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Ixekizumab With or Without Tirzepatide in Adults With Psoriasis and Overweight or Obesity
A Phase 3b Randomized Clinical Trial

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IMPORTANCE Overweight and obesity affect 60% to 78% of patients with psoriasis, affecting disease severity, treatment response, and clinical outcomes. However, no large, randomized, active-controlled clinical trial has evaluated a treatment strategy that addresses both diseases simultaneously.

OBJECTIVE To evaluate the efficacy and safety of ixekizumab with or without tirzepatide in participants with psoriasis and overweight or obesity.

DESIGN, SETTING, AND PARTICIPANTS This phase 3b, randomized, open-label, 52-week clinical trial was conducted at 72 sites in the US in adults with moderate to severe plaque psoriasis who have overweight with 1 or more weight-related comorbidities or obesity. The trial started on September 30, 2024, and completed the week 36 primary end point on January 8, 2026. Data were analyzed from January to February 2026.

INTERVENTIONS Participants were randomized (1:1) to ixekizumab plus tirzepatide or ixekizumab as adjunct to diet and exercise in both treatment arms.

MAIN OUTCOMES AND MEASURES At week 36, the primary end point was simultaneous achievement of Psoriasis Activity and Severity Index (PASI) 100 and 10% or greater weight reduction. Key secondary end points were PASI 100 and simultaneous PASI 75 and 5% or greater weight reduction, as well as 10% or greater weight reduction.

RESULTS Among the 274 randomized participants (mean [SD] age, 45.6 [12.7] years; 123 [44.9%] women and 151 [55.1%] men; mean [SD] screening body mass index [calculated as weight in kilograms divided by height in meters squared], 39.2 [9.1]; mean [SD] duration of psoriasis, 14.6 [13.0] years; mean [SD] PASI, 19.7 [8.1]), 231 (84.3%) completed the treatment through week 36. Overall, 27.1% of participants simultaneously achieved PASI 100 and a 10% or greater weight reduction with ixekizumab plus tirzepatide vs 5.8% with ixekizumab (risk difference [RD], 21.2%; 95% CI, 12.8%-29.7%; $P < .001$). Also, 40.6% vs 29.0% of participants achieved PASI 100 (RD, 11.6%; 95% CI, 0.3%-22.9%; $P = .04$), 79.9% vs 17.9% simultaneously achieved PASI 75 and a 5% or greater weight reduction (RD, 62.0%; 95% CI, 51.7%-72.2%; $P < .001$), and 69.2% vs 9.1% achieved a 10% or greater weight reduction (RD, 60.0%; 95% CI, 50.4%-69.7%; $P < .001$), respectively. Adverse events were generally consistent with established drug safety profiles, the most common being gastrointestinal tract events and injection site reactions. Gastrointestinal tract events occurred more frequently with ixekizumab plus tirzepatide vs ixekizumab.

CONCLUSIONS AND RELEVANCE The trial results suggest that concomitant ixekizumab and tirzepatide produced clinically meaningful, statistically significant improvements in skin clearance and reductions in weight in participants with moderate to severe psoriasis, with no new safety concerns, while providing additional cardiometabolic benefits and a potential to elevate care.

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Visual Abstract
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There is a well-established association between psoriasis and overweight or obesity.[1,2] The prevalence of overweight and obesity in people with psoriasis is 60% to 78%.[3-5] Patients with psoriasis have a more than 50% increased odds of developing obesity than the general population.[6] As body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) increases, psoriasis risk and incidence rise,[5,7-9] supporting the idea that psoriasis is a comorbidity of obesity. The fundamental mechanistic rationale underlying this association is chronic low-grade systemic inflammation with increased inflammatory cytokines, such as tumor necrosis factor α, interleukin 17, and interleukin 6,[10-12] which may substantially contribute to the development, severity, and progression of both conditions.[3] Patients with active psoriasis and overweight or obesity have poorer clinical outcomes and quality of life, including lower response to biologic treatments, compared with patients with a BMI ranging from 18.5 to 24.9, as well as greater risk of treatment discontinuation and a higher risk for developing psoriatic arthritis.[13-18] Clinical trial populations in pivotal psoriasis studies of biologics have had mean BMI values of approximately 29 to 30,[19-24] and additional data are needed regarding the effect of treatment in patients with psoriasis with a higher BMI.

Psoriasis and obesity are associated with increased cardiovascular and metabolic risk,[25,26] and their frequent coexistence underscores the relevance of treatment strategies that address both conditions simultaneously. Managing cutaneous inflammation alongside metabolic dysfunction may reduce overall disease burden and enhance cardiometabolic health, as well as reduce patient adversity. Professional guidelines from the American Academy of Dermatology/National Psoriasis Foundation, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, and the International Psoriasis Council recommend achieving complete skin clearance (Psoriasis Activity and Severity Index [PASI] improvement from baseline of 100% [PASI 100]) and emphasize routine assessment of comorbidities, including obesity, and expert recommendations support weight reduction for patients with overweight or obesity.[16,27]

Incretin-based therapies that target glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide pathways achieve substantial weight reduction, improve multiple cardiometabolic parameters, and attenuate inflammatory mediators implicated in psoriasis pathogenesis.[28-31] Consequently, combining an incretin-based therapy with a biologic agent for psoriasis may yield more comprehensive clinical benefits in patients with psoriasis and overweight or obesity.[32,33]

Ixekizumab, an interleukin 17A inhibitor, has consistently demonstrated rapid, robust, and durable skin clearance, with a well-established safety profile across pivotal phase 3 trials and superiority vs other biologics in 5 head-to-head psoriasis trials.[21,34-40] Tirzepatide, a dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist, demonstrated substantial weight reduction and cardiometabolic improvements in weight management clinical studies.[28,29,41] In a clinical trial involving individuals with psoriatic arthritis and overweight or obesity, concomitant ixekizumab (IXE) and tirzepatide (TZP) improved joint disease, physical function, and quality of life and resulted in weight reduction without evidence of new safety concerns.[42] In this article, we describe the TOGETHER-PsO trial, which evaluated the efficacy and safety of IXE as concomitantly administered with TZP compared with IXE alone in participants with moderate to severe psoriasis and overweight or obesity.

Key Points

Question What is the effect of ixekizumab plus tirzepatide on disease activity and weight in adults with psoriasis and overweight or obesity?

Findings In this randomized clinical trial of 274 participants, 27.1% receiving ixekizumab plus tirzepatide vs 5.8% receiving ixekizumab alone simultaneously achieved Psoriasis Area Severity Index (PASI) 100 and 10% or greater weight reduction; 40.6% vs 29.0% achieved PASI 100 at week 36, respectively. Treatment differences were significant.

Meaning The trial results suggest that, in adults with difficult-to-treat psoriasis due to overweight or obesity, concomitant ixekizumab and tirzepatide improved complete skin clearance (PASI 100) and reduced weight, supporting comprehensive management of obesity and psoriasis as a potential new treatment approach.

Methods

Trial Design

This phase 3b, randomized, multicenter, open-label clinical trial was conducted at 72 sites in the US. Masked assessors evaluated psoriasis-related assessments (details are included in the trial protocol in Supplement 1; the statistical analysis plan can be found in Supplement 2). The trial started on September 30, 2024, and completed the week 36 primary end point on January 8, 2026. The trial duration is 52 weeks (eFigure 1 in Supplement 3) and is estimated to finish in May 2026. The trial was conducted according to the ethical principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial protocol was approved by the ethical review board at each participating site. All participants provided written informed consent before participating in the trial.

Participants

Eligible participants were adults with moderate to severe plaque psoriasis for at least 6 months, a Static Physician Global Assessment (sPGA) score of 3 or more and PASI of 12 or greater, 10% or greater body surface area (BSA) involvement, and either overweight (BMI ≥27 to <30) in the presence of 1 or more weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes), or obesity (BMI ≥30). Key exclusion criteria included

previous treatment failure with or intolerance to an interleukin 17 inhibitor or GLP-1 receptor agonists, prior use of IXE or TZP, or having experienced no cure from more than 3 distinct classes of advanced therapy for psoriasis. Complete inclusion/exclusion criteria are included in eAppendix 1 in Supplement 3. The trial was not designed to represent racial diversity. Race and ethnicity were self-reported by participants using fixed selection categories.

Procedures

Participants were randomly assigned (1:1) to subcutaneous IXE+TZP or IXE. The randomization was performed using an interactive web response system and was stratified by sex, treatment history for psoriasis (those who had not received advanced therapy vs those who had), and BMI of 27 or greater to less than 30 vs 30 or greater.

IXE was administered as 2 injections of 80 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12 and then 80 mg, once every 4 weeks. TZP was initially administered at 2.5 mg, once weekly for 4 weeks, and then the dose was increased by 2.5 mg every 4 weeks until the maximum tolerated dose of 5 mg, 10 mg, or 15 mg was achieved by week 32 (additional details are included in eAppendix 2 in Supplement 3).

All participants received individualized counseling for a healthy diet and exercise (details are included in Supplement 1). The use of concomitant medications is described in eAppendix 3 in Supplement 3.

Outcomes

The primary end point was simultaneous achievement of PASI 100 and at least a 10% weight reduction from baseline at week 36. This multicomponent end point was driven by guideline recommendations of achieving complete skin clearance and cardiometabolic improvement in the treatment of psoriasis.[16,27] Key secondary end points at week 36 were PASI 100, simultaneous PASI 75 and at least 5% weight reduction, and at least 10% weight reduction.

Additional prespecified secondary end points at week 36 included PASI 75, PASI 90, change and percentage change from baseline in PASI, sPGA (0-1), Dermatology Life Quality Index (DLQI) (0-1) score in participants with a baseline DLQI score of more than 1, an at least 4-point improvement in itch numeric rating scale (NRS) in participants with an itch NRS score of 4 points or greater at baseline, percentage change from baseline in body weight, and change from baseline in cardiometabolic parameters, such as blood pressure, lipids, and hemoglobin A_{1c} levels. Dermatological assessments are included in eAppendix 4 in Supplement 3. Safety outcomes included a summary of treatment-emergent adverse events, discontinuation of the trial intervention due to adverse events, and serious adverse events.

Sample Size Calculation

A sample size of approximately 250 participants would provide more than 90% power to detect a treatment difference between the 2 trial arms for the primary end point using a 2-sided χ^2 test with an α of .05. It was assumed that the proportions of participants achieving a response were 37% and 3% for IXE+TZP or IXE, respectively.

Statistical Analysis

Efficacy analyses used data obtained during the treatment period from the modified intent-to-treat (mITT) population (ie, all randomly assigned participants with psoriasis and overweight with weight-related comorbidities or obesity), excluding data after treatment discontinuation or use of prohibited medication. In the primary estimand, the intercurrent events (ie, treatment discontinuation or prohibited medication use) were addressed by a hypothetical strategy in which the potential outcome of interest was the response in efficacy measure if participants would continue to receive their randomized treatment without prohibited medication use.[43] Missing data were handled with multiple imputation by treatment arm, using data up to intercurrent events for the primary and secondary end points.

For binary outcomes, a logistic regression was used as a working model to obtain unconditional risk differences (RDs) following the g-computation method.[44] For continuous efficacy outcomes used as input for components of primary and key secondary end points, an analysis of covariance with robust variance was performed. To consistently use the hypothetical estimand, other continuous efficacy outcomes with multiple postbaseline points used mixed-model repeated measures to estimate the treatment difference. The mean treatment difference, their 2-sided 95% CIs, and *P* values were reported for each outcome. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute).

Multiplicity adjustments were made for the primary and key secondary objectives to control the type I error rate at a 2-sided α level of .05 using graphical multiple testing procedure.[45,46] This method strongly controlled familywise type I errors, in which end points were tested in a dynamic nature with prespecified distribution of different α levels among them (eAppendix 5 in Supplement 3). No multiplicity adjustments were performed on other secondary, exploratory objectives, and safety assessments. *P* values and statistical significance reported for those end points were nominal.

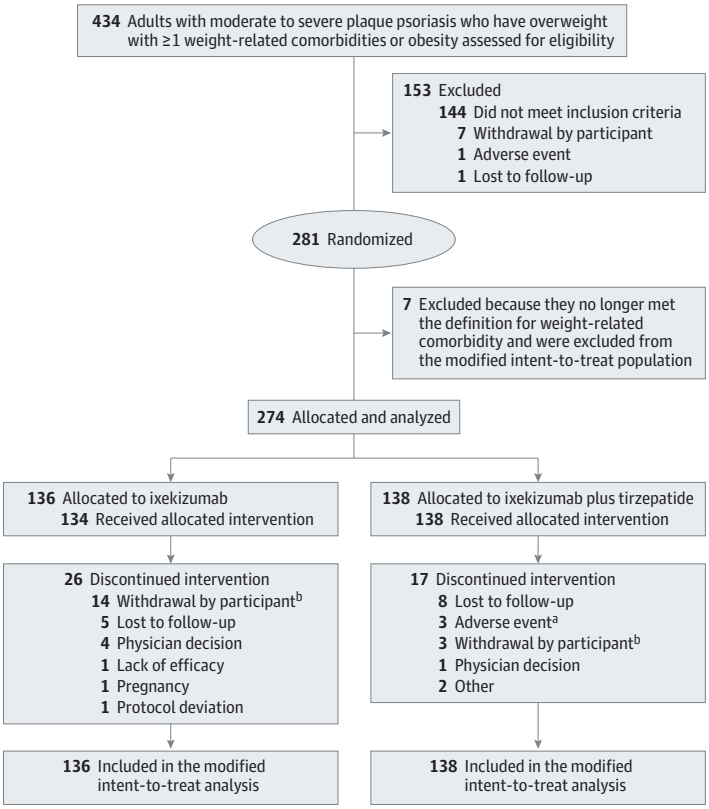
Safety analyses used data obtained during the treatment period plus safety follow-up period from the modified safety population (ie, participants in the mITT population who were exposed to at least 1 dose of any of the trial drugs) up to the cutoff date, regardless of adherence to trial drug. Further details are included in eAppendix 5 in Supplement 3 and the statistical analysis plan (Supplement 2).

Results

Participants

A total of 434 participants were assessed for eligibility and 274 were randomized to IXE+TZP (n = 138) or IXE (n = 136) and included in the mITT population (**Figure 1**). An additional randomized 7 participants who did not have weight-related comorbidity were excluded from the mITT popula-

Figure 1. Flow Diagram of Participants in the TOGETHER-PsO Trial through Week 36



Data were from the modified intent-to-treat population up to the week 36 visit.

[a]Three participants in the ixekizumab plus tirzepatide arm discontinued treatment due to adverse events (necrotizing fasciitis, bilateral axilla skin infection, and noncardiac chest pain).

[b]The most common reasons for withdrawal by participant included scheduling conflicts, personal issues that were unrelated to trial, a participant feeling like their condition was not improving, and a wish to initiate prohibited medications.

tion. In the mITT population, 121 (87.7%) completed IXE+TZP treatment and 110 (80.9%) completed IXE treatment through week 36. In the IXE+TZP treatment arm, 83.9% of participants with dosing data had TZP, 15 mg; 4.5% TZP, 10 mg; and 7.1% TZP, 5 mg as their maximum tolerated dose by week 32.

Baseline demographic and clinical characteristics were similar across treatment arms (**Table 1**). The mean (SD) age of the participants was 45.6 (12.7) years; 123 (44.9%) were women and 151 (55.1%) were men; 2 (0.7%) were American Indian or Alaska Native, 9 (3.3%) were Asian, 20 (7.3%) were Black or African American, 3 (1.1%) were multiracial, and 219 (79.9%) were White. The overall mean (SD) body weight was 113.8 (28.5) kg, mean (SD) BMI was 39.2 (9.1), mean (SD) time since psoriasis diagnosis was 14.6 (13.0) years, mean (SD) BSA was 26.4% (17.1%), mean (SD) PASI was 19.7 (8.1), and 266 participants (97.4%) had psoriasis that affected high-effect body sites. Ninety-four participants (34.3%) had prior experience with advanced therapies for psoriasis.

Primary End Point

Overall, 27.1% simultaneously achieved PASI 100 and a 10% or greater weight reduction at week 36 with IXE+TZP vs 5.8% with IXE (RD, 21.2%; 95% CI, 12.8%- 29.7%; $P < .001$; **Table 2**, eFigure 2 in Supplement 3; participants with imputed data: IXE+TZP, n = 18; IXE, n = 31; eAppendix 5 in Supplement 3).

Key Secondary End Points

A total of 40.6% of participants vs 29.0% achieved PASI 100 (RD, 11.6%; 95% CI, 0.3%-22.9; $P = .04$), 79.9% vs 17.9% simultaneously achieved PASI 75 and a 5% or greater weight reduction (RD, 62.0%; 95% CI, 51.7%-72.2%; $P < .001$), and 69.2% vs 9.1% experienced a 10% or greater weight reduction (RD, 60.0%; 95% CI, 50.4%- 69.7%; $P < .001$) with IXE+TZP vs IXE, respectively (Table 2, eFigure 2 in Supplement 3). Subgroup analyses by sex, treatment history, and screening BMI are included in eFigure 3 in Supplement 3.

Additional Secondary End Points

The treatment difference of IXE+TZP vs IXE alone for the proportion of participants achieving PASI 100 was significant as early as week 24 (**Figure 2**). Nonsignificantly greater proportions of participants receiving IXE+TZP achieved the individual end points of PASI 90 and PASI 75 at week 36 compared with IXE (Table 2; eFigure 4 in Supplement 3). The mean change (and percentage change) from baseline in PASI was greater with IXE+TZP than IXE at week 36 (Table 2). More participants receiving IXE+TZP achieved sPGA scores of 0 to 1 and DLQI scores of 0 to 1 compared with IXE (significant for DLQI) at week 36. The concomitant administration of IXE and TZP was associated with significant weight reduction through week 36 (Figure 2) and improvements in cardiometabolic parameters, such as systolic and diastolic blood pressure, total cholesterol levels,

triglyceride levels, and hemoglobin A_{1c} levels, compared with IXE.

Adverse Events

Overall, 98 participants (71.0%) who received IXE+TZP reported 1 or more treatment-emergent adverse events compared with 89 participants (66.4%) who received IXE, and most were mild to moderate in severity (**Table 3**). Serious adverse events were reported in 5 participants (3.6%) who received IXE+TZP and 8 (6.0%) who received IXE alone. There were no deaths reported. Adverse events leading to treatment discontinuation occurred for 5 participants (3.6%) who received IXE+TZP and 2 (1.5%) who received IXE, mainly due to gastrointestinal tract adverse events, noncardiac general disorders, and infections and infestations.

The most common events (occurring in ≥5% of participants in any treatment arm) were gastrointestinal tract adverse events and injection site reactions (Table 3). Gastrointestinal tract adverse events were more frequent among participants who received IXE+TZP than participants who received IXE (nausea, 34 [24.6%] vs 3 [2.2%]; diarrhea, 20 [14.5%] vs 2 [1.5%]; constipation, 18 [13%] vs 0; and vomiting, 12 [8.7%] vs 2 [1.5%]) and generally improved over time. Injection site

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Participants, No. (%)		
	Ixekizumab (n = 136)	Ixekizumab plus tirzepatide (n = 138)	Total (N = 274)
Age, mean (SD), y	45.7 (12.5)	45.6 (13.0)	45.6 (12.7)
Sex			
Female	61 (44.9)	62 (44.9)	123 (44.9)
Male	75 (55.1)	76 (55.1)	151 (55.1)
Screening BMI, mean (SD)[a]	39.2 (7.9)	39.3 (10.2)	39.2 (9.1)
Screening BMI category[a]			
≥27 to <30[b]	12 (8.8)	14 (10.1)	26 (9.5)
≥30	124 (91.2)	124 (89.9)	248 (90.5)
Weight, mean (SD), kg	115.5 (28.0)	112.1 (29.0)	113.8 (28.5)
Race[c]			
American Indian or Alaska Native	2 (1.5)	0	2 (0.7)
Asian	2 (1.5)	7 (5.1)	9 (3.3)
Black or African American	8 (5.9)	12 (8.7)	20 (7.3)
Multiracial	2 (1.5)	1 (0.7)	3 (1.1)
Not reported	8 (5.9)	13 (9.4)	21 (7.7)
White	114 (83.8)	105 (76.1)	219 (79.9)
Ethnicity[c]			
Hispanic or Latino	56 (41.2)	59 (42.8)	115 (42.0)
Not Hispanic or Latino	80 (58.8)	78 (56.5)	158 (57.7)
Not reported	0	1 (0.7)	1 (0.4)
Time since psoriasis diagnosis, mean (SD), y	16.0 (13.6)	13.2 (12.3)	14.6 (13.0)
Psoriatic arthritis	15 (11.0)	19 (13.8)	34 (12.4)
Treatment history			
Experience with advanced therapy[d]	49 (36.0)	45 (32.6)	94 (34.3)
No experience with advanced therapy[d]	87 (64.0)	93 (67.4)	180 (65.7)
No. of prior advanced therapies by class[e]			
0	87 (64.0)	93 (67.4)	180 (65.7)
1	39 (28.7)	30 (21.7)	69 (25.2)
2	7 (5.1)	10 (7.2)	17 (6.2)
>2	3 (2.2)	5 (3.6)	8 (2.9)
Baseline disease and quality of life scores, mean (SD)			
PASI[f]	19.1 (7.1)	20.4 (8.9)	19.7 (8.1)
BSA, %	24.7 (15.6)	28.1 (18.4)	26.4 (17.1)
sPGA of 3, No. (%)[g]	88 (64.7)	93 (67.4)	181 (66.1)
sPGA of 4, No. (%)[g]	48 (35.3)	45 (32.6)	93 (33.9)
Psoriasis in high-effect body sites[h]	132 (97.8)	134 (97.1)	266 (97.4)
DLQI[i]	11.0 (6.7)	11.2 (6.7)	11.1 (6.7)
Itch numeric rating scale[j]	7.4 (2.0)	7.1 (2.1)	7.2 (2.0)

(continued)

Table 1. Baseline Demographic and Clinical Characteristics (continued)

Characteristic	Participants, No. (%)		
	Ixekizumab (n = 136)	Ixekizumab plus tirzepatide (n = 138)	Total (N = 274)
Metabolic characteristics			
Hypertension	55 (40.4)	67 (48.6)	122 (44.5)
Dyslipidemia	18 (13.2)	37 (26.8)	55 (20.1)
Obstructive sleep apnea	16 (11.8)	12 (8.7)	28 (10.2)
Cardiovascular disease	5 (3.7)	8 (5.8)	13 (4.7)
Type 2 diabetes	10 (7.4)	20 (14.5)	30 (10.9)
Waist circumference, mean (SD), cm	121.4 (20.1)	119.4 (19.6)	120.4 (19.8)
Systolic blood pressure, mean (SD), mm Hg	131.9 (14.6)	133.8 (14.4)	132.9 (14.5)
Diastolic blood pressure, mean (SD), mm Hg	83.3 (9.6)	84.8 (10.1)	84.1 (9.9)
Lipid level, mean (SD), mg/dL			
LDL-C level	118.8 (33.9)	114.2 (36.2)	116.5 (35.1)
HDL-C level	45.0 (11.3)	46.2 (12.9)	45.6 (12.1)
Total cholesterol level	198.3 (40.3)	191.3 (40.9)	194.8 (40.7)
Triglyceride level	183.1 (116.8)	157.2 (88.7)	169.9 (104.0)
Hemoglobin A_{1c} level, mean (SD), %	5.8 (0.7)	5.8 (0.8)	5.8 (0.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; DLQI, Dermatology Life Quality Index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259; hemoglobin A_{1c} to the proportion of total hemoglobin, multiply by 0.01; triglycerides to mmol/L, multiply by 0.0113.

[a] Screening BMI category was used as it was the stratification variable.

[b] Weight-related comorbidity requirement.

[c] Race and ethnicity were determined by the participant according to fixed selection categories.

[d] Advanced therapy included tumor necrosis factor α inhibitors, interleukin 17 inhibitors, interleukin 12/23 inhibitors, interleukin 23 inhibitors, and Janus kinase or tyrosine kinase 2 inhibitors. Apremilast was not considered an advanced therapy.

[e] Prior therapies are categorized by drug class. Participants using more than 1 drug of the same class were counted once.

[f] Overall PASI ranges from 0 (clear skin) to 72 (worst possible psoriasis); a score of 12 indicates moderate disease.

[g] The sPGA determines the participant's psoriasis overall lesions and ranges from 0 (clear) to 4 (severe).

[h] High-effect sites included the face, genitalia, scalp, palm, sole, axilla, inframammary fold, abdominal skin fold, and inguinal region.

[i] DLQI ranges from 0 to 30, with higher scores indicating greater impairment of quality of life.

[j] Itch numeric rating scale ranges from 0 (no itch) to 10 (worst itch imaginable).

reactions were similar in both treatment arms (17 [12.3%] vs 17 [12.7%], respectively).

Discussion

This was a randomized clinical trial to evaluate the efficacy and safety of the concomitant administration of IXE and TZP in adults with psoriasis and overweight or obesity. At week 36, statistically significant greater proportions of participants who received IXE+TZP met the primary multicomponent end point of complete resolution of psoriasis (PASI 100) and clinically meaningful reduction of body weight (≥10%), as well as the key secondary end point of PASI 100, vs IXE alone, a highly effective treatment for skin clearance in psoriasis.[21,34-39] Achieving complete skin clearance (PASI 100) is associated with no effect of skin disease on quality of life, as represented by the DLQI (score, 0-1),[47] which is supported by this trial's findings. Nonsignificantly greater proportions of participants who received IXE+TZP vs IXE alone met PASI 90 and PASI 75. Furthermore, a statistically significant greater proportion of participants who received IXE+TZP vs IXE alone met the multicomponent key secondary end point of clinically meaningful response of PASI 75 and at least 5% weight reduction.

This trial enrolled participants with overweight or obesity, a population with psoriasis that is difficult to treat and characterized by generally lower response rates to biologic treatments compared with patients with a BMI from 18.5 to 24.9.[15] Participants had BMIs that were 9 to 10 points higher compared with prior advanced therapy pivotal trials[19-24] and had greater female representation as well as extensive skin BSA involvement. Nearly all participants (97%) had psoriasis that affected high-effect body sites (eg, face, scalp, palms/soles, or genitals), which is associated with substantial morbidity and itch.[48] Patients also had long mean psoriasis duration (14.6 years). Moreover, high disease activity and obesity are key independent risk factors for progression to psoriatic arthritis.[17]

Concomitant administration of IXE+TZP produced independent improvements in skin clearance and reductions in body weight, as individual or multicomponent end points, along with clinically meaningful improvements in key cardiometabolic parameters that reflected comprehensive benefits for these patients in the context of cardiovascular risk increase in psoriasis.[25] Future clinical and translational work is needed to determine to what extent improved psoriasis outcomes were related to weight change vs other potential effects of TZP.

Table 2. Primary and Secondary End Points at Week 36[a]

End point	Response % (95% CI)		Difference ixekizumab plus tirzepatide vs ixekizumab (95% CI)	*P* value
	Ixekizumab (n = 136)	Ixekizumab plus tirzepatide (n = 138)		
Primary end point[b]				
Simultaneous PASI 100 and ≥10% weight reduction	5.8 (1.9 to 9.8)	27.1 (19.6 to 34.5)	21.2 (12.8 to 29.7)	<.001
Key secondary end points[b]				
PASI 100	29.0 (21.3 to 36.7)	40.6 (32.3 to 48.9)	11.6 (0.3 to 22.9)	.04
Simultaneous PASI 75 and ≥5% weight reduction	17.9 (10.9 to 24.9)	79.9 (72.7 to 87.0)	62.0 (51.7 to 72.2)	<.001
≥10% Weight reduction	9.1 (3.8 to 14.5)	69.2 (61.1 to 77.3)	60.0 (50.4 to 69.7)	<.001
Additional secondary end points[c]				
PASI 75	87.2 (80.8 to 93.6)	91.5 (86.2 to 96.7)	4.3 (−3.8 to 12.3)	.30
PASI 90	65.1 (56.3 to 73.9)	75.6 (67.9 to 83.4)	10.5 (−1.3 to 22.3)	.08
Change from baseline in PASI, mean (SD)	−17.7 (0.54)	−18.1 (0.50)	−0.4 (−1.2 to 0.5)	.39
Change from baseline in PASI, mean (SD), %	−88.9 (1.43)	−92.2 (1.16)	−3.3 (−6.9 to 0.3)	.07
BSA ≤1%	57.4 (49.1 to 65.8)	64.4 (56.4 to 72.4)	7.0 (−4.6 to 18.6)	.24
sPGA score, 0-1	66.7 (57.9 to 75.5)	76.5 (68.8 to 84.2)	9.8 (−2.2 to 21.8)	.11
DLQI score of 0-1 in participants with baseline DLQI>1	58.3 (49.9 to 66.8)	71.7 (64.0 to 79.3)	13.3 (2.0 to 24.7)	.02
≥4-Point improvement in itch NRS in participants with baseline itch NRS score ≥4 points	80.6 (73.8 to 87.4)	81.8 (75.0 to 88.7)	1.2 (−8.3 to 10.8)	.80
Metabolic end points[c]				
Change from baseline in body weight, %	−1.2 (0.60)	−14.6 (0.77)	−13.4 (−15.3 to −11.4)	<.001
Change from baseline in BMI	−0.37 (0.30)	−5.71 (0.29)	−5.34 (−6.12 to −4.57)	<.001
Change from baseline in systolic blood pressure, mm Hg	−1.4 (1.15)	−9.9 (1.09)	−8.5 (−11.6 to −5.3)	<.001
Change from baseline in diastolic blood pressure, mm Hg	0.3 (0.83)	−3.6 (0.79)	−3.9 (−6.1 to −1.6)	<.001
Change from baseline in LDL-C level, mg/dL[d]	−3.2 (2.58)	−4.0 (2.34)	−0.8 (−7.6 to 6.1)	.82
Change from baseline in HDL-C level, mg/dL[d]	0.5 (0.61)	1.4 (0.59)	1.0 (−0.7 to 2.7)	.26
Change from baseline in total cholesterol level, mg/dL[d]	−1.3 (2.81)	−10.0 (2.54)	−8.7 (−16.2 to −1.2)	.02
Change from baseline in triglyceride level, mg/dL[d]	−0.2 (6.34)	−32.2 (4.73)	−31.9 (−47.5 to −16.4)	<.001
Change from baseline in hemoglobin A_{1c} level, %	0.1 (0.05)	−0.5 (0.05)	−0.6 (−0.7 to −0.5)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; DLQI, Dermatology Life Quality Index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index (75, 90, and 100 indicate percentage reduction from baseline); sPGA, static Physician Global Assessment.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259; hemoglobin A_{1c} to the proportion of total hemoglobin, multiply by 0.01; triglycerides to mmol/L, multiply by 0.0113.

[a] Hypothetical estimand evaluated treatment effects using data before discontinuation of trial drug or use of prohibited medication. Missing values were handled using multiple imputation for the primary and key secondary end points and continuous variables on which primary and key secondary end points were based. Mixed-model repeated measures without imputation were used for the rest of the continuous variables that were not used as input for the primary and key secondary end points. Other binary outcomes using those continuous variables were based on the mixed-model repeated measure predicted value. A logistic regression with treatment group, screening BMI group, sex, and treatment history as factors was used as a working model for binary outcomes to estimate unconditional risk difference. Change and percentage change from baseline in PASI and the percentage change from baseline in weight used an analysis of covariance with robust variance, including treatment group, baseline value, screening BMI group, sex, and treatment history as fixed factors. For other continuous variables with multiple postbaseline points, mixed-model repeated measures were used with treatment group, baseline value, randomization stratification factors, visit, and the interaction of treatment by visit as fixed effects.

[b] Tested for superiority, which controlled for type 1 errors.

[c] Not controlled for type 1 errors. Further details can be found in eAppendix 5 in Supplement 3.

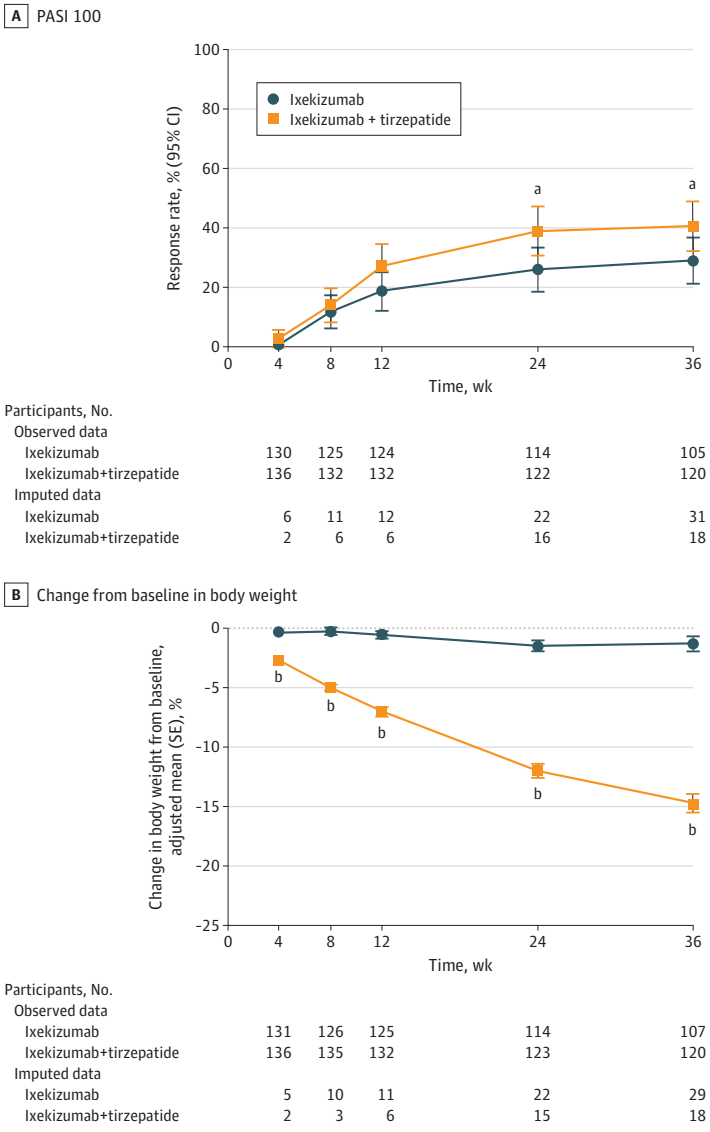
[d] Log-transformation was used.

The extent of weight reduction and improvement in cardiometabolic parameters with IXE+TZP was broadly consistent with that reported with TZP in the SURMOUNT studies in people with overweight or obesity, considering differences in the trial design and population, such as a lower female representation and higher baseline weight in the TOGETHER-PsO population compared with the SURMOUNT participants.[28,29] Also, the minimal effects of IXE with lifestyle counseling on weight and cardiometabolic parameters, such as blood pressure and lipid profiles, aligned with those suggested by an integrated analysis of the IXE UNCOVER studies at 60 weeks in participants with psoriasis.[49]

Adverse events were generally consistent with established drug safety profiles. The frequency of injection site reactions and treatment discontinuation due to injection site reactions with IXE alone was comparable with that observed in the UNCOVER trials.[21,34-36] The gastrointestinal tract adverse events and discontinuations due to gastrointestinal tract adverse events observed with IXE+TZP were consistent with previously reported rates for TZP in the SURMOUNT trials.[28,29]

Collectively, these findings support elevating the standard of care from treating psoriasis in isolation to a therapeutic approach that addresses the immunologic and

Figure 2. Bar Graphs of Psoriasis Area and Severity Index (PASI) 100 and Percentage Change From Baseline in Body Weight Through Week 36



Participants, No.					
Observed data					
Ixekizumab	130	125	124	114	105
Ixekizumab+tirzepatide	136	132	132	122	120
Imputed data					
Ixekizumab	6	11	12	22	31
Ixekizumab+tirzepatide	2	6	6	16	18

Participants, No.					
Observed data					
Ixekizumab	131	126	125	114	107
Ixekizumab+tirzepatide	136	135	132	123	120
Imputed data					
Ixekizumab	5	10	11	22	29
Ixekizumab+tirzepatide	2	3	6	15	18

Hypothetical estimand evaluated treatment effects using data before discontinuation of the trial drug or use of prohibited medication. Missing values were handled using multiple imputation. For PASI 100, a logistic regression with treatment group, screening body mass index (BMI) group, sex, and treatment history as factors was used as working model to estimate unconditional risk difference. For the percentage change from baseline in body weight, analysis of covariance with robust variance, including treatment group, baseline value, screening BMI group, sex, and treatment history as fixed factors was used. 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 point for PASI 100. Nominal *P* values were reported for other points and the percentage change from baseline in body weight.

[a]*P* < .05 vs ixekizumab.

[b]*P* < .001 vs ixekizumab.

metabolic (especially obesity) components of psoriasis-associated inflammation with IXE+TZP. This trial complements the findings for TOGETHER-PsA, which demonstrated clinically meaningful improvement of psoriatic arthritis, physical function, and quality of life and reductions in weight with IXE+TZP compared with IXE alone.[42] While effects on joints may be partially weight related, the skin outcomes were supported by this trial, which may represent a potential alternative mechanism of adding TZP beyond direct mechanical effects of weight reduction. In the context of current guidelines, to our knowledge, this trial and TOGETHER-PsA provide the first randomized clinical evidence to further support addressing comorbidities, such as overweight or obesity, in treating psoriatic disease, providing benefits on metabolic and inflammatory disease outcomes.

Strengths and Limitations

The strengths of this trial included the randomized, active-controlled design and appropriateness of the duration of the trial for the primary and key secondary end points based on the time course of IXE responses in the UNCOVER trials[34] and magnitude and rate of weight reduction in the SURMOUNT-1 trial.[28] Masked assessors evaluated psoriasis-related assessments.

Limitations of this trial included its open-label design, larger amount of imputed data in the IXE arm compared with the IXE+TZP arm with potential to introduce bias, and potential masked assessors' awareness of treatment allocation based on weight change. No TZP monotherapy arm was included to assess a potential direct effect on psoriasis severity. Participants with prior or current inadequate response to interleukin 17 inhibitor(s) were not included; they will be evaluated

Table 3. Adverse Events[a]

Adverse events	Participants, No. (%)	
	Ixekizumab (n = 134)[b]	Ixekizumab plus tirzepatide (n = 138)
Any treatment-emergent adverse event	89 (66.4)	98 (71.0)
Mild	45 (33.6)	44 (31.9)
Moderate	37 (27.6)	47 (34.1)
Severe	6 (4.5)	7 (5.1)
Missing	1 (0.7)	0
Adverse events occurring in ≥5% of participants in any treatment arm		
Nausea	3 (2.2)	34 (24.6)
Diarrhea	2 (1.5)	20 (14.5)
Constipation	0	18 (13.0)
Injection site reaction[c]	17 (12.7)	17 (12.3)
Overdose (dosing error)[d]	11 (8.2)	14 (10.1)
Vomiting	2 (1.5)	12 (8.7)
Dizziness	0	7 (5.1)
Nasopharyngitis	7 (5.2)	3 (2.2)
Serious adverse events	8 (6.0)	5 (3.6)
Deaths	0	0
Eye disorders	0	1 (0.7)
Optic ischemic neuropathy[e]	0	1 (0.7)
Gastrointestinal tract disorders	1 (0.7)	0
Ulcerative colitis[f]	1 (0.7)	0
Infections and infestations	4 (3.0)	2 (1.4)
Necrotizing fasciitis[g]	0	1 (0.7)
Pneumonia	1 (0.7)	1 (0.7)
Ear infection	1 (0.7)	0
Empyema	1 (0.7)	0
Kidney infection	1 (0.7)	0
Sepsis	2 (1.5)	0
Sinusitis	1 (0.7)	0
Tooth infection	1 (0.7)	0
Injury, poisoning, and procedural complications	1 (0.7)	0
Lower limb fracture	1 (0.7)	0
Musculoskeletal and connective tissue disorders	1 (0.7)	0
Sacroiliac joint dysfunction	1 (0.7)	0
Neoplasms that are benign, malignant, and unspecified (including cysts and polyps)	0	1 (0.7)
Uterine leiomyoma[h]	0	1 (1.6)
Reproductive system and breast disorders	0	1 (0.7)
Vaginal hemorrhage[h]	0	1 (1.6)
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	0
Asthma	1 (0.7)	0
Surgical and medical procedures	0	1 (0.7)
Cholecystectomy	0	1 (0.7)
Vascular disorders	1 (0.7)	0
Hypertension	1 (0.7)	0
Adverse events leading to treatment discontinuation	2 (1.5)	5 (3.6)
Gastrointestinal tract disorders	1 (0.7)	1 (0.7)
Nausea	0	1 (0.7)
Ulcerative colitis[f]	1 (0.7)	0
General disorders and administration site conditions	0	1 (0.7)
Noncardiac chest pain	0	1 (0.7)
Infections and infestations	0	2 (1.4)
Necrotizing fasciitis[g]	0	1 (0.7)
Skin infection	0	1 (0.7)
Investigations	0	1 (0.7)
Lipase increased	0	1 (0.7)
Metabolism and nutrition disorders	1 (0.7)	0
Diabetes	1 (0.7)	0
Selected adverse events of special interest		
Infection	40 (29.9)	37 (26.8)
Inflammatory bowel disease[f]	1 (0.7)	0
Injection site reaction[c,i]	17 (12.7)	19 (13.8)
Pancreatitis[j]	0	1 (0.7)
Severe or serious gastrointestinal tract events	1 (0.7)	2 (1.4)
Abdominal pain	0	1 (0.7)
Fecaloma	0	1 (0.7)
Vomiting	0	1 (0.7)
Ulcerative colitis[f]	1 (0.7)	0

[a] Data represent the number of participants with at least 1 event reported from modified safety population up to the cutoff date.

[b] One participant was randomized to the ixekizumab arm but inadvertently took a dose of tirzepatide, 2.5 mg, at week 0. Given that only 1 dose of tirzepatide was taken at the lowest level and the short half-life of tirzepatide, this participant was summarized per the randomized arm (ie, ixekizumab arm) in all safety analyses.

[c] Injection site reactions referred to either ixekizumab or tirzepatide in the ixekizumab plus tirzepatide arm.

[d] Any administration of trial drug that exceeded the protocol-specified number of injections was classified as an overdose (dosing error). For ixekizumab, this referred to any dose greater than the intended amount. For tirzepatide, this referred to any amount greater than the intended dose administered within a 72-hour period. Most events were associated with ixekizumab.

[e] Optic ischemic neuropathy occurred on day 85 of trial treatment; there was a participant with multiple predisposing risk factors for optic ischemic neuropathy, and the drug was withdrawn.

[f] Inflammatory bowel disease was defined as ulcerative colitis as reported in treatment-emergent adverse events. Ulcerative colitis occurred on day 193 of trial treatment; the drug was withdrawn.

[g] Necrotizing fasciitis occurred on day 13 of trial treatment; the drug was withdrawn.

[h] Denominator was adjusted because of sex-specific event for female individuals (ixekuzumab: 60; ixekizumab plus tirzepatide: 62; total: 122).

[i] Injection site reaction is a cluster of individual adverse events by preferred term.

[j] Pancreatitis (suspected) occurred on day 256 of trial treatment and was reported as a treatment-emergent adverse event (nonserious); treatment was interrupted for further assessment at the time of database lock; the participant recovered from the adverse event.

in another ongoing trial (NCT06857942) in psoriasis that is assessing the addition of TZP to IXE therapy. Finally, this trial was conducted solely in the US with 274 patients, in contrast to historical large, global phase 3/4 active-controlled psoriasis trials.

Conclusions

This randomized clinical trial evaluated an incretin and biologic therapy in participants with psoriasis and overweight or obesity. Concomitant administration of IXE+TZP was superior to IXE alone in achieving key efficacy outcomes at 36 weeks of treatment, including complete skin clearance, with no new safety concerns. Furthermore, these results highlight improvements in psoriatic and cardiometabolic end points and the overall health of patients, as evidenced by patient-reported outcomes. Combined, the findings from this trial support the multifaceted health benefits of concomitant therapy with IXE and TZP for treating psoriasis and management of comorbidities and may help to inform future clinical practice and guideline recommendations for these patients.

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Author Contributions: Dr Lebwohl had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Administrative, technical, or material support: Kartman, Leatherwood, Cardoso, Armstrong.
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