TALTZ® (ixekizumab): Efficacy on Psoriasis in Psoriatic Arthritis

SPIRIT-P1 Analysis

SPIRIT-P1 was a phase 3, 24-week, double-blind, placebo- and active-controlled trial in patients with active psoriatic arthritis who were naïve to biologic, disease modifying antirheumatic drugs (bDMARDs), with an open-label extension period of up to 3 years.[1]

Adalimumab at the approved psoriatic arthritis dosing of 40 mg every 2 weeks (Q2W) was selected as an active reference arm to validate study design. The study was not powered to compare adalimumab with ixekizumab.[1]

The primary objective of SPIRIT-P1 was to assess whether ixekizumab was superior to placebo in the treatment of bDMARD-naïve patients with active psoriatic arthritis, as measured by the proportion of patients who achieved ACR20 response at week 24.[1]

Patients who failed to demonstrate at least 20% improvement from baseline in both tender joint count and swollen joint count at week 32 or any subsequent visit were required to discontinue from the study.[1]

Other key secondary measures including 75% improvement in Psoriasis Area and Severity Index (PASI 75), PASI 90, and PASI 100 response rates were only assessed in patients with psoriatic lesions involving at least 3% of body surface area (BSA) at baseline.[1]

Figure 1 shows the SPIRIT-P1 study design.

Figure 1. SPIRIT-P1 Study Design: Double-Blind Treatment and Extension Periods[1,2]

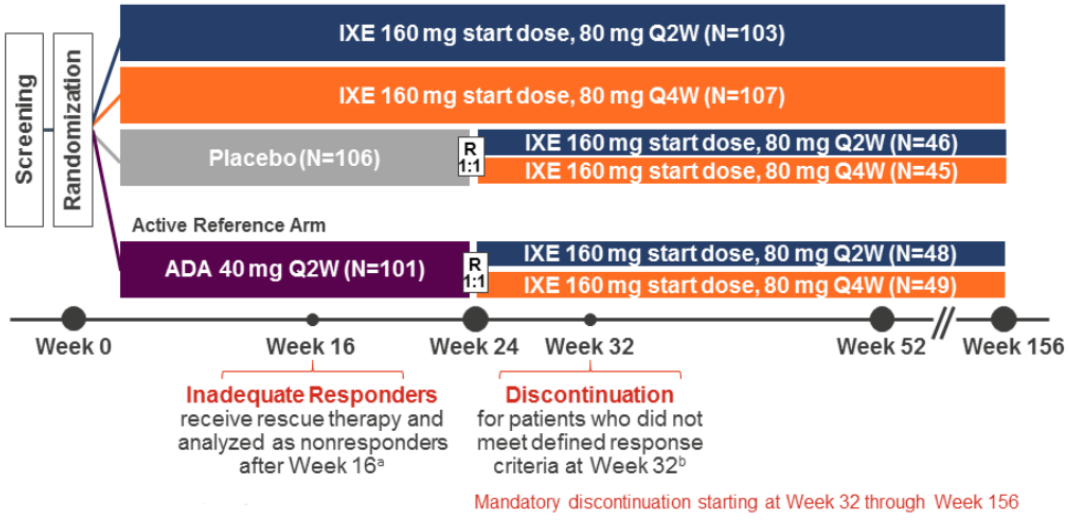

Figure 1 description: Patients were initially randomized in a 1:1:1:1 ratio to receive ixekizumab 80 mg every 4 weeks after a 160-mg starting dose, ixekizumab 80 mg every 2 weeks after a 160-mg starting dose, adalimumab every 2 weeks, or placebo at week 0. Adalimumab represents an active reference arm. The study was not powered to test equivalence or noninferiority of active treatment groups to each other, including ixekizumab vs adalimumab. Among patients initially randomized to receive ixekizumab every 2 weeks (N=103), 96 entered the extension period and remained on ixekizumab every 2 weeks. Among patients initially randomized to receive ixekizumab every 4 weeks (N=107), 97 entered the extension period and remained on ixekizumab every 4 weeks.
Abbreviations: ADA = adalimumab; IR = inadequate responder; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomization; SJC = swollen joint count; TJC = tender joint count.
[a]All IRs (as determined by prespecified, blinded TJC and SJC criteria) at week 16 received rescue therapy and were analyzed as nonresponders at week 24. Placebo-IRs received their first dose of IXE at week 16, whereas ADA-IRs had an 8-week placebo washout period before beginning their first dose of IXE at week 24.
[b] Patients were discontinued from the study if they did not demonstrate a ≥20% improvement from baseline in both TJC and SJC criteria at week 32 or at any subsequent visit during the study.

24-Week PASI Results

A significantly greater percentage of patients taking ixekizumab achieved PASI 75 at week 24 compared with placebo (p≤.001). Table 1 describes the results.[1]

Table 1. SPIRIT-P1 Efficacy Results: PASI Response at 24 Weeks in the Double-Blind Treatment Period in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, ITT Population, NRI[1]

Efficacy Measure	PBO (n=106)	IXE 80 mg Q4W (n=107)	IXE 80 mg Q2W (n=103)	ADA 40 mg Q2W (n=101)
PASI 75, %	10.4	71.2[a]	79.7[a]	54.4[a]
PASI 90, %	6.0	56.2[a]	67.8[a]	36.8[a]
PASI 100, %	3.0	42.5[a]	52.5[a]	23.5[b]

Abbreviations: ADA = adalimumab; ITT = intent-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PASI = Psoriasis Area Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] p≤.001 vs PBO.
[b] p≤.01 vs PBO.

52-Week PASI Results

The PASI analysis consisted only of patients who had baseline psoriatic lesions ≥3% BSA and were sustained up to 52 weeks of treatment (Table 2).[2]

Table 2. SPIRIT-P1 Efficacy Results: PASI Response at 52 Weeks in the Double-Blind Treatment Period in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, ITT Population, NRI[2]

Efficacy Measure	IXE 80 mg Q4W (N=73)	IXE 80 mg Q2W (N=59)
PASI 75, %	71	76
PASI 90, %	60	73
PASI 100, %	51	63

Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PASI = Psoriasis Area Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

156-Week PASI Results

Through 156 weeks, patients treated with ixekizumab experienced sustained improvements in PASI 75, PASI 90, and PASI 100 scores as shown in Table 3.[3]

Table 3. SPIRIT-P1 PASI Response Rates for ITT Population at Week 156, mNRI Analysis[3]

Efficacy Outcome	IXE Q4W (n=107)	IXE Q2W (n=103)
PASI 75, n/Nx (%)	46/73 (63)	41/59 (69)
PASI 90, n/Nx (%)	37/73 (51)	38/59 (65)
PASI 100, n/Nx (%)	32/73 (44)	36/59 (61)

Abbreviations: ITT = Intent-to-treat; IXE = ixekizumab; mNRI =modified nonresponder imputation; Nx = patients with psoriatic lesions ≥3% of body surface area at baseline; PASI = Psoriasis Area and Severity Index; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index; PASI 90 = 90% improvement from baseline in Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

SPIRIT-P2 Analysis

SPIRIT-P2, a multicenter, randomized clinical trial, compared the safety and efficacy of ixekizumab with that of placebo in adult patients with active psoriatic arthritis and prior inadequate response or intolerance to 1 or 2 tumor necrosis factor (TNF) inhibitors.[4]

After the 24-week, double-blind, placebo-controlled clinical trial period, there was an open-label extension period from weeks 24 to 156. Figure 2shows the study design. The results for SPIRIT-P2 at 156 weeks are ongoing.[4]

Patients who failed to demonstrate at least 20% improvement from baseline in both TJC and SJC at week 32 or any subsequent visit were required to discontinue from the study.[4]

Figure 2. SPIRIT-P2 Study Design: Double-Blind Treatment and Extension Periods[4,5]

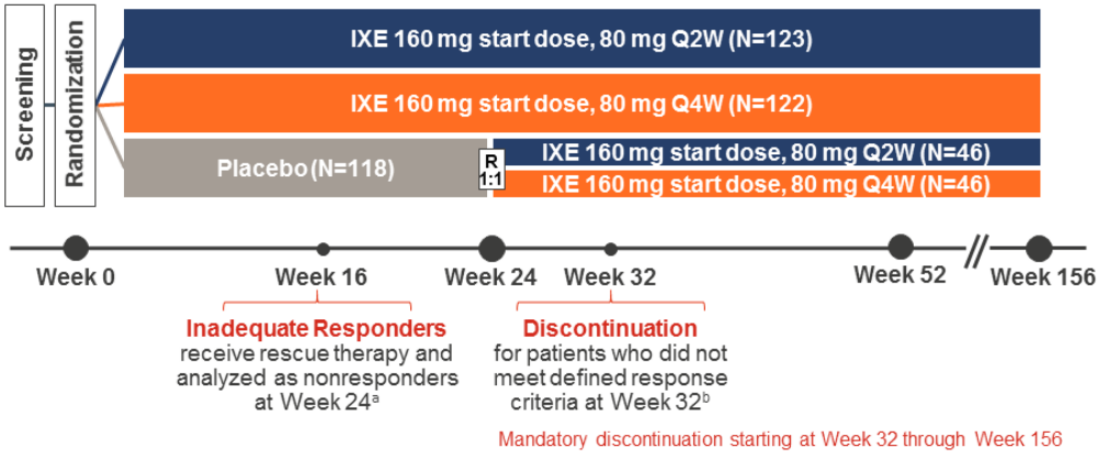

Figure 2 description: Patients were initially randomized in a 1:1:1 ratio to receive ixekizumab 80 mg every 4 weeks after a 160-mg starting dose, ixekizumab 80 mg every 2 weeks after a 160-mg starting dose, or placebo at week 0. Among patients initially randomized to ixekizumab every 2 weeks (N=123), 107 entered the extension period on ixekizumab every 2 weeks. Among patients initially randomized to ixekizumab every 4 weeks (N=122), 111 entered the extension period on ixekizumab every 4 weeks.
Abbreviations: IR = inadequate responder; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; SJC = swollen joint count; TJC = tender joint count.
[a] All IRs (as determined by prespecified, blinded TJC and SJC criteria) at week 16 received rescue therapy and were analyzed as nonresponders at week 24. Placebo-IRs received their first dose of IXE at week 16.
[b] Patients were discontinued from the study if they did not demonstrate a ≥20% improvement from baseline in both TJC and SJC at week 32 or at any subsequent visit during the study.

24-Week PASI Results

A significantly greater percentage of patients who were on ixekizumab achieved PASI 75 at week 24 compared with placebo (p<.0001).[4] Table 4 describes these results.

Table 4. SPIRIT-P2 Efficacy Results: Percent PASI Response at 24 Weeks for the Double-Blind Treatment Period, ITT Population, NRI[4]

Efficacy Measure	PBO (n=118)	IXE 80 mg Q4W (n=122)	IXE 80 mg Q2W (n=123)
PASI 75, n/Nx (%)	10/67 (15)	38/68 (56)[a]	41/68 (60)[a]
PASI 90, n/Nx (%)	8/67 (12)	30/68 (44)[a]	34/68 (50)[a]
PASI 100, n/Nx (%)	3/67 (4)	24/68 (35)[b]	19/68 (28)[c]

Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; Nx = patients with psoriatic lesions ≥3% of body surface area at baseline; NRI = nonresponder imputation; PASI = Psoriasis Area Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] p<.0001 vs PBO.
[b] p=.0001 vs PBO.
[c] p=.0006 vs PBO.

52-Week PASI Results

In patients with plaque psoriasis ≥3% BSA at baseline, the proportion of patients who achieved PASI 75, PASI 90, and PASI 100 responses persisted through 52 weeks in the ITT population (Table 5).[5]

Table 5. SPIRIT-P2 Efficacy Results: PASI Response at 52 Weeks in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, ITT Population, NRI[5]

Efficacy Measure	IXE 80 mg Q4W	IXE 80 mg Q2W
PASI 75, %	60.3	54.4
PASI 90, %	50.0	39.7
PASI 100, %	39.7	35.3

Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; NRI = nonresponder imputation; PASI = Psoriasis Area Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

108-Week PASI Results

In patients with prior inadequate response or intolerance to TNF inhibitors, ixekizumab treatment provided clinically meaningful and sustained improvements in psoriatic arthritis through 2 years (Table 6).[6]

Table 6. SPIRIT-P2 Efficacy Results: PASI Response at 108 Weeks in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, ITT Population, mNRI[6]

Efficacy Measure	IXE 80 mg Q4W	IXE 80 mg Q2W
PASI 75, %	65	48
PASI 90, %	55	40
PASI 100, %	39	35

Abbreviations: ITT = intent-to-treat; IXE = ixekizumab; mNRI = modified nonresponder imputation; PASI = Psoriasis Area Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

156-Week PASI and sPGA Results

In patients with active psoriatic arthritis and a prior inadequate response or intolerance to TNF inhibitors, ixekizumab treatment resulted in persistent reduction and clearance of psoriatic skin lesions through 156 weeks (Figure 3, Figure 4, Figure 5, Figure 6, and Figure 7).[7]

Figure 3. SPIRIT-P2 Efficacy Results: PASI 75 Response Through 156 Weeks in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, Observed[7]

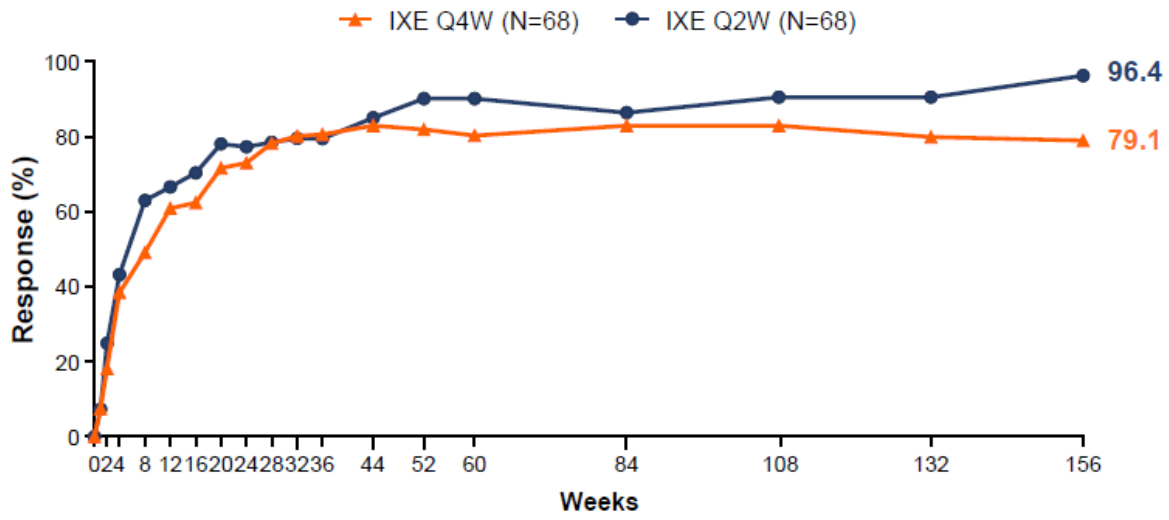

Figure 3 description: At week 156, 79.1% and 96.4% of patients achieved 75% improvement in Psoriasis Area and Severity Index response with ixekizumab every 4 weeks and ixekizumab every 2 weeks, respectively.
Abbreviations: IXE = ixekizumab; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 4. SPIRIT-P2 Efficacy Results: PASI 90 Response Through 156 Weeks in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, Observed[7]

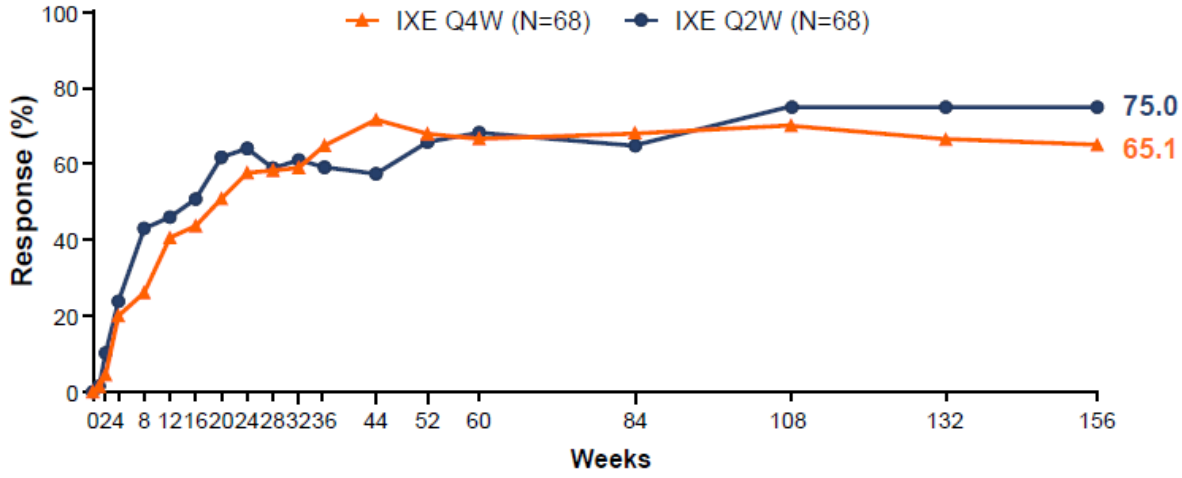

Figure 4 description: At week 156, 65.1% and 75.0% of patients achieved 90% improvement in Psoriasis Area and Severity Index response with ixekizumab every 4 weeks and ixekizumab every 2 weeks, respectively.
Abbreviations: IXE = ixekizumab; PASI 90 = 90% improvement from baseline in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 5. SPIRIT-P2 Efficacy Results: PASI 100 Response Through 156 Weeks in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, Observed[7]

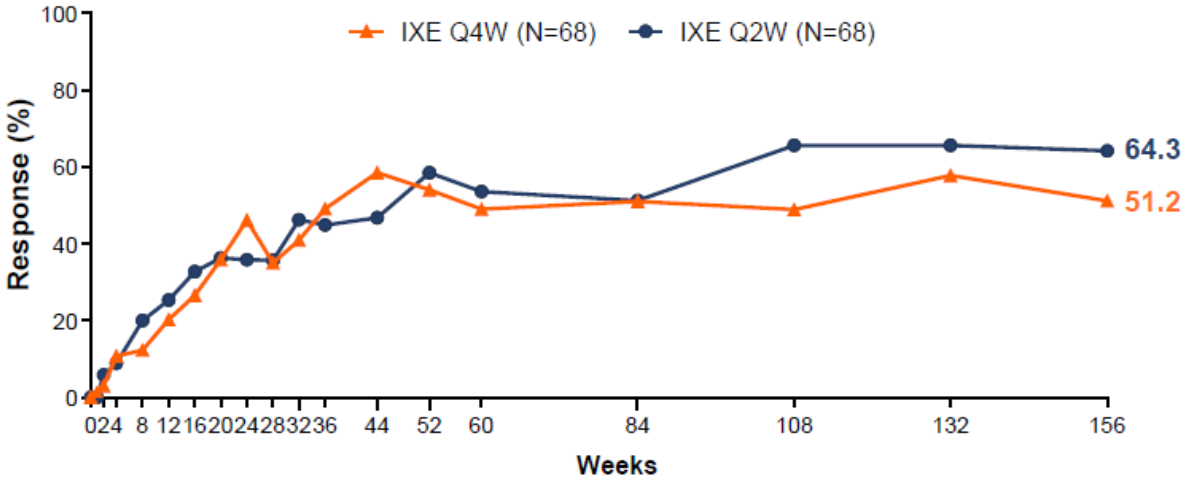

Figure 5 description: At week 156, 51.2% and 64.3% of patients achieved 100% improvement in Psoriasis Area and Severity Index response with ixekizumab every 4 weeks and ixekizumab every 2 weeks, respectively.
Abbreviations: IXE = ixekizumab; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 6. SPIRIT-P2 Efficacy Results: sPGA (0,1) Response Through 156 Weeks in Patients With Baseline sPGA ≥3, Observed[7]

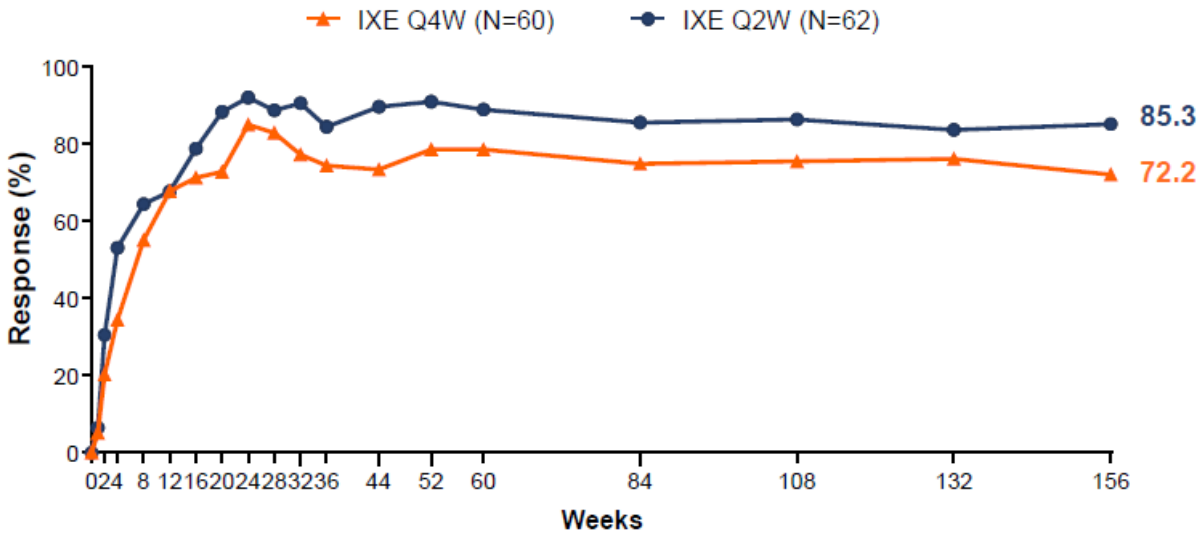

Figure 6 description: At week 156, 72.2% and 85.3% of patients achieved static Physician's Global Assessment (0,1) response with ixekizumab every 4 weeks and ixekizumab every 2 weeks, respectively.
Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

Figure 7. SPIRIT-P2 Efficacy Results: sPGA (0) Response Through 156 Weeks in Patients With Baseline sPGA ≥3, Observed[7]

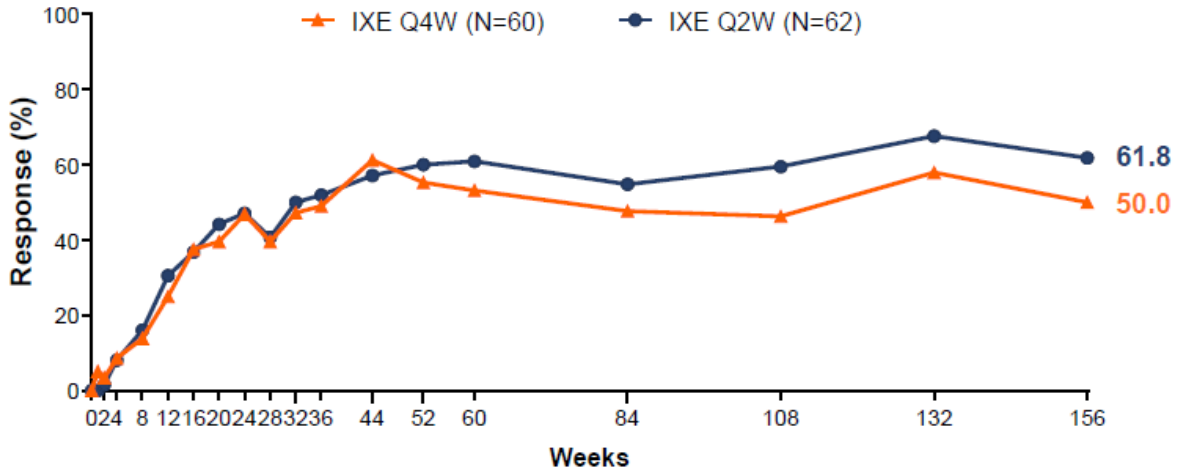

Figure 7 description: At week 156, 50.0% and 61.8% of patients achieved static Physician's Global Assessment (0) response with ixekizumab every 4 weeks and ixekizumab every 2 weeks, respectively.
Abbreviations: IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; sPGA = static Physician's Global Assessment.

INTEGRATED SPIRIT-P1 AND SPIRIT-P2 PASI ANALYSIS

In an integrated analysis of SPIRIT-P1 and SPIRIT-P2, patients with baseline psoriatic skin lesions involving at least 3% of BSA who were treated with ixekizumab had significantly greater PASI 75, PASI 90, and PASI 100 response rates compared with placebo at week 24 ($p<.001$) (Figure 8).[8]

Figure 8. SPIRIT-P1 and SPIRIT-P2: PASI Responses at Week 24, Integrated Efficacy Dataset in Patients With Baseline Psoriatic Lesions ≥3% Body Surface Area, NRI[8]

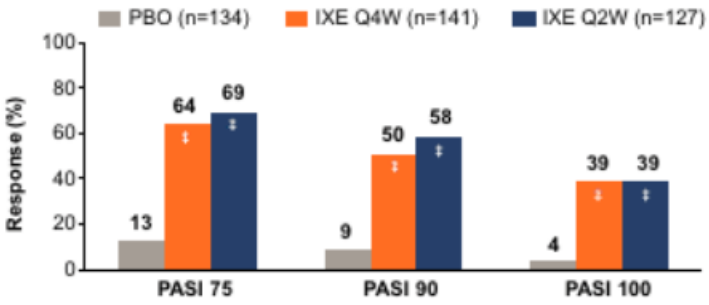

Figure 8 description: At week 24, patients treated with ixekizumab had significantly greater 75%, 90%, and 100% improvement in Psoriasis Area and Severity Index response rates compared with placebo.
Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; IXE = ixekizumab; NRI = nonresponder imputation; NSAIDs = nonsteroidal anti-inflammatory drugs; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index; PASI 90 = 90% improvement from baseline in Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SJC = swollen joint count; TJC = tender joint count.
‡ p<.001 vs PBO using logistic regression analysis.
Patients who had <20% improvement in TJC and SJC at week 16 were considered inadequate responders and were required to modify their concomitant medication by adjusting the dose of existing medication(s) and/or the introduction of new medication(s) until week 24. The following medications were eligible for modification: NSAIDs, opiate analgesics, cDMARDs; methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, and oral corticosteroids.

UNCOVER-1, -2, AND -3 ANALYSIS

Three multicenter, randomized, double-blind, placebo-controlled studies (UNCOVER-1, UNCOVER-2, and UNCOVER-3) enrolled a total of 3866 plaque psoriasis patients, aged 18 years and older, who were candidates for phototherapy and/or systemic therapy with

- BSA ≥10% involvement
- sPGA ≥3 on a severity scale of 0 to 5, and
- PASI ≥12 on a severity scale of 0 to 72.[9]

Table 7 summarizes PASI response rates in patients receiving the approved psoriasis dosing regimen with or without PsA at baseline in the UNCOVER clinical trials. The authors concluded that ixekizumab demonstrated high and sustained efficacy in skin clearance through 5 years of treatment and a consistent safety profile in patients with moderate-to-severe plaque psoriasis irrespective of baseline PsA status.[10]

Table 7. UNCOVER-1, -2, and -3: Efficacy Response Rates at Week 264 in Patients Receiving the Approved Psoriasis Dosing Regimen[a] With or Without Psoriatic Arthritis[10]

	PASI 75		PASI 90		PASI 100	
Response rate, %	**Observed**	**mNRI**	**Observed**	**mNRI**	**Observed**	**mNRI**
UNCOVER-1 and -2						
Patients with baseline PsA (N=49)	96.9	89.0	81.3	67.5	56.3	45.6

	PASI 75		PASI 90		PASI 100	
Response rate, %	**Observed**	**mNRI**	**Observed**	**mNRI**	**Observed**	**mNRI**
Patients without baseline PsA (N=157)	98.0	90.7	88.0	72.7	58.0	46.3
UNCOVER-3						
Patients with baseline PsA (N=74)	97.6	82.6	92.9	72.6	78.6	55.6
Patients without baseline PsA (N=288)	97.4	80.1	89.5	68.0	63.2	45.2

Abbreviations: mNRI = modified nonresponder imputation; PASI 75 = 75% improvement from baseline in Psoriasis Area and Severity Index; PASI 90 = 90% improvement from baseline in Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in Psoriasis Area and Severity Index; PsA = psoriatic arthritis.

[a] The approved dosing regimen for moderate-to-severe plaque psoriasis is ixekizumab 160 mg at week 0 followed by ixekizumab 80 mg every 2 weeks through week 12 and ixekizumab 80 mg every 4 weeks thereafter.

Last Reviewed: 16-January-2024

ENCLOSED PRESCRIBING INFORMATION

TALTZ® (ixekizumab) injection, for subcutaneous administration, Lilly

REFERENCES

The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

1. 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-naive 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. http://dx.doi.org/10.1136/annrheumdis-2016-209709

2. van der Heijde D, Gladman DD, Kishimoto M, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). *J Rheumatol*. 2018;45(3):367-377. http://dx.doi.org/10.3899/jrheum.170429

3. Chandran V, Fleischmann R, Lespessailles E, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: three year results from a phase 3 study (SPIRIT-P1). *Ann Rheum Dis*. 2018;77(suppl 2):385. Annual European Congress of Rheumatology (EULAR 2018) abstract THU0333. http://dx.doi.org/10.1136/annrheumdis-2018-eular.2137

4. 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. http://dx.doi.org/10.1016/S0140-6736(17)31429-0

5. Genovese MC, Combe B, Kremer JM, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. *Rheumatology*. 2018;57(11):2001-2011. http://dx.doi.org/10.1093/rheumatology/key182

6. Orbai AM, Gellett AM, Kerr L, Constantin A. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis and previous inadequate response to TNF inhibitors: two-year follow-up from a phase 3 study [abstract]. *Arthritis Rheumatol.* 2018;70(suppl 10). 2018 ACR/ARHP Annual Meeting abstract 2559. https://acrabstracts.org/abstract/efficacy-and-safety-of-ixekizumab-in-patients-with-active-psoriatic-arthritis-and-previous-inadequate-response-to-tnf-inhibitors-two-year-follow-up-from-a-phase-3-study/

7. Armstrong AW, Tillet W, Somani N, et al. Ixekizumab improves nail and skin lesions in patients with active psoriatic arthritis and prior TNF-inhibitor inadequate response: 3-year results from SPIRIT-P2. Poster presented at: 29th Annual Meeting of the European Academy of Dermatology and Venereology (EADV Virtual); October 28-31, 2020.

8. Combe B, Nash P, Adams D, et al. Integrated efficacy and safety results from SPIRIT-P1 and SPIRIT-P2, two phase 3 trials of ixekizumab for the treatment of psoriatic arthritis. Poster presented at: 26th Congress of the European Academy of Dermatology and Venereology (EADV); September 13-17, 2017; Geneva, Switzerland.

9. Gordon KB, Blauvelt A, Papp KA, et al; UNCOVER-1, UNCOVER-2, and UNCOVER-3 Study Groups. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356. http://dx.doi.org/10.1056/NEJMoa1512711

10. Gottlieb A, de Vlam K, Wang Y, et al. Efficacy and safety of ixekizumab in patients with moderate-to-severe plaque psoriasis with and without psoriatic arthritis at baseline: results from UNCOVER studies through 5 years. Poster presented at: American Academy of Dermatology Virtual Meeting Experience; April 23-25, 2021.