MBChB, PhD,⁵  Daniel Aletaha, MD, MS, MBA,⁶ Cynthia E. Kartman, RN,⁷ Peter Fischer, MD,⁷ Luna Sun, PhD,⁷ Píndaro Martínez-Osuna, MD,⁷ Andris Kronbergs, PhD,⁷ Purvi Prajapati, PhD,⁷ Anabela Cardoso, MD,⁷ Mark C. Genovese, MD,⁷ and Alexis Ogdie, MD, MSCE⁸

Objective. Overweight or obesity is prevalent in 72% to 82% of individuals with psoriatic arthritis (PsA). We assessed the efficacy and safety of ixekizumab (IXE) concomitantly administered with tirzepatide (TZP) compared with IXE alone in adult participants with active PsA and overweight with at least one weight-related comorbidity or obesity.

Methods. TOGETHER-PsA ([ClinicalTrials.gov](#) identifier: NCT06588296) is a phase 3b, randomized, 52-week trial in adults with active PsA and overweight (body mass index [BMI] ≥ 27 to < 30) with at least one weight-related comorbidity or obesity (BMI ≥ 30) using US-approved doses for IXE and TZP. The primary end point was simultaneous achievement of 50% improvement in American College of Rheumatology response criteria (ACR50) and $\geq 10\%$ weight reduction at 36 weeks. Key secondary outcomes included ACR50. Additional secondary outcomes and patient-reported outcomes (PROs) were assessed. Safety was assessed as adverse events (AEs), treatment-emergent AEs, and serious AEs.

Results. A total of 271 participants were randomized (IXE + TZP, $n = 138$; IXE, $n = 133$). The primary end point was achieved with significant improvements in the IXE + TZP arm (31.7%) compared to IXE alone (0.8%) ($P < 0.001$). Greater improvements in ACR50 were demonstrated in IXE + TZP (33.5%) versus IXE alone (20.4%) ($P = 0.02$), with significant early separation at week 4 (nominal $P < 0.05$). IXE + TZP demonstrated nominally significant improvements in ACR20 ($P < 0.001$), minimal disease activity ($P < 0.05$), and absolute Psoriasis Area and Severity Index score ($P < 0.01$) compared to IXE alone. IXE + TZP demonstrated significant improvements in PROs, including Health Assessment Questionnaire–Disability Index ($\Delta -0.2$; nominal $P < 0.001$) and Functional Assessment of Chronic Illness Therapy–Fatigue (improvement of 3.8; nominal $P < 0.01$) compared to IXE alone. Safety profiles were consistent with previous studies for each drug.

Conclusion. Participants with active PsA and complex inflammatory-metabolic disease achieved clinically meaningful improvement of PsA, physical function, weight reduction, and quality of life when treated with IXE + TZP compared to IXE alone, with no new safety concerns.

[ClinicalTrials.gov](#) identifier NCT06588296.

Supported by Eli Lilly and Company.

¹Department of Dermatology and Department of Medicine, Division of Rheumatology, University of Texas Southwestern Medical Center and O'Donnell School of Public Health, Dallas; ²Department of Rheumatology, Providence-Swedish Medical Center and University of Washington, Seattle; ³Altoona Center for Clinical Research, Duncansville, Pennsylvania; ⁴School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom; ⁵Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; ⁶Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; ⁷Eli Lilly and Company, Indianapolis,

Indiana; ⁸Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request six months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory disease characterized by synovitis, enthesitis, dactylitis, spondylitis, and coexisting psoriasis (PsO). Additionally, up to 30% to 40% of individuals with PsO develop PsA.^{1,2} These manifestations contribute to joint pain, swelling, and potential irreversible structural damage when inadequately treated.³ Patients with enthesitis, dactylitis, or substantial peripheral involvement often experience poorer general health and reduced quality of life (QoL).⁴ PsA is further complicated by a higher burden of cardiometabolic comorbidities, including obesity, hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease (CVD), and nonalcoholic fatty liver disease compared to the general population.^{3,5}

Overweight or obesity is disproportionately prevalent in PsA compared with the general population, with estimates ranging⁶ from 72% to 82% (Curtis J, et al: unpublished observations). Obesity is associated with increased prevalence of PsA up to two-fold higher compared to those with normal weight, which highlights obesity as a key modifiable risk factor⁷ (Curtis J, et al: unpublished observations). Obesity promotes a chronic, low-grade inflammatory state through adipokine release and up-regulation of cytokines such as tumor necrosis factor α (TNF α), interleukin-17 (IL-17), and IL-6,⁸ while mechanical stress at enthesal sites and reduced physical activity exacerbate musculoskeletal symptoms. Conversely, inflammation associated with PsA can contribute to weight gain and increased cardiovascular risk, emphasizing the link between these conditions.^{9,10}

The coexistence of obesity and active PsA is clinically important, as higher body weight is associated with increased disease activity, attenuated response to biologic therapies, reduced likelihood of achieving minimal disease activity (MDA), and greater cardiovascular morbidity.¹¹ Obesity has been shown to negatively influence treatment response to biologics, such as TNF α inhibitors¹² and IL-17 inhibitors, although ixekizumab (IXE) maintains efficacy across body mass index (BMI) categories despite reduced absolute response rates in individuals with obesity.¹³ Weight loss of $\geq 5\%$ has been associated with improved PsA outcomes, including higher rates of MDA and reductions in proinflammatory mediators.^{14–16} Consequently, major international guidelines (American College of Rheumatology [ACR]/National Psoriasis Foundation, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis [GRAPPA], the EULAR) advocate for assessment and management of obesity as part of comprehensive PsA care.^{17–19}

IXE, a humanized monoclonal antibody targeting IL-17A,²⁰ is an established therapy for PsA, demonstrating efficacy in biologic-naïve and TNF inhibitor-experienced populations, superiority over adalimumab in a head-to-head trial, and sustained long-term benefit.^{21–28} Tirzepatide (TZP), a long-acting dual glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide 1 (GLP-1) receptor agonist,²⁹ is approved for treatment of overweight in the presence of at least one weight-related comorbid condition or obesity and produces substantial, durable weight reduction accompanied by improvements in cardiometabolic risk factors and physical function.^{30–33} TZP has also demonstrated anti-inflammatory effects, including reductions in high-sensitivity C-reactive protein (hsCRP) and IL-6 levels.³⁴ TZP has demonstrated superiority to semaglutide in participants with obesity and without diabetes mellitus in reduction in body weight and waist circumference at 72 weeks.³⁵

Given the interplay between obesity, systemic inflammation, and PsA disease activity, use of an IL-17A inhibitor with an effective weight loss therapy may offer additive clinical benefits. IXE and TZP were used to treat two comorbid conditions, PsA and overweight/obesity, in this trial. Therefore, a multicomponent primary end point of simultaneous achievement of 50% improvement in ACR response criteria (ACR50)³⁶ and at least a 10% weight reduction at week 36 was selected to incorporate clinically meaningful end points for both diseases to evaluate the overall treatment benefits, and key secondary end points were selected to correspond to individual disease outcomes.

Therefore, this trial tested the efficacy and safety of IXE and TZP used concomitantly compared to IXE alone in participants with active PsA and overweight with at least one weight-related comorbidity or obesity.

METHODS

Trial design. TOGETHER-PsA is an ongoing 52-week, phase 3b, randomized, multicenter, open-label trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06588296) identifier NCT06588296) conducted in the United States, including Puerto Rico (Figure S1). This trial was designed to assess the treatment of IXE and concomitantly administered TZP (IXE + TZP) at the maximum tolerated dose (MTD) or IXE in participants with active PsA and overweight (BMI ≥ 27 to <30) in the presence of at least one weight-related comorbidity or obesity (BMI ≥ 30). All participants received individualized counseling from a dietician or equivalent delegate for a healthy diet and exercise. To minimize potential bias due to observed efficacy, a blinded assessor

report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Additional supplementary information cited in this article can be found online in the Supporting Information section (<https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.70134>).

Author disclosures and graphical abstract are available at <https://onlinelibrary.wiley.com/doi/10.1002/art.70134>.

Address correspondence via email to Mark C. Genovese, MD, at Mark.Genovese@lilly.com.

Submitted for publication February 3, 2026; accepted in revised form March 13, 2026.

completed assessments of tender joint count (TJC), swollen joint count (SJC), the Leeds Enthesitis Index, dactylitis count, the Psoriasis Area and Severity Index (PASI), and body surface area. To minimize interobserver variation, the same assessor was used to perform all the assessments of a participant, whenever possible. The primary outcome was assessed at week 36. After the week 36 visit, if the patient failed to demonstrate at least 20% improvement in TJC and SJC, the investigator could adjust the background standard-of-care therapy and use rescue medications.

IXE and TZP were administered according to the approved US prescribing information for each drug.^{22,30} IXE was administered as a 160-mg subcutaneous (SC) injection at week 0, followed by 80 mg once every four weeks or the PsO-approved dosing for those with coexistent moderate-to-severe PsO. TZP was administered as an SC injection once weekly, with a starting dose of 2.5 mg for four weeks and dose escalation by 2.5-mg increments every four weeks to achieve MTD (5, 10, or 15 mg). From week 32 onward, the permitted maintenance dose was 5, 10, or 15 mg.

All participants were required to provide written informed consent before entering the trial. The trial was conducted according to the protocol and in line with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice Guidelines, and applicable laws and regulations. The protocol, protocol amendments, informed consent form, investigator brochure, and other relevant documents were reviewed and approved by the institutional review board/independent ethics committee before initiation of the trial. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier NCT06588296).

Participants. TOGETHER-PsA enrolled participants between 18 and 80 years of age with signs and/or symptoms or documented diagnosis of PsA for a minimum of six months and currently fulfilling the Classification of Psoriatic Arthritis (CASPAR) criteria.³⁷ Participants were required to have active PsA, defined as having at least 3 or more of 68 tender joints and at least 3 or more of 66 swollen joints. Participants were also required to have overweight with at least one weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, CVD, or type 2 diabetes mellitus [T2DM]) or obesity.

Key exclusion criteria included failure of more than three distinct classes of advanced therapies, prior use of IXE or TZP, and/or previous failure of or intolerance to an IL-17 inhibitor or GLP-1 receptor agonist. Participants were permitted to use background standard of care. Full details on prior and concomitant therapies, as well as full eligibility criteria, are provided in the Supplementary Material (see Tables S1–S3 and study protocol). Race and ethnicity were self-reported by participants using fixed selection categories.

Outcomes. The primary efficacy end point was simultaneous achievement of ACR50 and at least 10% weight reduction at week 36. Key secondary end points were achievement of ACR50, simultaneous achievement of ACR20 and at least 5% weight reduction, and achievement of at least 10% weight reduction at week 36. These end points were multiplicity controlled. Achievement of ACR50 over time was also assessed as a non-gated end point.

Additional secondary end points that were not adjusted for multiplicity included Disease Activity Index for Psoriatic Arthritis (DAPSA)³⁸, MDA,³⁹ ACR20, ACR70, and ACR subcomponents. Dermatologic end points included PASI,⁴⁰ PASI75, PASI90, PASI100, and absolute PASI change from baseline (CFB).

Additional patient-reported outcomes (PROs), including CFB measurements for Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Psoriatic Arthritis Impact of Disease (PsAID) total score, and Short-Form 36 Version 2 Health Survey (SF-36) mental component score (MCS) and physical component score (PCS), were evaluated. Metabolic outcomes assessed were BMI, body weight, glucose, hemoglobin A_{1c} (HbA_{1c}), lipids (namely, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), and systolic and diastolic blood pressure.

Safety assessments included incidence of adverse events (AEs). Treatment-emergent AEs (TEAEs), AEs of special interest, serious AEs (SAEs), and gastrointestinal (GI) AEs were assessed. Laboratory assessments were conducted according to the protocol.

Statistical analysis. Participants with active PsA and overweight or obesity were randomly assigned in a 1:1 ratio to either IXE + TZP or IXE (N = 271). Stratification factors for randomization were sex, treatment history (advanced therapy [biologic disease-modifying antirheumatic drug (bDMARD) and targeted synthetic DMARD (tsDMARD), except apremilast] naïve vs advanced therapy experienced), and BMI category (BMI ≥ 27 to <30 vs ≥ 30) at screening. The sample size was based on the primary end point assuming response rates were 46% and 4% for IXE + TZP and IXE, respectively. Using the two-sided chi-square test with an α of 0.05, a trial with an overall sample size of 250 has $>90\%$ power to detect such a treatment difference. Multiplicity-adjusted analyses were performed on the primary and key secondary objectives to control the overall family-wise Type 1 error rate at a two-sided α level of 0.05. The graphical multiple testing procedure was used as previously described.^{41,42} This approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all hypotheses.⁴³

Efficacy outcomes were assessed in the modified intent-to-treat (mITT) population, consisting of all randomly assigned participants with PsA and overweight with weight-related comorbidities or obesity. This mITT population was used to answer our key scientific question, which was to assess the treatment

efficacy difference between IXE and IXE with concomitantly administered TZP as an adjunct to a reduced-calorie diet and increased physical activity in the randomly assigned participants with active PsA and overweight in the presence of at least one weight-related comorbid condition or active PsA and obesity, had they continued taking their randomized treatment without prohibited medication use.

The hypothetical strategy⁴⁴ with intercurrent events of treatment discontinuation or initiation of prohibited medication was used to address this scientific question. This primary estimand⁴⁴ assessed average treatment effects of IXE + TZP and IXE under the condition that all participants who had undergone randomization continued receiving their randomized trial intervention for the entire treatment duration without initiation of prohibited medication. Data collected after an intercurrent event were excluded from the analyses and handled using multiple imputation. Imputations were performed separately by treatment arm to allow for differences in correlation patterns, dropout rates, and treatment responses between groups. The imputation model included stratification factors (sex, prior advanced treatment use, and BMI category), baseline values, and all available outcome data collected before the intercurrent event. All postbaseline visits up to week 36 were imputed simultaneously.

For binary outcomes, logistic regression was used as the working model to estimate unconditional risk difference with stratification variables included as covariates.⁴⁵ For continuous end points that were used for primary and key secondary end point derivation, analysis of covariance (ANCOVA) with robust variance was performed: the model included treatment, baseline value, and stratification variables as fixed factors. For continuous end points that were not used in derivation and had more than one postbaseline data collection per schedule of activities up to week 36, mixed model for repeated measures analysis was used: the model included treatment group, baseline value, randomization stratification factors, visit, and treatment interaction as fixed effects. For those with only one postbaseline data collection up to week 36, last observation carried forward was applied when early discontinuation data were available and ANCOVA was used.

Safety outcomes were assessed using the modified safety population, defined as mITT participants who were exposed to at least one dose of any of the trial treatments. Participants were included according to the trial intervention they received irrespective of adherence to trial drug.

RESULTS

Baseline characteristics and patient demographics.

In keeping with the Consolidated Standards of Reporting Trials guidelines for reporting randomized trials,⁴⁶ the TOGETHER-PsA participant flow diagram is provided (Figure 1). Of 405 participants screened, the mITT population was composed of 271 participants (IXE + TZP, $n = 138$; IXE, $n = 133$). An additional eight participants

without a specified weight-related comorbidity were excluded from the mITT population. In the mITT population, 116 (84.1%) completed IXE + TZP treatment and 89 (66.9%) completed IXE treatment (Figure 1). For the IXE + TZP treatment arm, 78.9% of participants with reported dosing data had TZP 15 mg, 8.3% TZP 10 mg, and 9.2% TZP 5 mg as their MTD.

The summary of baseline demographics and disease characteristics by treatment group is shown in Table 1. Overall, 69.7% of participants were female; the mean age was 55.0 (SD 11.9) years, the mean baseline weight was 106.1 (SD 24.8) kg, the mean screening BMI was 37.6 (SD 7.6), the mean FACIT-F score was 27.1 (SD 11.7), and the mean duration since PsA diagnosis was 8.9 (SD 9.8) years. Further, 71.6% of the participants had coexistent PsO, of which 4.4% had moderate-to-severe PsO and were assigned the approved PsO dosing regimen. Overall, 63.1% of participants were advanced therapy experienced (inclusive of prior exposure to bDMARD and tsDMARD, with the exception of apremilast; see Table S4), while 18.8% had failed two or more classes of advanced therapy.

Efficacy outcomes. The primary outcome and all key secondary outcomes were achieved. ACR50 and at least 10% weight reduction was statistically significant at week 36 with IXE + TZP (31.7%) versus 0.8% with IXE alone (treatment difference 30.9% [95% confidence interval (CI) 22.6%–39.1%]; $P < 0.001$) (Figure 2). From the key secondary outcomes, 69.7% of participants achieved simultaneous ACR20 and at least 5% weight reduction with IXE + TZP versus 10.3% with IXE alone (treatment difference 59.5% [95% CI 49.8%–69.2%]; $P < 0.001$) (Figure 2). Furthermore, 33.5% of participants achieved ACR50 with IXE + TZP versus 20.4% with IXE alone (treatment difference 13.1% [95% CI 2.1%–24.1%]; $P = 0.020$). Improvements in ACR50 were seen as early as week 4, with a significant difference between IXE + TZP and IXE alone (nominal $P < 0.05$), as shown in Figure 3. In addition, 84.5% achieved at least 10% weight reduction with IXE + TZP versus 4.5% with IXE alone (treatment difference 80.0% [95% CI 72.2%–87.9%]; $P < 0.001$) (Figure 2). Clinically significant improvements were observed for percentage CFB in body weight for the IXE + TZP treatment group versus IXE alone (Figure S2).

Additional prespecified nongated clinically relevant secondary outcomes showed improvements in IXE + TZP and IXE treatment arms, with higher responses in IXE + TZP compared to IXE alone. Significantly more participants achieved ACR20 response (71.3% vs 48.5%, treatment difference 22.8 [95% CI 10.0–35.6]; $P < 0.001$), MDA (26.3% vs 15.3%, treatment difference 11.0% [95% CI 1.3–20.6]; $P < 0.05$), and CFB in DAPSA (–32.4 vs –23.7, treatment difference –8.7 [95% CI –12.7 to –4.7]; $P < 0.001$) with IXE + TZP compared to IXE, with numerical improvements noted in ACR70 response in IXE + TZP compared to IXE alone (15.7% vs 8.4%, treatment difference 7.3 [95% CI –0.3 to 14.9]; $P = 0.060$). For the dermatologic outcomes, there

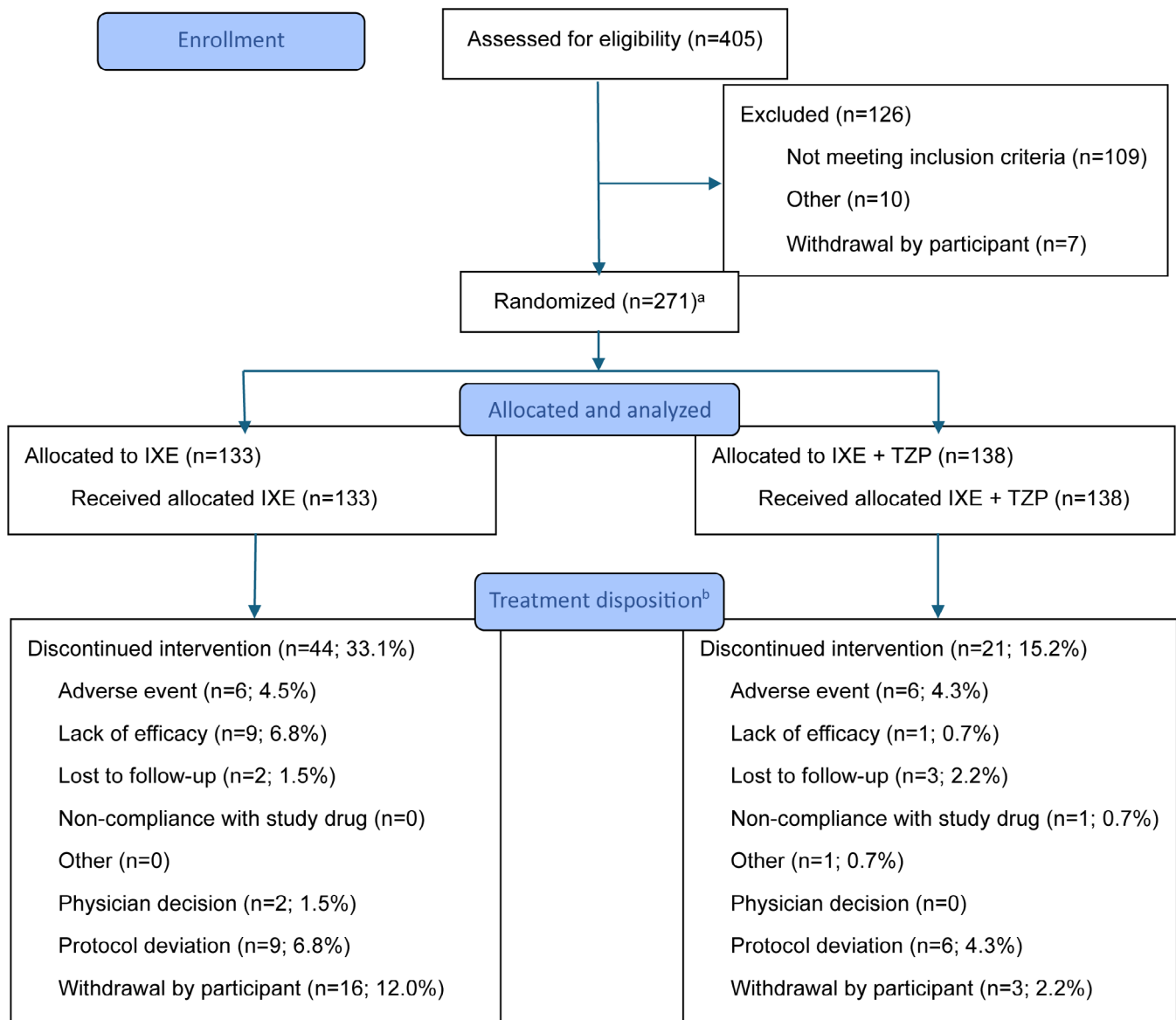


Figure 1. Flow of participants in the TOGETHER-PsA trial through week 36. Data from the modified intent-to-treat population up to the week 36 visit. ^aA total of 279 participants were randomized. Among them, eight participants did not have weight-related comorbidity due to early change in inclusion criteria and were excluded from the modified intent-to-treat population and the modified safety population. ^bOne participant ongoing in the IXE + TZP arm. Although more participants in the IXE alone arm discontinued study intervention due to lack of efficacy compared to the IXE + TZP arm, no consistent pattern of discontinuation was identified for withdrawal by participant. Reasons for withdrawal included personal circumstances such as moving, scheduling conflicts, personal issues unrelated to the trial, and concern with study procedures, and only three participants suggested specifically that they wanted to pursue glucagon-like peptide-1 receptor agonist therapy. Discontinuation due to lack of efficacy did not delineate whether it was due to psoriatic disease activity or lack of weight loss. IXE, ixekizumab; TZP, tirzepatide.

was a significant difference in CFB between both treatment groups for absolute PASI score ($P < 0.01$). In participants with body surface area $\geq 3\%$ at baseline, numerically higher response rates were achieved for the IXE + TZP treatment group compared to IXE alone for PASI75, PASI90, and PASI100 (Table 2).

There were improvements from baseline for the ACR core components and PROs with IXE + TZP and IXE alone. Among ACR components, significant differences were observed in the IXE + TZP arm in mean CFB for each of the following: TJC 68, SJC

66, patient global assessment of disease activity numerical rating scale, Health Assessment Questionnaire disability index (HAQ DI), and hsCRP (all nominal $P < 0.001$), with a significant difference also observed for physician global assessment of disease activity (nominal $P < 0.01$). Numerical improvements were observed in patient pain visual analog scale (VAS) in the IXE + TZP arm compared with IXE alone. Among PROs, significant improvements were observed in the CFB scores for FACIT-F, PsAID, and SF-36 MCS and PCS with IXE + TZP versus IXE alone (Table 2). The IXE + TZP arm had

Table 1. Key baseline demographics and disease characteristics*

Parameter	IXE (n = 133)	IXE + TZP (n = 138)	Total (N = 271)
Age, mean (SD), y	54.8 (11.9)	55.3 (11.8)	55.0 (11.9)
Female, n (%)	92 (69.2)	97 (70.3)	189 (69.7)
Baseline weight, mean (SD), kg	107.6 (24.4)	104.6 (25.2)	106.1 (24.8)
Screening BMI, mean (SD) ^a	38.3 (7.4)	37.0 (7.8)	37.6 (7.6)
Screening BMI category, n (%) ^a			
BMI \geq 27 to $<$ 30 ^b	14 (10.5)	20 (14.5)	34 (12.5)
BMI \geq 30	119 (89.5)	118 (85.5)	237 (87.5)
Race, n (%)			
White	109 (82.0)	119 (86.2)	228 (84.1)
Black or African American	6 (4.5)	3 (2.2)	9 (3.3)
Asian	2 (1.5)	4 (2.9)	6 (2.2)
Multiple	3 (2.3)	2 (1.4)	5 (1.8)
Ethnicity, n (%)			
Hispanic or Latino	35 (26.3)	36 (26.1)	71 (26.2)
Non-Hispanic or non-Latino	97 (72.9)	98 (71.0)	195 (72.0)
Time since PsA diagnosis, mean (SD), y	8 (8.3)	10 (11.0)	8.9 (9.8)
csDMARDs experienced, n (%)			
No	63 (47.4)	59 (42.8)	122 (45.0)
Yes	70 (52.6)	79 (57.2)	149 (55.0)
csDMARDs inadequate response, n (%)			
No	95 (71.4)	93 (67.4)	188 (69.4)
Yes	38 (28.6)	45 (32.6)	83 (30.6)
DMARDs experienced, n (%)			
No	25 (18.8)	18 (13.0)	43 (15.9)
Yes	108 (81.2)	120 (87.0)	228 (84.1)
No. of prior advanced therapies by class, n (%) ^c			
0	51 (38.3)	49 (35.5)	100 (36.9)
1	60 (45.1)	60 (43.5)	120 (44.3)
2	15 (11.3)	24 (17.4)	39 (14.4)
$>$ 2	7 (5.3)	5 (3.6)	12 (4.4)
Treatment history, n (%)			
Advanced therapy experienced ^d	82 (61.7)	89 (64.5)	171 (63.1)
Advanced therapy naïve	51 (38.3)	49 (35.5)	100 (36.9)
Advanced therapies inadequate response, n (%)			
No	79 (59.4)	80 (58.0)	159 (58.7)
Yes	54 (40.6)	58 (42.0)	112 (41.3)
Participants with specific disease characteristics			
PsO, n (%) ^e	98 (73.7)	96 (69.6)	194 (71.6)
PASI total score, mean (SD)	3.3 (5.9)	3.2 (4.7)	3.3 (5.3)
BSA, mean (SD)	8.1 (15.1)	7.8 (12.3)	7.9 (13.7)
BSA \geq 3%	75 (56.4)	76 (55.1)	151 (55.7)
sPGA, mean (SD)	2 (1.0)	2 (1.0)	2 (1.0)
Moderate-to-severe plaque PsO, n (%) ^f	7 (5.3)	5 (3.6)	12 (4.4)
Dactylitis count $>$ 0, n (%)	46 (34.6)	46 (33.3)	92 (33.9)
Baseline disease and quality of life scores			
TJC (68 joints), mean (SD)	27.9 (17.7)	25.5 (15.8)	26.7 (16.8)
SJC (66 joints), mean (SD)	12.8 (10.6)	11.9 (9.0)	12.3 (9.8)
PhGADA NRS, mean (SD)	6.2 (1.9)	6.3 (1.8)	6.2 (1.8)
PaGADA NRS, mean (SD)	6.6 (2.0)	6.5 (1.8)	6.5 (1.9)
Patient-reported pain VAS, mean (SD)	60.6 (22.5)	57 (21.6)	58.8 (22.1)
HAQ DI total score, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
hsCRP (mg/L), mean (SD)	7.9 (11.4)	8.0 (14.7)	7.9 (13.2)
DAPSA, mean (SD)	55.4 (24.3)	47.2 (22.7)	51.3 (23.8)
LEI $>$ 0, n (%) ^g	110 (82.7)	111 (80.4)	221 (81.5)
FACIT-F, mean (SD)	27.3 (11.6)	27.0 (11.9)	27.1 (11.7)
PsAID-12 score, mean (SD)	5.9 (1.8)	5.8 (2.0)	5.9 (1.9)
SF-36 MCS, mean (SD)	48.8 (12.2)	48.4 (10.8)	48.6 (11.5)
SF-36 PCS, mean (SD)	33.1 (9.0)	32.8 (9.0)	33.0 (9.0)
EQ-5D 5L, mean (SD)	0.65 (0.16)	0.67 (0.15)	0.66 (0.15)
Metabolic characteristics			
Hypertension, n (%)	76 (57.1)	89 (64.5)	165 (60.9)
Dyslipidemia, n (%)	60 (45.1)	61 (44.2)	121 (44.6)

(Continued)

Table 1. (Cont'd)

Parameter	IXE (n = 133)	IXE + TZP (n = 138)	Total (N = 271)
Obstructive sleep apnea, n (%)	21 (15.8)	13 (9.4)	34 (12.5)
CVD, n (%)	11 (8.3)	13 (9.4)	24 (8.9)
T2DM, n (%)	16 (12.0)	14 (10.1)	30 (11.1)
Systolic blood pressure, mean (SD), mm Hg	132.5 (14.9)	130.3 (13.1)	131.4 (14.0)
Diastolic blood pressure, mean (SD), mm Hg	83.1 (9.3)	82.1 (7.7)	82.6 (8.5)
LDL cholesterol, mean (SD), mg/dL	107 (36.5)	104.1 (36.7)	105.5 (36.6)
HDL cholesterol, mean (SD), mg/dL	50.2 (12.9)	51.0 (12.6)	50.6 (12.7)
Total cholesterol, mean (SD), mg/dL	188.8 (41.5)	185.6 (38.3)	187.1 (39.9)
Triglycerides, mean (SD), mg/dL	161 (80.3)	156.9 (87.3)	158.9 (83.8)
Glucose, mean (SD), mg/dL	101.3 (23.5)	106.8 (40.0)	104.2 (33.2)
HbA _{1c} , mean (SD), %	5.8 (0.7)	5.8 (0.8)	5.8 (0.7)

* Baseline characteristics and disease characteristics are shown for the mITT (efficacy) population. BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CVD, cardiovascular disease; DAPSA, Disease Activity Index for Psoriatic Arthritis; DMARD, disease-modifying antirheumatic drug; EQ-5D 5L, European Quality of Life-5 dimensions 5 level; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ DI, Health Assessment Questionnaire disability index; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IXE, ixekizumab; LDL, low-density lipoprotein; LEI, Leeds Enthesitis Index; MCS, mental component score; mITT, modified intent-to-treat; NRS, numerical rating scale; PaGADA, patient's global assessment of disease activity; PASI, Psoriasis Area and Severity Index; PCS, physical component score; PhGADA, physician's global assessment of disease activity; PsA, psoriasis arthritis; PsAID-12, Psoriatic Arthritis Impact of Disease 12; PsO, psoriasis; SF-36, 36-Item Short Form Health Survey; SJC, swollen joint count; sPGA, static physician's global assessment; T2DM, type 2 diabetes mellitus (non-insulin dependent); TJC, tender joint count; TZP tirzepatide; VAS, visual analog scale.

^a Screening BMI used because it is the stratification variable.

^b Comorbidity requirement.

^c Prior therapies are categorized by drug class for stratification. Prior exposure to apremilast was not considered an advanced therapy. Patients using more than one drug of the same class were counted once here.

^d Inclusive of prior exposure to biologic DMARDs and targeted synthetic DMARDs, with the exception of apremilast.

^e Evaluated in participants with PsO, as qualitatively assessed by the investigator, at baseline.

^f Moderate-to-severe plaque PsO was defined as having minimum BSA involvement of 10%, an sPGA score of ≥ 3 in the overall assessment (plaque thickness or induration, erythema, and scaling) of PsO on a severity scale of 0 to 4, and a PASI score ≥ 12 . If applicable, participants must fulfill the above definition of moderate-to-severe plaque PsO at visit 2 to receive the PsO dosing regimen.

^g Evaluated in participants with enthesitis, as qualitatively assessed by the investigator, at baseline.

higher responses than IXE alone in achieving 50% improvement in all individual components of ACR50 at week 36 (Figure S3).

Nominally statistically significant improvements were observed in metabolic outcomes in the IXE + TZP treatment group compared with the IXE treatment group for BMI, body weight, systolic blood pressure, glucose, HbA_{1c}, total cholesterol, and triglycerides (Table 2).

Safety outcomes. Overall, 73.7% of participants reported at least one TEAE, with the majority being mild to moderate in severity (Table 3). The most commonly reported TEAEs were GI AEs, including nausea (IXE + TZP: 29.7%; IXE: 3.0%), diarrhea (IXE + TZP: 18.1%; IXE: 3.8%), constipation (IXE + TZP: 16.7%; IXE: 3.0%), and vomiting (IXE + TZP: 10.9%; IXE: 0.8%), which were more prevalent in the IXE + TZP arm compared to IXE alone. The incidence of injection site reactions (ISRs) was similar in both arms (IXE + TZP: 15.2%; IXE: 16.7%). SAEs were lower in the IXE + TZP arm compared to the IXE arm (3.6% vs 7.6%). There were no deaths (Table 3) or other significant differences in SAEs between treatment arms (Table S5). Discontinuation from study treatment due to an AE was similar in both arms (IXE + TZP: 5.1%; IXE: 5.3%) (Table 3).

DISCUSSION

This is the first randomized controlled trial to provide a robust assessment of concomitant use of an incretin therapy approved for weight loss (TZP) with a biologic (IXE) in patients with active PsA and overweight or obesity. The comprehensive body of evidence from this trial demonstrated improvements across and beyond both primary and all key secondary end points, indicating the concomitant use of IXE + TZP yielded meaningful benefits across all major domains of psoriatic disease, including clinical manifestations (TJC), acute-phase reactants (hsCRP), physical function (HAQ DI), PROs, QoL (SF-36 and FACIT-F), and cardio-metabolic and weight-related parameters, surpassing the efficacy observed with IXE alone in this population.

The multicomponent primary objective requiring simultaneous achievement of ACR50 and at least a 10% weight reduction was statistically significant and clinically relevant given the high prevalence of overweight and obesity in the PsA population. These data suggest that PsA may be considered a weight-related comorbidity.

The improvement in ACR50 at week 36 as a key secondary composite measure suggests direct improvement of psoriatic disease activity with IXE + TZP versus IXE monotherapy. Furthermore, the statistically significant improvement as early as

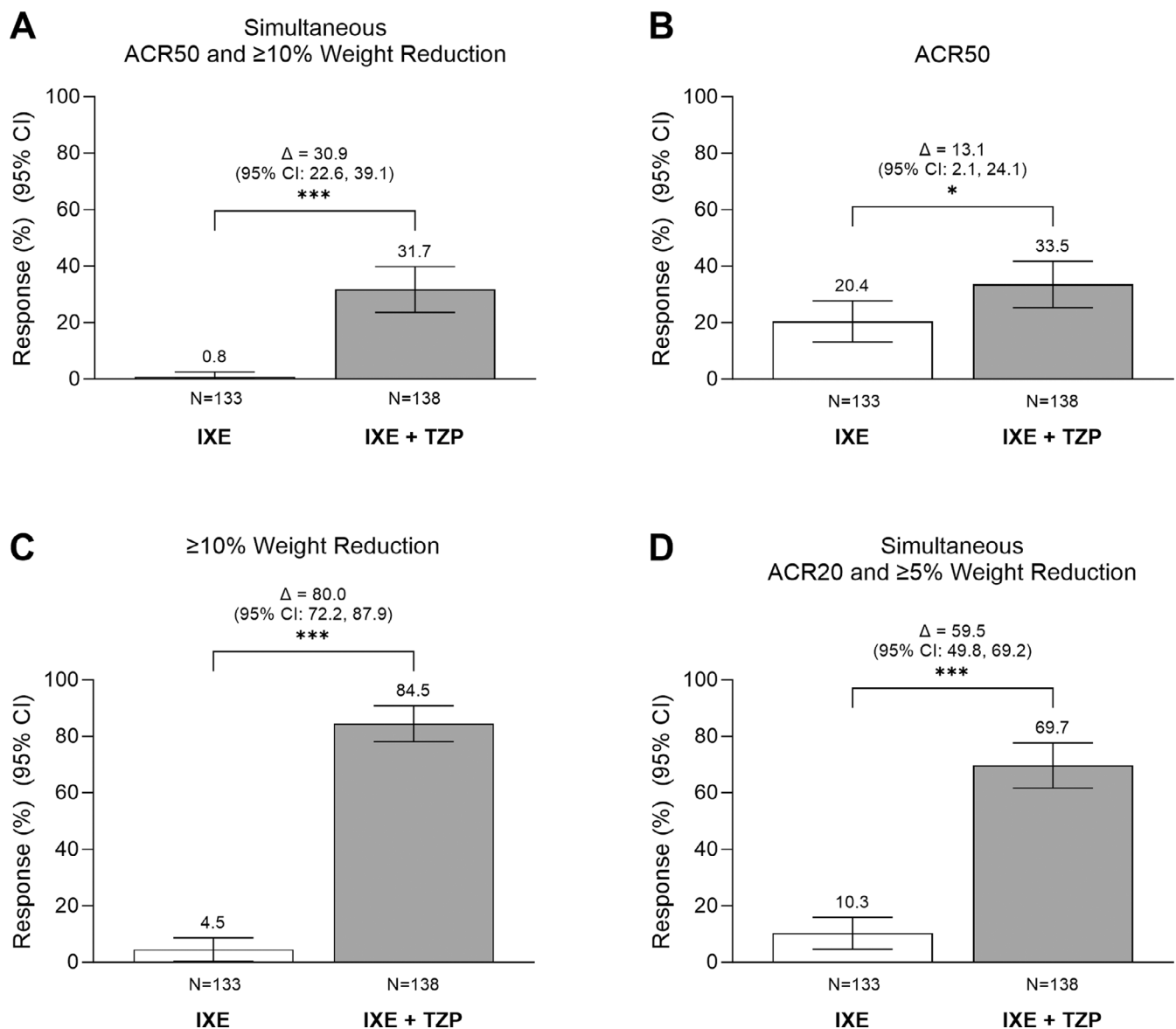


Figure 2. IXE with TZP demonstrated superiority in primary and key secondary outcomes versus IXE alone at week 36. Data are shown for (A) the primary outcome and (B–D) key secondary outcomes. Hypothetical estimand was used with multiple imputation. Logistic regression (with treatment, screening body mass index category, sex, and treatment history as factors) was used as a working model to estimate unconditional risk difference. Primary and key secondary outcomes were controlled for multiplicity. Δ = treatment difference of IXE + TZP versus IXE. * $P < 0.05$; *** $P < 0.001$. ACR20/50, 20%/50% improvement in American College of Rheumatology response criteria; CI, confidence interval; IXE, ixekizumab; TZP, tirzepatide.

week 4 observed in ACR50 at a nominal level and in numerical reductions in hsCRP levels with IXE + TZP versus IXE before clinically meaningful weight loss suggests a weight-independent benefit of TZP on PsA disease measures.

The impact in key domains of PsA was demonstrated by improvements in measurements of individual ACR components for both treatment groups, with significant improvements observed in the IXE + TZP arm versus IXE alone, except for pain VAS. In addition, significant improvements in PROs, such as HAQ DI and fatigue, and in QoL, such as PsAID, are meaningful outcomes of the concomitant IXE + TZP treatment, which are

impactful for patients. The improvement in physical function (as measured by HAQ DI) is considered clinically meaningful with IXE + TZP, exceeding the well-defined HAQ DI minimally clinical important difference of -0.35 .⁴ A significant difference in the reduction of DAPSA CFB was observed in the IXE + TZP arm compared to IXE alone. Furthermore, significantly more patients treated with IXE + TZP versus IXE alone achieved MDA at week 36, a comprehensive aim and recommended goal for the management of patients with PsA.^{17,18,39} The observed weight loss and improvement of systolic blood pressure, total cholesterol, triglycerides, HbA_{1c}, and glucose in the IXE + TZP arm are

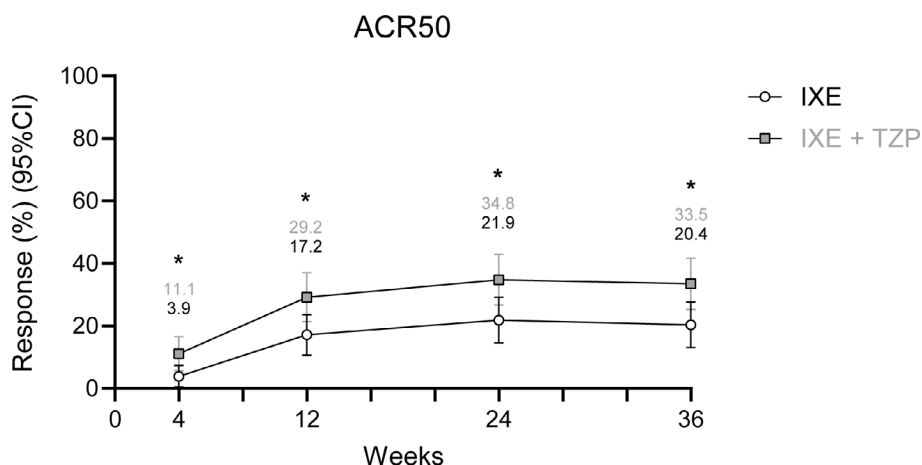


Figure 3. IXE and TZP showed significantly higher ACR50 responses versus IXE alone at week 4 and over time through week 36. Hypothetical estimand was used with multiple imputation. Logistic regression (with treatment, screening body mass index category, sex, and treatment history as factors) was used as a working model to estimate unconditional risk difference. Error bars represent 95% CIs for group-specific estimates. Statistical significance was assessed using formal tests of the between-group difference, not visual inspection of interval overlap. The week 36 end point was the only multiplicity-controlled time point. * $P < 0.05$. ACR50, 50% improvement in American College of Rheumatology response criteria; CI, confidence interval; IXE, ixekizumab; TZP, tirzepatide.

consistent with those reported for TZP in the SURMOUNT trials^{31,32} and are additional considerations in the comprehensive treatment of PsA given the high prevalence and burden of overweight and obesity and greater risks for worse cardiovascular outcomes in PsA.

PsO end points were not the focus of TOGETHER-PsA because enrollment criteria did not include a requirement for participants to have PsO, although PsO is considered as a contributor to meeting CASPAR requirements. Only a minority of participants (4.4%) had moderate-to-severe PsO per protocol definition. Although assessments of PsO are limited, significant change in PASI from baseline and numerical improvements in PASI75/90/100 were observed, which may suggest an improved effect in the skin domain of the disease with the concomitant treatment. A specific trial of IXE + TZP to treat PsO ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06588283) identifier NCT06588283) is underway.

The participants in TOGETHER-PsA represent a more difficult to treat cohort than historical pivotal trials of current approved therapies for several reasons. At screening, 87.5% of patients had obesity (BMI ≥ 30), and the mean BMI was high at 37.6, which is associated with poor outcomes and negatively impacts response to biologics.⁴⁷ In addition, there was a high proportion of women among the participants in this trial at 69.7%. Women with PsA have consistently demonstrated lower efficacy responses compared with men, particularly with respect to the effectiveness of TNF inhibitors as reflected by lower remission rates.^{48,49} Further, women present with higher disease burden at diagnosis, such as longer symptom duration and less favorable PROs, than men.⁵⁰ Furthermore, this trial recruited patients with failure of up to three classes of advanced therapies, including bDMARDs and/or

tsDMARDs, which led to 18.8% of participants with previous failure of at least two classes of advanced therapy, representing a high proportion of patients with high unmet need.

Given the unique and complex inflammatory-metabolic disease of the study population in TOGETHER-PsA, the focus on the incremental benefit of the concomitant use of TZP with IXE compared with IXE alone, rather than the overall numerical improvement in composite measures of disease activity, is more meaningful for patient care, especially the changes in PROs, including fatigue, and in body weight (plus accompanying cardiometabolic improvements), with a near seven-unit difference in BMI seen by 36 weeks. For that reason, but also in general, it is challenging to directly compare numerical improvements in these measurements of PsA in this trial versus historical ones. However, given the high proportion (72%–82%) of patients with PsA with overweight or obesity⁶ (Curtis J, et al: unpublished observations), the results of this trial are relevant to many patients with PsA.

AEs were consistent with established drug profiles. No unexpected safety concerns were observed for the IXE + TZP treatment arm, with fewer SAEs in the IXE + TZP arm compared with IXE alone (Table S4). The frequency of GI AEs in the IXE + TZP arm was generally comparable to that in trials that investigated TZP alone for weight management,^{31,32} with nausea, diarrhea, constipation, and vomiting being the most common TEAEs in the IXE + TZP arm. Discontinuations due to GI AEs in the IXE + TZP arm (2.9%) were comparable to those observed in the weight management trial (SURMOUNT-1). ISRs have been associated with IXE administration in patients with PsA.^{23,24} In our analysis, the frequency of ISRs was similar in both treatment arms and higher than that observed in conventional TZP trials, which could be attributed to the administration of IXE. Furthermore, the

Table 2. Additional secondary outcomes at week 36*

Parameter	IXE (n = 133) ^a	IXE + TZP (n = 138) ^a	Treatment difference (95% CI)	P value
Composite measures and enthesitis assessments				
ACR20	48.5 (38.4 to 58.6)	71.3 (63.4 to 79.1)	22.8 (10.0 to 35.6)	<0.001
ACR70	8.4 (3.6 to 13.2)	15.7 (9.6 to 21.8)	7.3 (-0.3 to 14.9)	0.060
MDA	15.3 (9.2 to 21.5)	26.3 (18.8 to 33.8)	11.0 (1.3 to 20.6)	0.026
DAPSA (CFB)	-23.7	-32.4	-8.7 (-12.7 to -4.7)	<0.001
Enthesitis (adjusted mean CFB)	-0.9	-1.6	-0.7 (-1.1 to -0.3)	0.002
Dermatologic outcomes ^b				
PASI75	52.5 (40.3 to 64.8)	64.4 (52.8 to 76.0)	11.9 (-5.5 to 29.2)	0.177
PASI90	35.6 (24.2 to 47.0)	52.2 (40.1 to 64.2)	16.6 (-0.0 to 33.1)	0.050
PASI100	26.6 (16.5 to 36.8)	36.9 (25.9 to 47.8)	10.2 (-4.7 to 25.2)	0.179
Absolute PASI (CFB) ^c	-3.3	-4.3	-0.9 (-1.6 to -0.2)	0.008
ACR components				
TJC 68	-12.1	-16.9	-4.8 (-7.6 to -2.1)	<0.001
SJC 66	-7.2	-9.7	-2.5 (-3.9 to -1.1)	<0.001
Patient assessment of arthritis pain VAS	-21.9	-25.3	-3.4 (-8.8 to 2.0)	0.217
PaGADA NRS	-2.1	-3.0	-1.0 (-1.5 to -0.4)	<0.001
PhGADA NRS	-3.3	-4.0	-0.7 (-1.2 to -0.2)	0.009
HAQ DI	-0.3	-0.5	-0.2 (-0.3 to -0.1)	<0.001
hsCRP (mg/L)	-0.44	-1.79	-1.35 (-2.10 to -0.61)	<0.001
PROs				
FACIT-F	4.8	8.6	3.8 (1.4 to 6.1)	0.002
PsAID total score	-2.0	-2.7	-0.7 (-1.2 to -0.2)	0.005
SF-36				
MCS	0.4	3.1	2.7 (0.1 to 5.2)	0.041
PCS	6.2	9.7	3.5 (1.5 to 5.6)	<0.001
Metabolic outcomes				
BMI	-0.45	-6.72	-6.27 (-6.93 to -5.62)	<0.001
Body weight, %	-1.1	-18.0	-16.9 (-18.6 to -15.2)	<0.001
Glucose, mg/dL	8.5	-15.3	-23.7 (-30.9 to -16.6)	<0.001
HbA _{1c} , %	0.1	-0.6	-0.7 (-0.9 to -0.5)	<0.001
HDL cholesterol, mg/dL	-0.29	-0.039	0.25 (-1.48 to 1.98)	0.777
LDL cholesterol, mg/dL	-2.52	-2.71	-0.19 (-9.97 to 9.60)	0.970
Total cholesterol, mg/dL	-0.80	-11.03	-10.24 (-19.0 to -1.52)	0.021
Triglycerides, mg/dL	2.5	-36.2	-38.8 (-51.8 to -25.7)	<0.001
Systolic blood pressure, mm Hg	-3.93	-10.81	-6.88 (-10.31 to -3.46)	<0.001
Diastolic blood pressure, mm Hg	-2.84	-4.69	-1.85 (-4.16 to 0.45)	0.114

* Hypothetical estimand was used. Nominal *P* values were reported. ACR20/70, 20%/70% improvement in American College of Rheumatology response criteria; BMI, body mass index; CFB, change from baseline; CI, confidence interval; DAPSA, Disease Activity Index for Psoriatic Arthritis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ DI, Health Assessment Questionnaire disability index; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IXE, ixekizumab; LDL, low-density lipoprotein; MCS, mental component score; MDA, minimal disease activity; NRS, numerical rating scale; PaGADA, patient global assessment of disease activity; PASI75/90/100, Psoriasis Area Severity Index criteria for 75%/90%/100% improvement; PCS, physical component score; PhGADA, physician global assessment of disease activity; PRO, patient-reported outcome; PsAID, Psoriatic Arthritis Impact of Disease; SF-36, 36-item Short Form Health Survey; SJC, swollen joint count; TJC, tender joint count; TZP, tirzepatide; VAS, visual analog scale.

^a Data are presented as response % (95% CI) or as CFB.

^b Assessed in participants with ≥3% body surface area at baseline: IXE, n = 75; IXE + TZP, n = 76.

^c Post hoc.

frequency of upper respiratory tract infections was lower than that in historical SPIRIT phase 3 trials.

The limitations of this trial include the open-label approach for sites, participants, and the sponsor, mitigated with the use

of blinded joint and skin assessors. An open-label design was selected to reflect real-world clinical practice given the likelihood that participants would be able to ascertain their treatment allocation based on early weight loss for those receiving

Table 3. Summary of safety outcomes*

Parameter	IXE (N = 132), ^a n (%)	IXE + TZP (N = 138), n (%)
TEAEs	95 (72.0)	104 (75.4)
Mild	40 (30.3)	42 (30.4)
Moderate	49 (37.1)	58 (42.0)
Severe	6 (4.5)	4 (2.9)
Most frequent TEAEs by PT ^b		
Nausea	4 (3.0)	41 (29.7)
Diarrhea	5 (3.8)	25 (18.1)
Constipation	4 (3.0)	23 (16.7)
ISR	22 (16.7)	21 (15.2)
Vomiting	1 (0.8)	15 (10.9)
Sinusitis	3 (2.3)	9 (6.5)
Urinary tract infection	4 (3.0)	9 (6.5)
Dizziness	1 (0.8)	8 (5.8)
Headache	1 (0.8)	8 (5.8)
Upper respiratory tract infection	7 (5.3)	5 (3.6)
SAEs	10 (7.6)	5 (3.6)
Deaths	0	0
Discontinued from study treatment due to AE	7 (5.3)	7 (5.1)
Discontinuation due to GI AEs	1 (0.8)	4 (2.9)
Abdominal pain upper	0	1 (0.7)
Colitis ulcerative	0	1 (0.7)
Diarrhea	0	1 (0.7)
Nausea	0	1 (0.7)
Colitis ^c	1 (0.8)	0
AEs of special interest		
Hypersensitivity reactions	0	0
ISRs ^d	24 (18.2)	21 (15.2)
Hypoglycemia for those with T2DM at baseline	0	1 (0.7)
Severe/serious hypoglycemia	0	0
Pancreatitis	0	0
Serious/severe GI AEs	1 (0.8)	1 (0.7)
Upper abdominal pain	0	1 (0.7)
Nausea	0	1 (0.7)
Colitis ^c	1 (0.8)	0
Infections and infestations	49 (37.1)	51 (37.0)
Opportunistic infections	2 (1.5)	2 (1.4)
Suicidal ideation	1 (0.8)	0
Inflammatory bowel disease	1 (0.8)	1 (0.7)

* Data from the modified safety population up to the cutoff date. AEs are represented as MedDRA version 28.1 PTs. AE, adverse event; GI, gastrointestinal; ISR, infection site reaction; IXE, ixekizumab; N, number of participants in the patient population; n, number of participants with at least one event reported; PT, preferred term; SAE, serious adverse event; T2DM, type 2 diabetes mellitus; TEAE, treatment-emergent adverse event; TZP, tirzepatide.

^a One participant was randomized but did not receive the study treatment.

^b AEs occurring in ≥5% of participants.

^c Reported as colitis with ulceration, which could not be definitively confirmed as inflammatory bowel disease. Study drug was withdrawn.

^d ISRs are a cluster of individual AE PTs.

TZP. We also observed that more participants in the IXE alone arm discontinued study intervention due to lack of efficacy and withdrawal by participant, the latter of which showed no consistent pattern of discontinuation. Because this was an open-label trial, reasons for discontinuation due to lack of efficacy were captured at a high level and did not systematically ascertain whether insufficient response was driven by inadequate joint improvement, lack of weight loss, or a combination of both.

This trial did not include patients with a normal BMI or patients with overweight with a BMI of 25 to <27 to follow the TZP approved label at the time of protocol development. This trial did not evaluate participants if they had any prior or current inadequate response to IL-17 inhibitor(s), which will be addressed in an ongoing trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06864026) identifier NCT06864026) in PsA that includes participants currently taking IXE and evaluates the addition of TZP. Lastly, it should be noted that this trial was conducted solely in the United States in contrast to historical IXE large, global phase 3 PsA trials.

Concomitant administration of IXE and TZP was superior to IXE alone in achieving key efficacy outcomes by 36 weeks, as well as improvement in ACR50 as early as 4 weeks of treatment in patients with complex inflammatory-metabolic disease, with no new safety concerns. Specifically, these results highlight improvements in rheumatic and dermatologic disease activity end points, weight and cardiometabolic end points, biomarkers and laboratory measures, and overall health of patients, as evidenced by significant improvements in PROs and QoL.

This is the first randomized controlled trial of TZP and IXE in patients with PsA and overweight or obesity that addresses the comprehensive management needs of this patient population with a positive meaningful impact in multiple domains of PsA disease, including disease control and its comorbidities. These data strengthen the EULAR and GRAPPA treatment guidelines, which recommend that clinicians consider comorbidities in the patient's treatment approach to achieve low disease activity or remission.^{18,19}

Additional studies are warranted to evaluate a possible anti-inflammatory effect of TZP in PsA. The addition of TZP to IXE represents a potential paradigm shift to optimize comprehensive clinical outcomes and patient QoL in the appropriate patient population.

ACKNOWLEDGMENTS

The authors would like to thank all the participants and investigators who took part in this trial. The authors would also like to thank Mathijs C. Bunck, MD, PhD, of Eli Lilly and Company for his significant contribution to the trial design and development, as well as medical expertise, and Ann Leung, MS, Yurong Chen, PhD, Fangui Sun, PhD, and Jordan Bauer, MS, for their considerable contributions to statistical analysis.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Genovese confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

Eli Lilly and Company contributed to the trial design, data collection, data analysis, data interpretation, preparation of the manuscript, and the decision to submit the paper for publication. All authors had full access to all of the data in the trial and had final responsibility for the decision to submit for publication. All authors critically revised the manuscript. Medical writing support was provided by Alexandre Chappard, PhD, Amelia Torcello Gomez, PhD, Himanshi Bhatia, PhD, and Nancy Tan, PharmD, all of Eli Lilly and Company. Publication of this article was not contingent upon approval by Eli Lilly and Company.

REFERENCES

- Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs* 2014;74(4):423–441. doi:10.1007/s40265-014-0191-y
- Kharouf F, Gladman DD. Advances in the management of psoriatic arthritis in adults. *BMJ* 2024;387:e081860. doi:10.1136/bmj-2024-081860
- Williams JC, Hum RM, Rogers K, et al. Metabolic syndrome and psoriatic arthritis: the role of weight loss as a disease-modifying therapy. *Ther Adv Musculoskelet Dis* 2024;16:1759720X241271886. doi:10.1177/1759720X241271886
- Walsh JA, Ogdie A, Michaud K, et al. Impact of key manifestations of psoriatic arthritis on patient quality of life, functional status, and work productivity: findings from a real-world study in the United States and Europe. *Joint Bone Spine* 2023;90(3):105534. doi:10.1016/j.jbspin.2023.105534
- Ruiz-Ponce M, Cuesta-López L, López-Montilla MD, et al. Decoding clinical and molecular pathways of liver dysfunction in psoriatic arthritis: impact of cumulative methotrexate doses. *Biomed Pharmacother* 2023;168:115779. doi:10.1016/j.biopha.2023.115779
- Eder L, Thavaneswaran A, Chandran V, et al. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. *Ann Rheum Dis* 2015;74(5):813–817. doi:10.1136/annrheumdis-2013-204448
- Haberman RH, Ogdie A, Merola JF, et al. The obesity-inflammation axis in psoriatic disease: mechanisms and therapeutic strategies. *Nat Rev Rheumatol* 2026;22(3):151–164. doi:10.1038/s41584-025-01326-6
- Kumthekar A, Ogdie A. Obesity and psoriatic arthritis: a narrative review. *Rheumatol Ther* 2020;7(3):447–456. doi:10.1007/s40744-020-00215-6
- Porta S, Otero-Losada M, Kölliker Frers RA, et al. Adipokines, cardiovascular risk, and therapeutic management in obesity and psoriatic arthritis. *Front Immunol* 2021;11:590749. doi:10.3389/fimmu.2020.590749
- Jamnitski A, Symmons D, Peters MJ, et al. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. *Ann Rheum Dis* 2013;72(2):211–216. doi:10.1136/annrheumdis-2011-201194
- Klingberg E, Bilberg A, Björkman S, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. *Arthritis Res Ther* 2019;21(1):17. doi:10.1186/s13075-019-1810-5
- di Minno MN, Peluso R, Iervolino S, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. *Arthritis Care Res (Hoboken)* 2013;65(1):141–147. doi:10.1002/acr.21711
- Eder L, Odhav S, Korkosz M, et al. FRI0430 Ixekizumab improves the signs and symptoms of psoriatic arthritis regardless of sex, duration of disease, or body mass index in two randomized, phase 3 clinical trials [abstract]. *Ann Rheum Dis* 2019;78(suppl 2):904–905. doi:10.1136/annrheumdis-2019-eular.1474
- Di Minno MN, Peluso R, Iervolino S, et al; CaRRDs Study Group. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor α blockers. *Ann Rheum Dis* 2014;73(6):1157–1162. doi:10.1136/annrheumdis-2012-202812
- Leung YY, Eder L, Orbai AM, et al. Association between obesity and likelihood of remission or low disease activity status in psoriatic arthritis applying index-based and patient-based definitions of remission: a cross-sectional study. *RMD Open* 2023;9(3):e003157. doi:10.1136/rmdopen-2023-003157
- Landgren AJ, Jonsson CA, Bilberg A, et al. Serum IL-23 significantly decreased in obese patients with psoriatic arthritis six months after a structured weight loss intervention. *Arthritis Res Ther* 2023;25(1):131. doi:10.1186/s13075-023-03105-8
- Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol* 2019;71(1):5–32. doi:10.1002/art.40726
- Coates LC, Soriano ER, Corp N, et al; GRAPPA Treatment Recommendations domain subcommittees. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol* 2022;18(8):465–479. doi:10.1038/s41584-022-00798-0
- Gossec L, Kerschbaumer A, Ferreira RJO, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann Rheum Dis* 2024;83(6):706–719. doi:10.1136/ard-2024-225531
- Liu L, Lu J, Allan BW, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. *J Inflamm Res* 2016;9:39–50. doi:10.2147/JIR.S100940
- Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. *Clin Rev Allergy Immunol* 2018;55(3):379–390. doi:10.1007/s12016-018-8702-3
- Eli Lilly and Company. Taltz highlights of prescribing information. 2024. Updated August 2024. <https://pi.lilly.com/us/taltz-uspi.pdf>
- Mease PJ, van der Heijde D, Ritchlin CT, et al; SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017;76(1):79–87. doi:10.1136/annrheumdis-2016-209709
- Nash P, Kirkham B, Okada M, et al; SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017;389(10086):2317–2327. doi:10.1016/S0140-6736(17)31429-0

25. Mease PJ, Smolen JS, Behrens F, et al; SPIRIT H2H study group. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis* 2020;79(1):123–131. doi:[10.1136/annrheumdis-2019-215386](https://doi.org/10.1136/annrheumdis-2019-215386)
26. Orbai AM, Gratacós J, Turkiewicz A, et al. Efficacy and safety of ixekizumab in patients with psoriatic arthritis and inadequate response to TNF inhibitors: 3-year follow-up (SPIRIT-P2). *Rheumatol Ther* 2021; 8(1):199–217. doi:[10.1007/s40744-020-00261-0](https://doi.org/10.1007/s40744-020-00261-0)
27. Chandran V, van der Heijde D, Fleischmann RM, et al. Ixekizumab treatment of biologic-naïve patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1). *Rheumatology (Oxford)* 2020;59(10):2774–2784. doi:[10.1093/rheumatology/kez684](https://doi.org/10.1093/rheumatology/kez684)
28. Smolen JS, Sebba A, Ruderman EM, et al. Efficacy and safety of ixekizumab with or without methotrexate in biologic-naïve patients with psoriatic arthritis: 52-week results from SPIRIT-H2H study. *Rheumatol Ther* 2020;7(4):1021–1035. doi:[10.1007/s40744-020-00250-3](https://doi.org/10.1007/s40744-020-00250-3)
29. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab* 2018;18: 3–14. doi:[10.1016/j.molmet.2018.09.009](https://doi.org/10.1016/j.molmet.2018.09.009)
30. Eli Lilly and Company. Zepbound highlights of prescribing information. 2025. Updated September 2025. <https://pi.lilly.com/us/zepbound-uspi.pdf>
31. Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;387(3):205–216. doi:[10.1056/NEJMoa2206038](https://doi.org/10.1056/NEJMoa2206038)
32. Garvey WT, Frias JP, Jastreboff AM, et al; SURMOUNT-2 investigators. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023; 402(10402):613–626. doi:[10.1016/S0140-6736\(23\)01200-X](https://doi.org/10.1016/S0140-6736(23)01200-X)
33. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Nat Med* 2023;29(11):2909–2918. doi:[10.1038/s41591-023-02597-w](https://doi.org/10.1038/s41591-023-02597-w)
34. Sattar N, Verma S, Sourij H, et al. Abstract 4139912: Inflammatory biomarkers in people treated with tirzepatide living with overweight or obesity, without and with T2D: a post-hoc analysis from SURMOUNT-1 and SURMOUNT-2 [abstract]. *Circulation* 2024;150-(suppl 1). doi:[10.1161/circ.150.suppl_1.4139912](https://doi.org/10.1161/circ.150.suppl_1.4139912)
35. Aronne LJ, Horn DB, le Roux CW, et al; SURMOUNT-5 Trial Investigators. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med* 2025;393(1):26–36. doi:[10.1056/NEJMoa2416394](https://doi.org/10.1056/NEJMoa2416394)
36. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38(6):727–735. doi:[10.1002/art.1780380602](https://doi.org/10.1002/art.1780380602)
37. Taylor W, Gladman D, Helliwell P, et al; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54(8):2665–2673. doi:[10.1002/art.21972](https://doi.org/10.1002/art.21972)
38. Ogdie A, Coates LC, Mease P. Measuring outcomes in psoriatic arthritis. *Arthritis Care Res (Hoboken)* 2020;72(suppl 10):82–109. doi:[10.1002/acr.24242](https://doi.org/10.1002/acr.24242)
39. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69(1):48–53. doi:[10.1136/ard.2008.102053](https://doi.org/10.1136/ard.2008.102053)
40. Mease PJ. Measures of psoriatic arthritis: tender and swollen joint assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res (Hoboken)* 2011;63-(suppl 1):S64–S85.
41. Bretz F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J* 2011;53(6):894–913. doi:[10.1002/bimj.201000239](https://doi.org/10.1002/bimj.201000239)
42. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. *Stat Med* 2009;28(4): 586–604. doi:[10.1002/sim.3495](https://doi.org/10.1002/sim.3495)
43. Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med* 2014;33(4):693–713. doi:[10.1002/sim.5974](https://doi.org/10.1002/sim.5974)
44. European Medicines Agency. ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. Committee for Medicinal Products for Human Use; 2020.
45. US Food and Drug Administration. Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products Guidance for Industry. US Department of Health and Human Services; 2023.
46. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ* 2025;389: e081123. doi:[10.1136/bmj-2024-081123](https://doi.org/10.1136/bmj-2024-081123)
47. Højgaard P, Grintborg B, Kristensen LE, et al. The influence of obesity on response to tumour necrosis factor- α inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. *Rheumatology (Oxford)* 2016;55(12):2191–2199. doi:[10.1093/rheumatology/kew326](https://doi.org/10.1093/rheumatology/kew326)
48. Siebert S, Sattar N, Ferguson LD. Weighing in on obesity and psoriatic arthritis - time to move beyond association to robust randomised trials. *Joint Bone Spine* 2025;92(5):105904. doi:[10.1016/j.jbspin.2025.105904](https://doi.org/10.1016/j.jbspin.2025.105904)
49. Baciu T, Neagu AE, Saulescu IC, et al. Unveiling sex-related variability in psoriatic arthritis: a call for personalized care. *J Clin Med* 2025; 14(12):4124. doi:[10.3390/jcm14124124](https://doi.org/10.3390/jcm14124124)
50. Passia E, Vis M, Coates LC, et al. Sex-specific differences and how to handle them in early psoriatic arthritis. *Arthritis Res Ther* 2022;24(1): 22. doi:[10.1186/s13075-021-02680-y](https://doi.org/10.1186/s13075-021-02680-y)