Ixekizumab
Η νέα θεραπευτική προσέγγιση στη ΨΑ μέσω της αναστολής της IL-17A

Απρίλιος 2018
ΕΠΕΜΥ
Πόρτο Χέλι

ΣΤΑΜΑΤΗΣ-ΝΙΚΟΣ ΛΙΟΣΗΣ
Καθηγ. Ρευματολογίας
Ιατρική Σχολή Παν. Πατρών

ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

Honoraria

- Genesis Pharma
- GSK
- MSD
- Novartis
- Janssen
- Pfizer
- Roche
- Actelion

Χρηματοδότηση Ερευν. προγραμμάτων (ΕΛΚΕ Πανεπ. Πατρών)

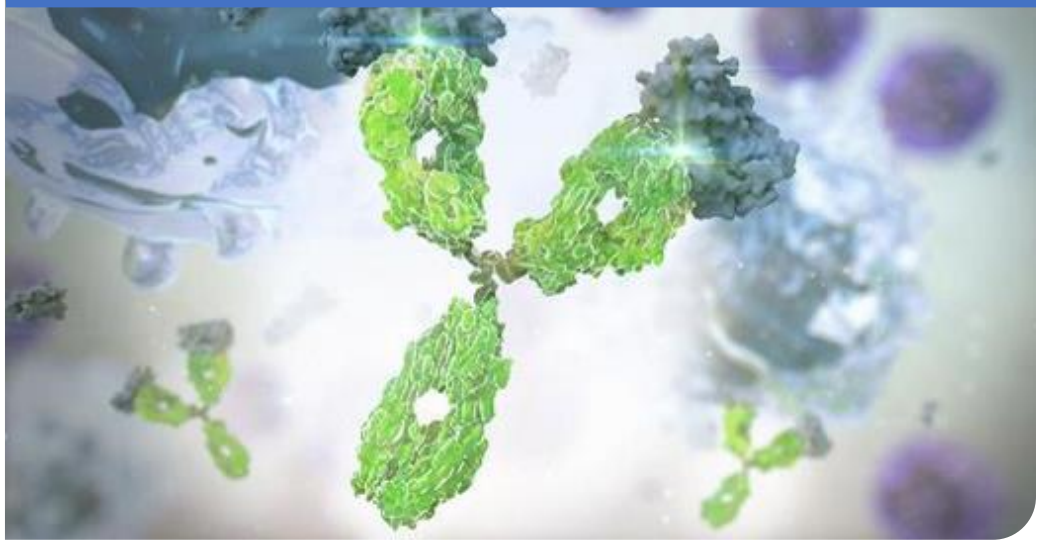
- Aenorasis
- ΕΡΕ-ΕΠΕΡΕ
- Specifar
- BMS
- Hospital Line
- MSD

Ixekizumab

- Στοιχεία για το mAb
- Μελέτες του ixekizumab στην ΨΑ
- Αναφορά για το ixekizumab στην Ψ

Ixekizumab is Designed to Specifically Target IL-17A

- Ixekizumab is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- Ixekizumab is also indicated for the treatment of adult patients with active psoriatic arthritis



Interleukin 17A (IL-17A) has been implicated in the pathogenesis of psoriasis and psoriatic arthritis[1,2]

- IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses

Ixekizumab pharmacology

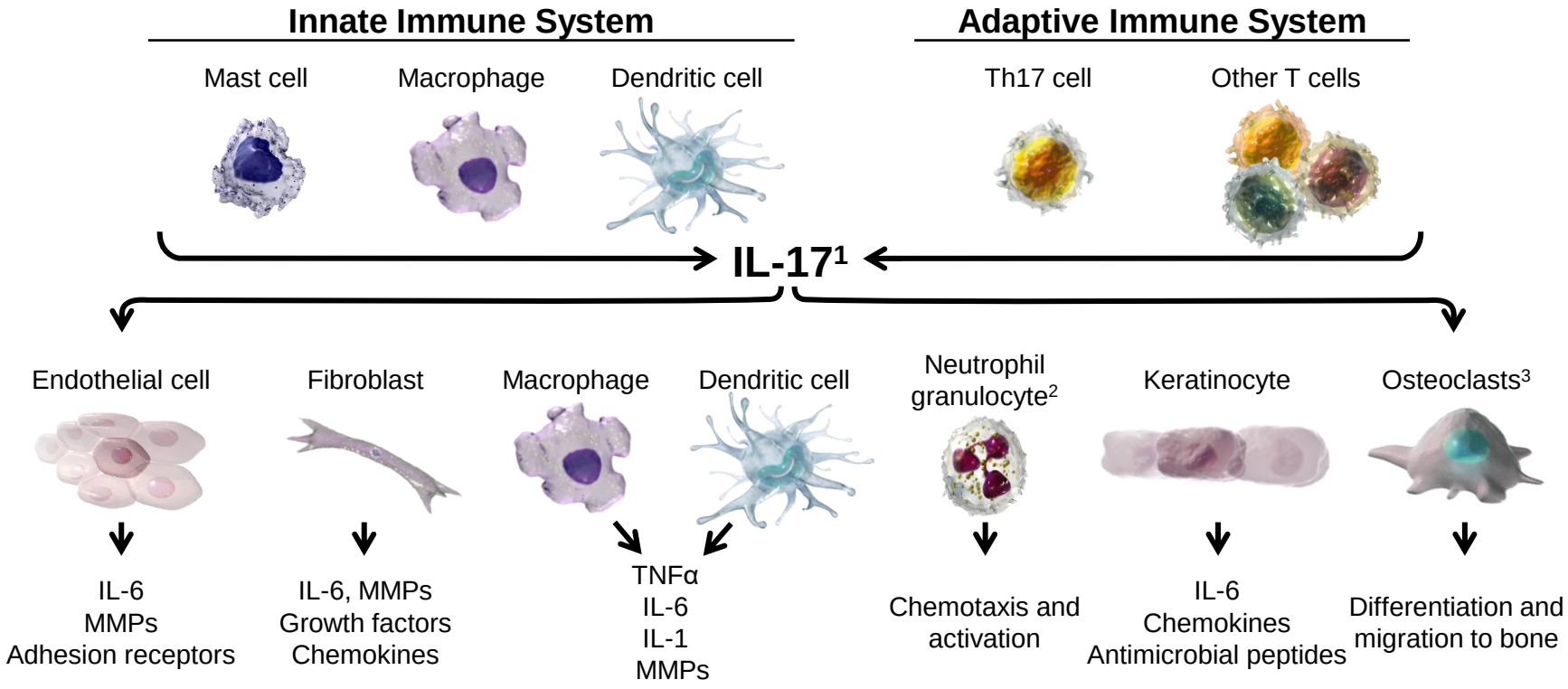
- Ixe is a humanized IgG4 monoclonal antibody that selectively binds with IL-17A and inhibits its interaction with the IL-17 receptor*
- Half-life of ~13 days
- No formal pharmacodynamics studies have been conducted with Ixekizumab

*The relationship between the mechanism of action and clinical outcomes has not been determined.

1. Martin DA, et al. *J Invest Dermatol*. 2013;133:17-26. 2. Kirkham BW, et al. *Immunology*. 2013;141:133-142.

Activity of IL-17

IL-17 is produced by many cells and acts on cells involved in psoriasis and psoriatic arthritis



MMP=matrix metalloproteinase.

1. Chart adapted from: Schön MP. *Exp Dermatol*. 2014;23:804-806. 2. Griffin GK, et al. *J Immunol.* 2012;188:6287-6899. Raychaudhuri SK, et al. *Clin Rheumatol.* 2015;34:1019-1023.

Phase 3 Trial Design SPIRIT-P1 and SPIRIT-P2

SPIRIT-P1 and SPIRIT-P2 Both trials:

- Phase 3, randomized, double-blind, placebo-controlled trials to evaluate efficacy and safety of Ixekizumab vs placebo
- Adult patients with active psoriatic arthritis (≥3 swollen and ≥3 tender joints)
- Randomized to placebo or Ixekizumab 80 mg every 2 or 4 weeks following a 160 mg starting dose

SPIRIT-P1 (N=417)[1]

Biologic-naïve

Allowed to continue stable background therapy

Primary endpoint: ACR20 at week 24

***Adalimumab 40 mg every 2 weeks was included as an active reference arm.** The study was not designed to test the noninferiority or superiority of Ixekizumab directly against adalimumab; no statistical analyses were done comparing Adalimumab to Ixekizumab.

SPIRIT-P2 (N=363)[2]

TNF inhibitor-experienced

Allowed to continue stable background therapy
Inadequate response and/or intolerance to 1-2 prior TNFi

Primary endpoint: ACR20 at week 24

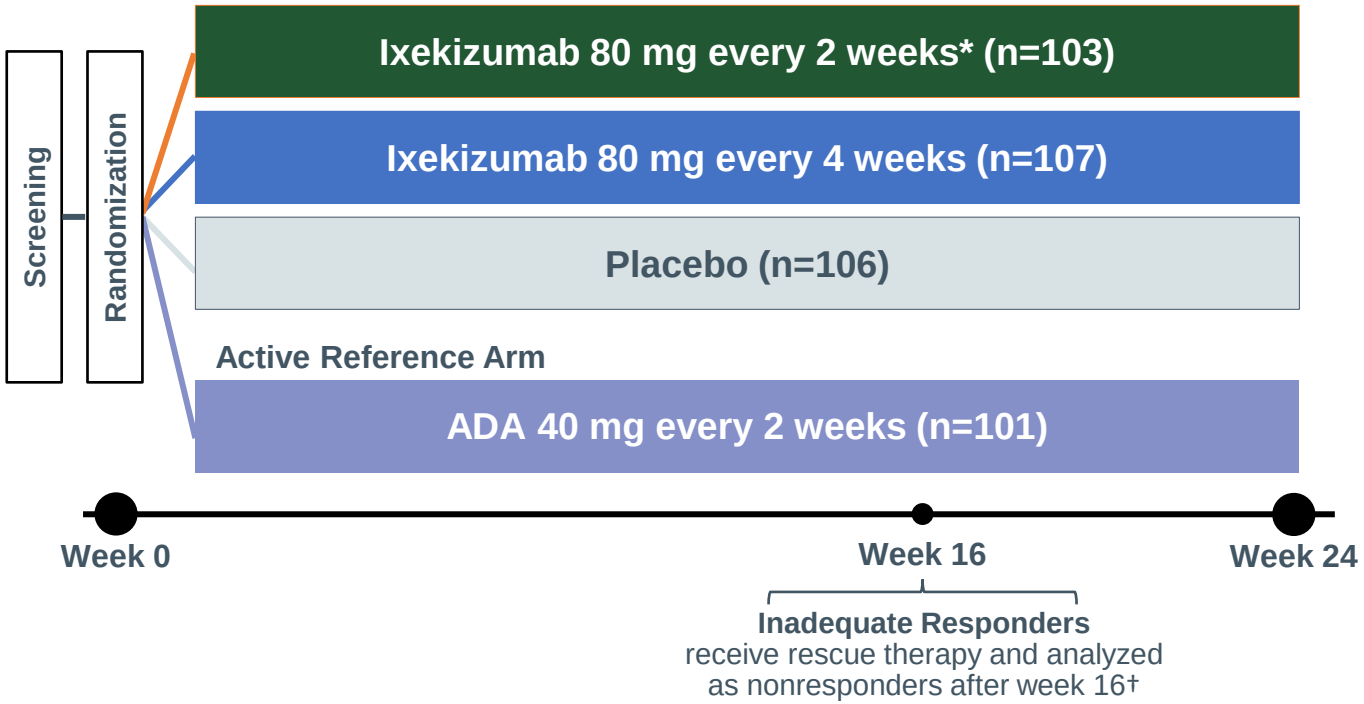
Inadequate responders (<20% improvement in tender and in swollen joint counts) at week 16 received rescue therapy and were analyzed as nonresponders after week 16 until week 24 (primary endpoint) and if not already on Ixekizumab were re-randomized to Ixekizumab every 2 or 4 weeks following a 160 mg starting dose.

Nonresponder imputation (NRI) methods were used for categorical efficacy analyses during the double-blind treatment period.

TNFi = tumor necrosis factor (TNF) inhibitor.

1. Mease PJ, et al. *Ann Rheum Dis*. 2017;76(suppl):1-30. 2. Nash P, et al. *Lancet*. 2017;389:2317-2327.

Trial Design: SPIRIT-P1 (N=417) Double-Blind Treatment Period (Biologic-Naïve)



Key inclusion criteria:

- Adult patients
- Confirmed diagnosis of active PsA ≥6 months
- Met CASPAR criteria
- Active PsA (≥3 tender and ≥3 swollen joints)
- Either ≥1 PsA-related hand or foot joint erosion on centrally read X-rays or CRP >6 mg/L
- Active psoriatic skin lesions or a documented history of plaque psoriasis

Adalimumab was an active reference arm. The study was not powered to make direct comparisons between the Ixekizumab and Adalimumab arms.

Patients randomized to Ixekizumab 80 mg every 2 or 4 weeks received a 160 mg starting dose at week 0.

After week 24, patients knew they were taking active treatment, but remained blind to the dose until the last patient completed week 24. Patients will be followed through 3 years.

*Ixekizumab 80 mg every 2 weeks in not an approved dosing regimen for psoriatic arthritis.

†All IRs (<20% improvement in tender and in swollen joint counts) at week 16 received rescue therapy and were analyzed as nonresponders after week 16 until the primary endpoint and if not already on Ixekizumab were re-randomized 1:1 to Ixekizumab every 2 or 4 weeks following a 160 mg starting dose. IRs from the placebo arm received their first dose of Ixekizumab at week 16, while IRs from the adalimumab arm had an 8-week placebo washout period before beginning their first dose of Ixekizumab at week 24.

CASPAR = Classification Criteria for Psoriatic Arthritis; CRP = C-reactive protein; IR = inadequate responder (imputed as nonresponder).

Mease PJ, et al. *Ann Rheum Dis*. 2017;76(suppl):1-30.

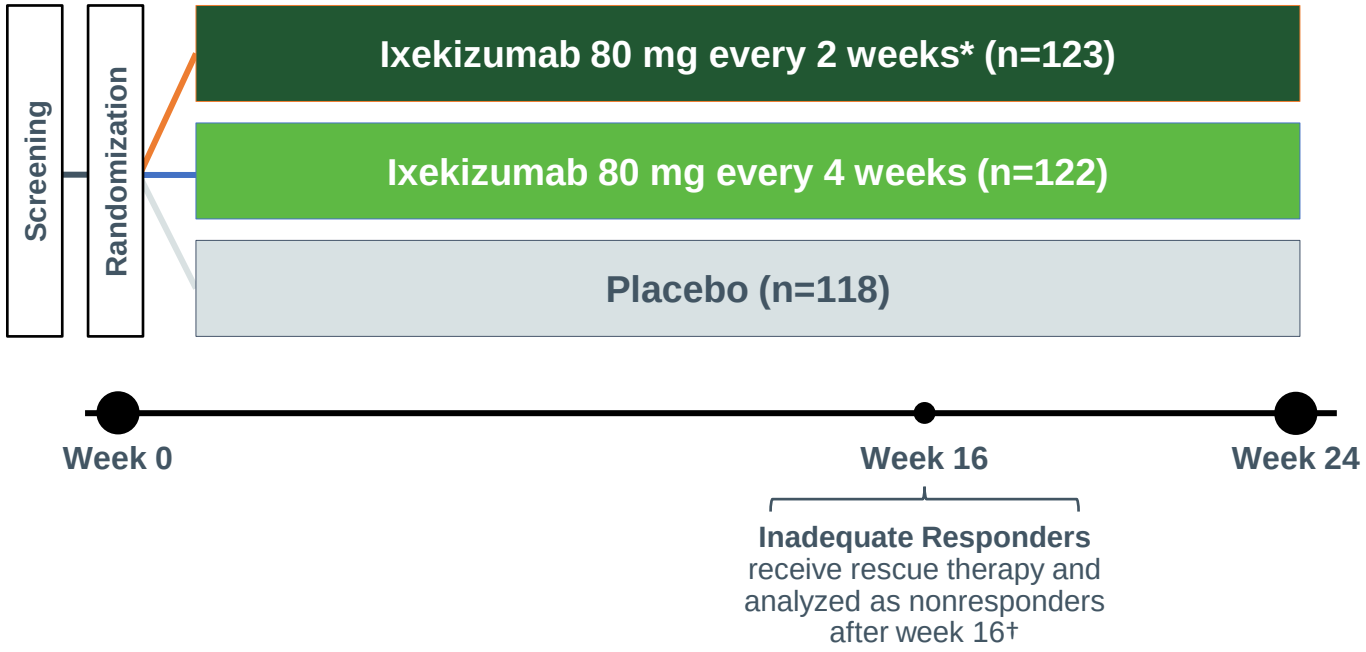
Ixekizumab Psoriatic Arthritis Trial Baseline Characteristics: Biologic-Naïve

	Ixekizumab 80 mg Every 4 Weeks (N=107)[1]	Placebo (N=106)[1]
Age (years), mean (SD)	49.1 (10)	50.6 (12)
Male, n (%)	45 (42%)	48 (45%)
Weight (kg), mean (SD)	85.5 (23)	83.8 (20)
Tender joint count, mean (SD)	20.5 (14)	19.2 (13)
Swollen joint count, mean (SD)	11.4 (8)	10.6 (7)
CRP (mg/L), mean (SD)	12.8 (16)	15.1 (24)
Patients currently using cDMARDs, n (%)	68 (64%)	69 (65%)
Patients currently using MTX, n (%)	**57 (53%)**	**59 (56%)**
Patients with current plaque psoriasis,* n (%)	100 (94%)	102 (96%)
Plaque psoriasis BSA ≥3%,* n (%)	73 (68%†)	67 (63%†)

*Qualitatively assessed by investigator at baseline.
†Calculated percentage uses total population (n). Percentage in Mease reference calculated using evaluable patients.
BSA = body surface area; CRP = C-reactive protein; cDMARD = conventional disease-modifying antirheumatic drug; MTX = methotrexate.

Mease PJ, et al. *Ann Rheum Dis*. 2017;76:79-87.

Trial Design: SPIRIT-P2 (N=363) Double-Blind Treatment Period (TNFi-Experienced)



Key inclusion criteria:

- Adult patients
- Confirmed diagnosis of active PsA ≥6 months
- Met CASPAR criteria
- Active PsA (≥3 tender and ≥3 swollen joints)
- Prior treatment with ≥1 cDMARD (methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine)
- Prior treatment with 1 or 2 TNF inhibitors (inadequate response based on ≥12 weeks on therapy) or a documented intolerance
- Active psoriatic skin lesions or a documented history of plaque psoriasis

Patients randomized to Ixekizumab 80 mg every 2 or 4 weeks received a 160 mg starting dose at week 0.

After week 24, patients knew they were taking active treatment, but remained blind to the dose until the last patient completed week 24. Patients will be followed through 3 years.

*Ixekizumab 80 mg every 2 weeks in not an approved dosing regimen for psoriatic arthritis.

†All IRs (<20% improvement in tender and in swollen joint counts) at week 16 received rescue therapy and were analyzed as nonresponders after week 16 until the primary endpoint and placebo IRs were re-randomized 1:1 to Ixekizumab every 2 or 4 weeks following a 160 mg starting dose.

CASPAR = Classification Criteria for Psoriatic Arthritis; cDMARD = conventional disease-modifying anti-rheumatic drug; IR = inadequate responder (imputed as nonresponder).

Nash P, et al. *Lancet.* 2017;389:2317-2327.

Ixekizumab Psoriatic Arthritis Trial Baseline Characteristics: TNFi-Experienced

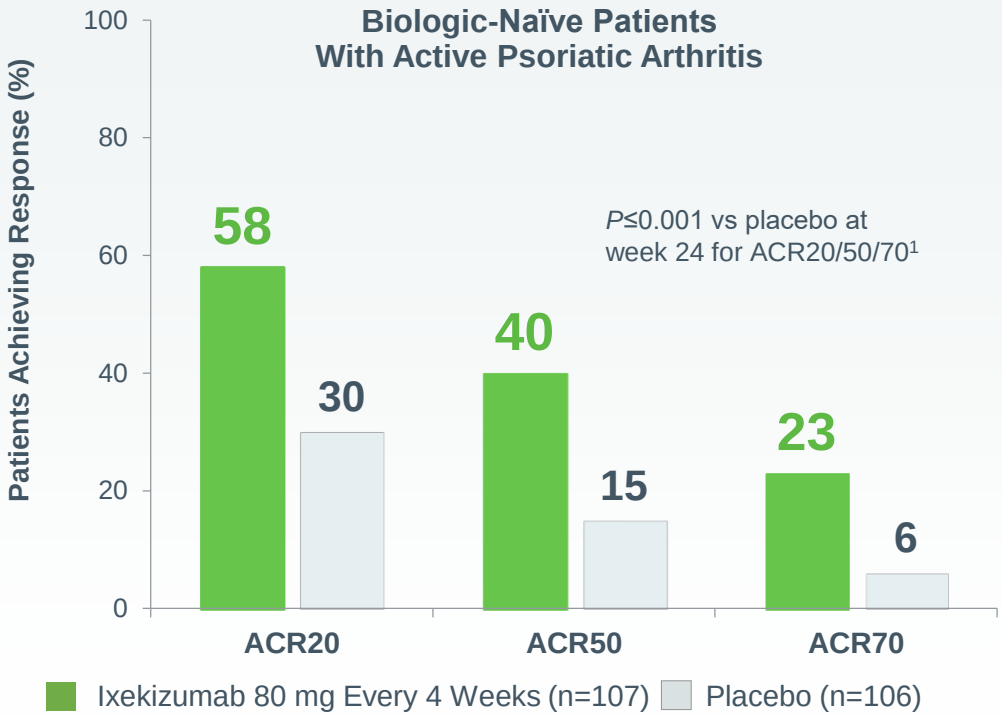
	Ixekizumab 80 mg Every 4 Weeks (N=122)[1]	Placebo (N=118)[1]
Age (years), mean (SD)	52.6 (14)	51.5 (10)
Male, n (%)	63 (52%)	56 (47%)
Weight (kg), mean (SD)	89.9 (22)	91.0 (22)
Previous TNF inhibitor treatment, n (%)		
Inadequate response to 1 TNF inhibitor	**71 (58%)**	**68 (58%)**
Inadequate response to 2 TNF inhibitors	**41 (34%)**	41 (35%)
Intolerance to a TNF inhibitor*	10 (8%)	9 (8%)
Tender joint count, mean (SD)	22.0 (14)	23.0 (16)
Swollen joint count, mean (SD)	13.1 (11)	10.3 (7)
CRP (mg/L), mean (SD)	17.0 (28)	12.1 (20)
Patients currently using cDMARDs, n (%)	60 (49%)	52 (44%)
Patients currently using MTX, n (%)	48 (39%)	40 (34%)
Patients with current plaque psoriasis,† n (%)	118 (97%)	108 (92%)
Plaque psoriasis BSA ≥3%,† n (%)	68 (56%‡)	67 (57%‡)

*Patients had previously received and discontinued a TNF inhibitor.
†Qualitatively assessed by investigator at baseline.
‡Calculated percentage uses total population (n).
BSA = body surface area; CRP = C-reactive protein; cDMARD = conventional disease-modifying antirheumatic drug; MTX = methotrexate; TNFi = tumor necrosis factor inhibitor.

1. Nash P, et al. *Lancet*. 2017;389:2317-2327.

SPIRIT-P1 (Biologic-Naïve)

Significant Improvement in ACR Clinical Response Criteria vs Placebo at Week 24
ACR response rates during double-blind period, NRI1



Of patients taking **ADALIMUMAB** 40 mg Every 2 Weeks (n=101)[1]

57% ACHIEVED **ACR20**

39% ACHIEVED **ACR50**

26% ACHIEVED **ACR70**

The study was not designed to test the noninferiority or superiority of Ixekizumab directly against adalimumab. Adalimumab was an active reference arm; no statistical analyses were done comparing adalimumab to Ixekizumab.

In SPIRIT-P2 (TNF-experienced) (Ixekizumab 80 mg every 4 weeks n=122; placebo n=118), 53% of Ixekizumab patients achieved ACR20 at week 24 vs 20% for placebo. Additionally, 35% and 22% of Ixekizumab patients achieved ACR50 and AC70, respectively, at week 24 vs 5% and 0% for placebo.[2]

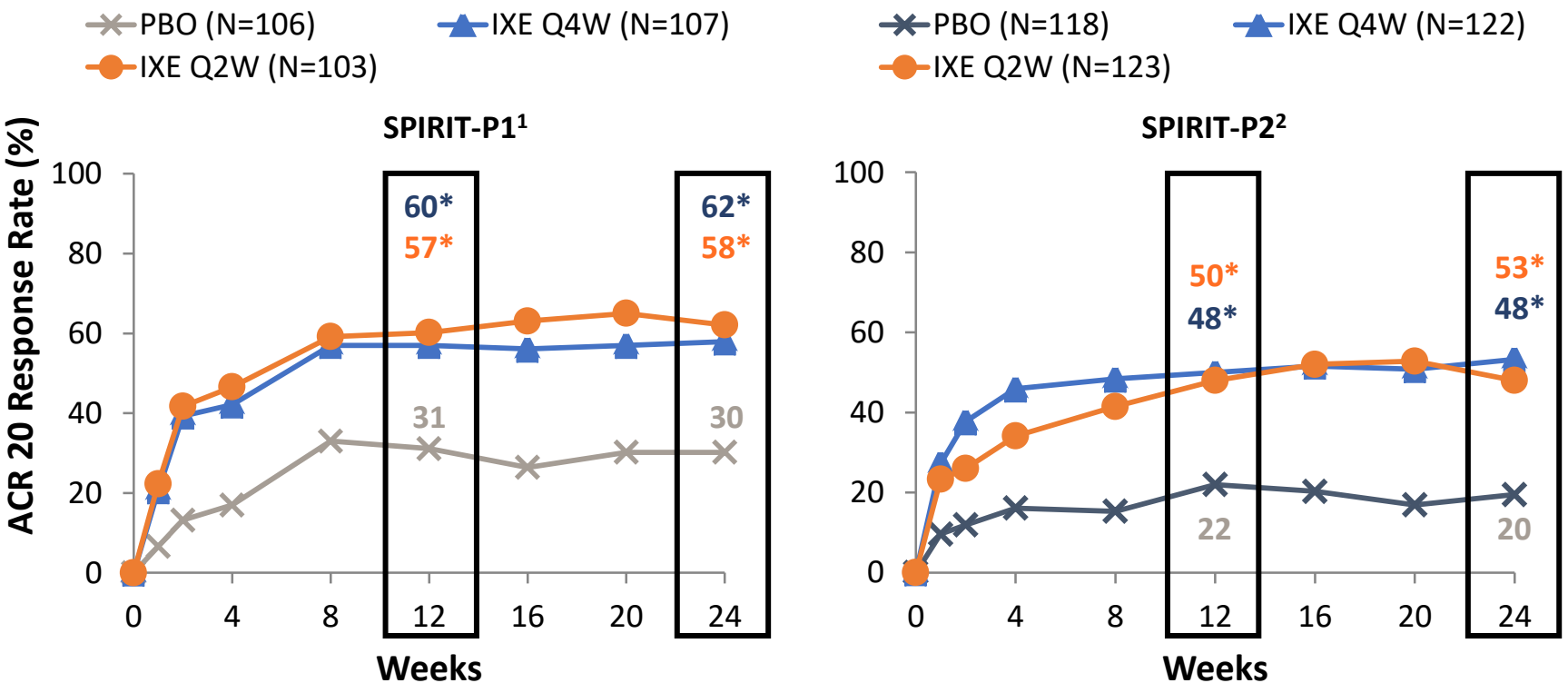
Primary endpoint = ACR20 response at week 24. Nonresponder imputation (NRI) of intent-to-treat population through week 24. Inadequate responders (<20% improvement in tender and in swollen joint counts) at week 16 were analyzed as nonresponders after week 16 until the primary endpoint.[1,2] ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rate.

1. Mease PJ, et al. *Ann Rheum Dis*. 2017;76:79-87. 2. Nash P, et al. *Lancet*. 2017;389:2317-2327.

ACR20 Response by Treatment Week, NRI

Double-Blind Treatment Period, ITT Population (SPIRIT-P1 and SPIRIT-P2)

Similar treatment advantage for ixekizumab compared with placebo for ACR20 response was observed in both SPIRIT studies



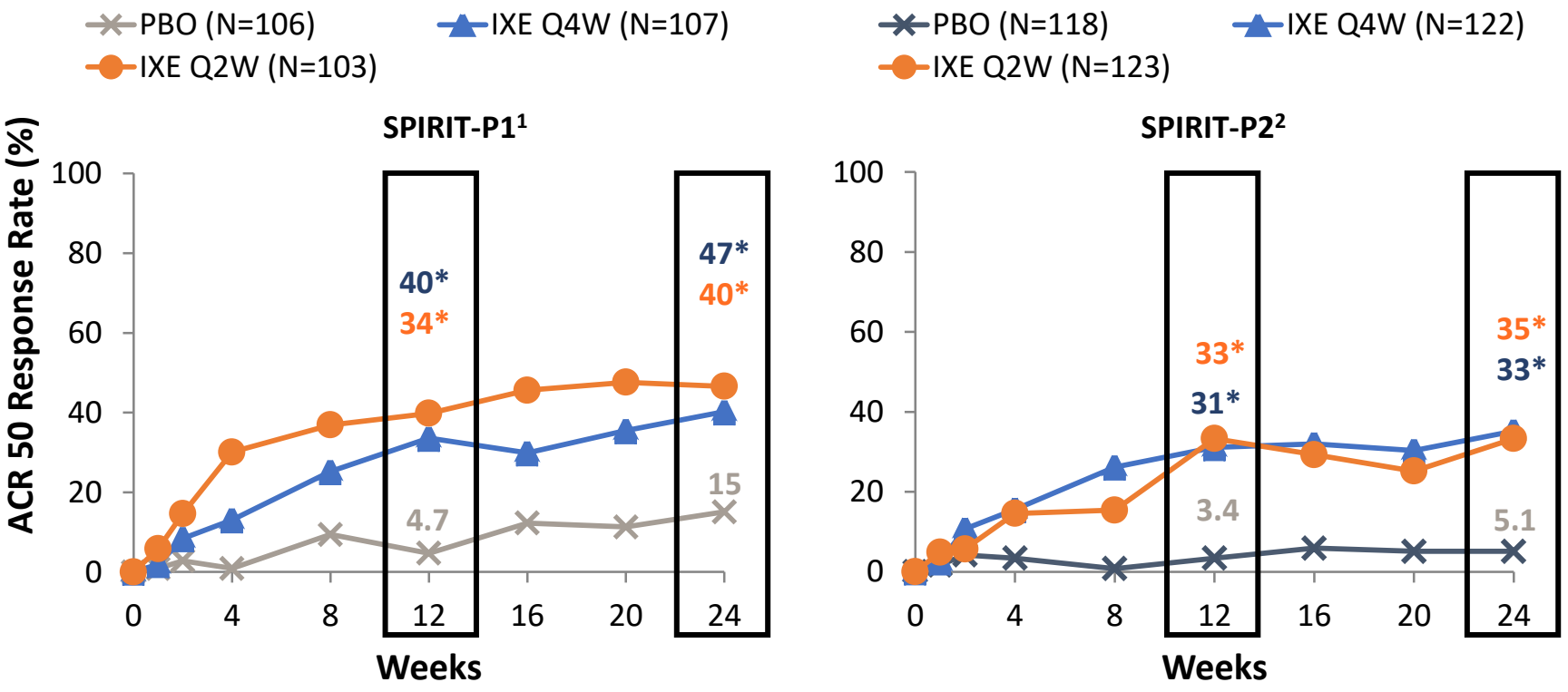
*p≤.001 vs. PBO. Note: During the double-blind treatment period, NRI was applied for IRs at Week 16 and patients who discontinued on or prior to Week 24.

1.Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327.

ACR50 Response by Treatment Week, NRI

Double-Blind Treatment Period, ITT Population (SPIRIT-P1 and SPIRIT-P2)

Similar treatment advantage for ixekizumab compared with placebo for ACR50 was observed in both SPIRIT studies



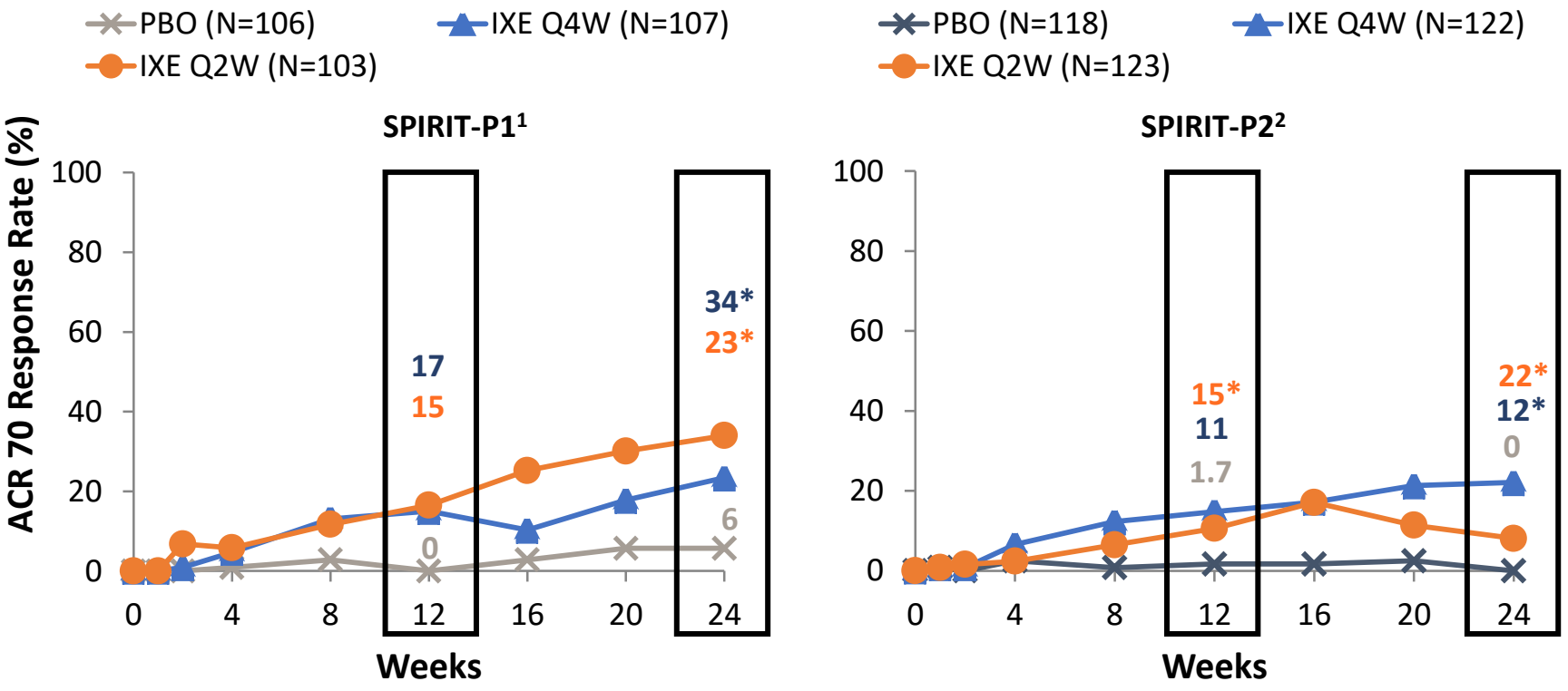
*p≤.001 vs. PBO. Note: During the double-blind treatment period, NRI was applied for IRs at Week 16 and patients who discontinued on or prior to Week 24.

1.Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327.

ACR70 Response by Treatment Week, NRI

Double-Blind Treatment Period, ITT Population (SPIRIT-P1 and SPIRIT-P2)

Similar treatment advantage in ACR70 response rates for ixekizumab compared with placebo was observed in both SPIRIT studies



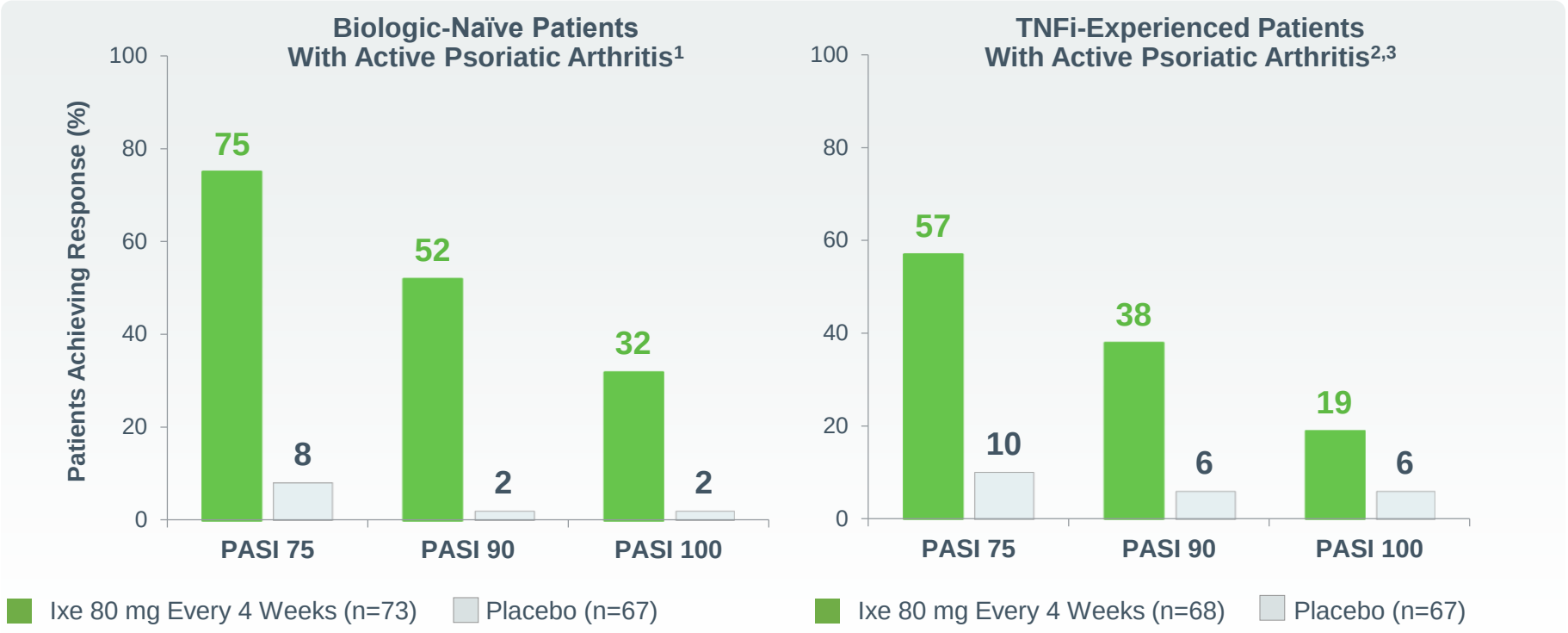
*p≤.001 vs. PBO. Note: During the double-blind treatment period, NRI was applied for IRs at Week 16 and patients who discontinued on or prior to Week 24.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327.

SPIRIT-P1 (Biologic-Naïve) and SPIRIT-P2 (TNFi-Experienced)

Clinically Significant Skin Clearance vs Placebo at Week 12, as Measured by PASI 75

PASI response rates at week 12 in PsA patients with plaque psoriasis ≥3% BSA, NRI



sPGA response rates at week 12 in PsA patients with plaque psoriasis sPGA ≥3, NRI

In SPIRIT-P1, among patients with sPGA ≥3 at baseline (Ixekizumab n=52; placebo n=41) 75% of patients taking Ixekizumab achieved sPGA 0,1 at week 12 vs 7% of patients who received placebo. Additionally, 31% of Ixekizumab patients achieved sPGA 0, vs 2% for placebo.

In SPIRIT-P2, among patients with sPGA ≥3 at baseline (Ixekizumab n=60, placebo n=55), 63% of patients taking Ixekizumab achieved sPGA 0,1 at week 12 vs 4% of patients who received placebo. Additionally, 23% of Ixekizumab patients achieved sPGA 0, vs 2% for placebo.

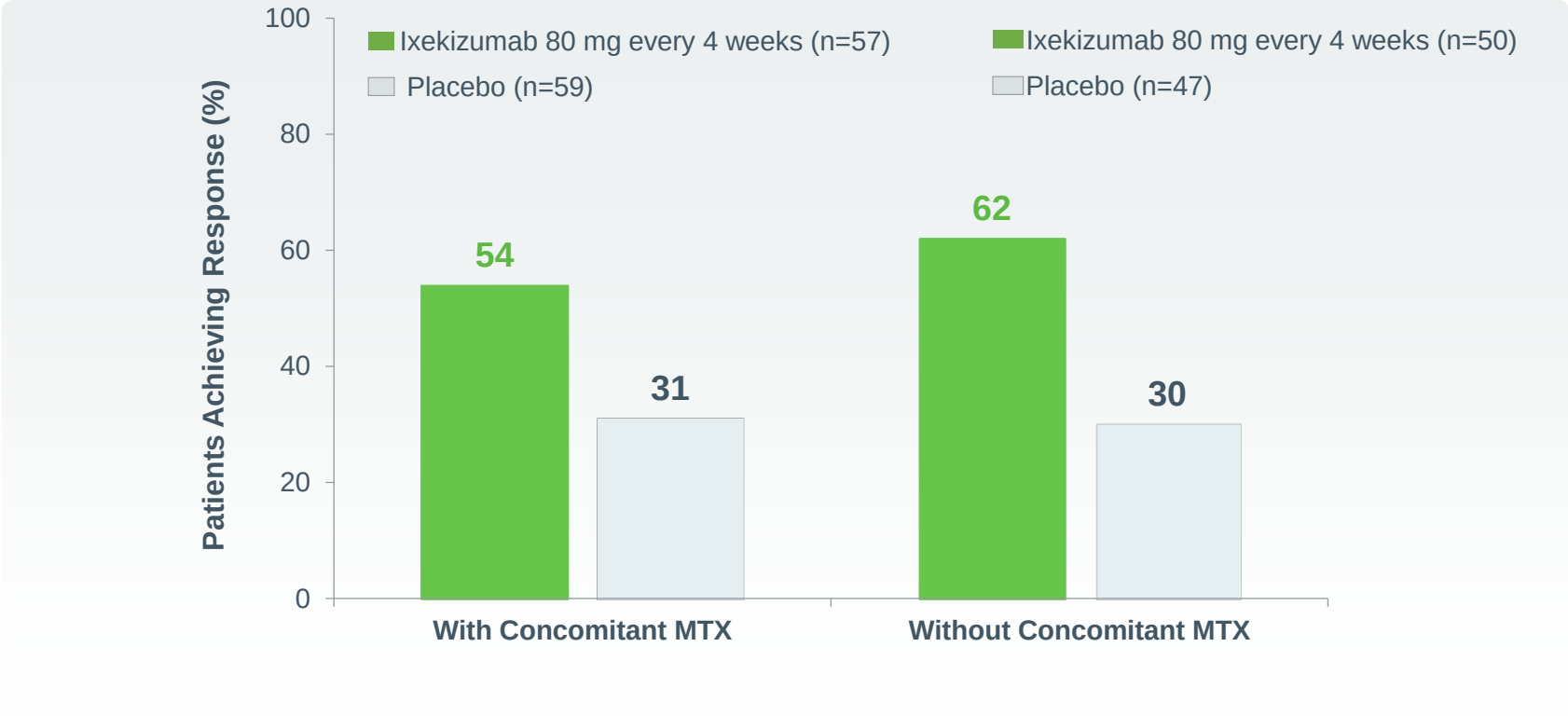
NRI of intent-to-treat population through week 12.

1. Mease PJ, et al. *Ann Rheum Dis*. 2017;76:79-87. 2. Nash P, et al. *Lancet*. 2017;389:2317-2327. 3. Nash P, et al. *Lancet*. 2017;389:2317-2327. Supplementary appendix.

SPIRIT-P1 (Biologic-Naïve)

Patients achieving ACR20 responses at week 24, NRI

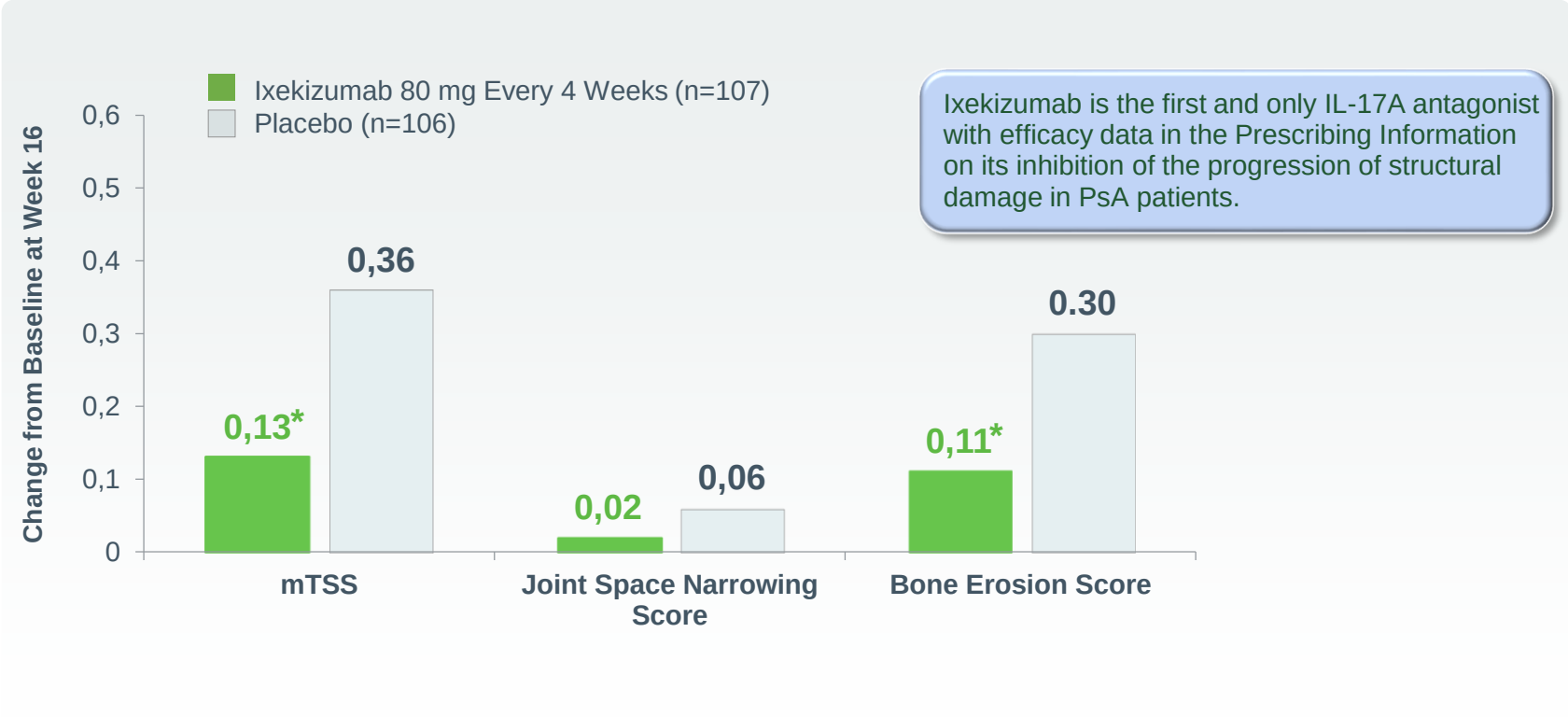
ACR20 Response vs Placebo With or Without Concomitant Methotrexate (MTX)



All patients were allowed to remain on stable background therapy. NRI of intent-to-treat population through week 24. Inadequate responders (<20% improvement in tender and in swollen joint counts) at week 16 were analyzed as nonresponders after week 16 until the primary endpoint.
In SPIRIT-P2 (TNFi-experienced) (Ixe 80 mg every 4 weeks n=48; placebo n=40), 50% of Ixe patients achieved ACR20 with concomitant MTX at week 24 vs 18% for placebo. Additionally (Ixe n=74; placebo n=78), 55% of Ixe patients achieved ACR20 without MTX use at week 24 vs 21% for placebo. All patients in SPIRIT-P2 previously treated with ≥1 cDMARD (methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine).

Nash P, et al. *Lancet*. 2017;389:2317-2327. Supplementary appendix.

Ixekizumab Inhibited Progression of Joint Damage at Week 16 vs Placebo



*$P \leq 0.05$ vs placebo. Primary endpoint = ACR20 response at week 24.

Inhibition of progression of structural damage was assessed radiographically and expressed as the mean change in mTSS and its components, the joint space narrowing score and bone erosion score, at week 16 vs baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints.

SPIRIT-P2 (TNFi-experienced) did not include an assessment of radiographic progression.

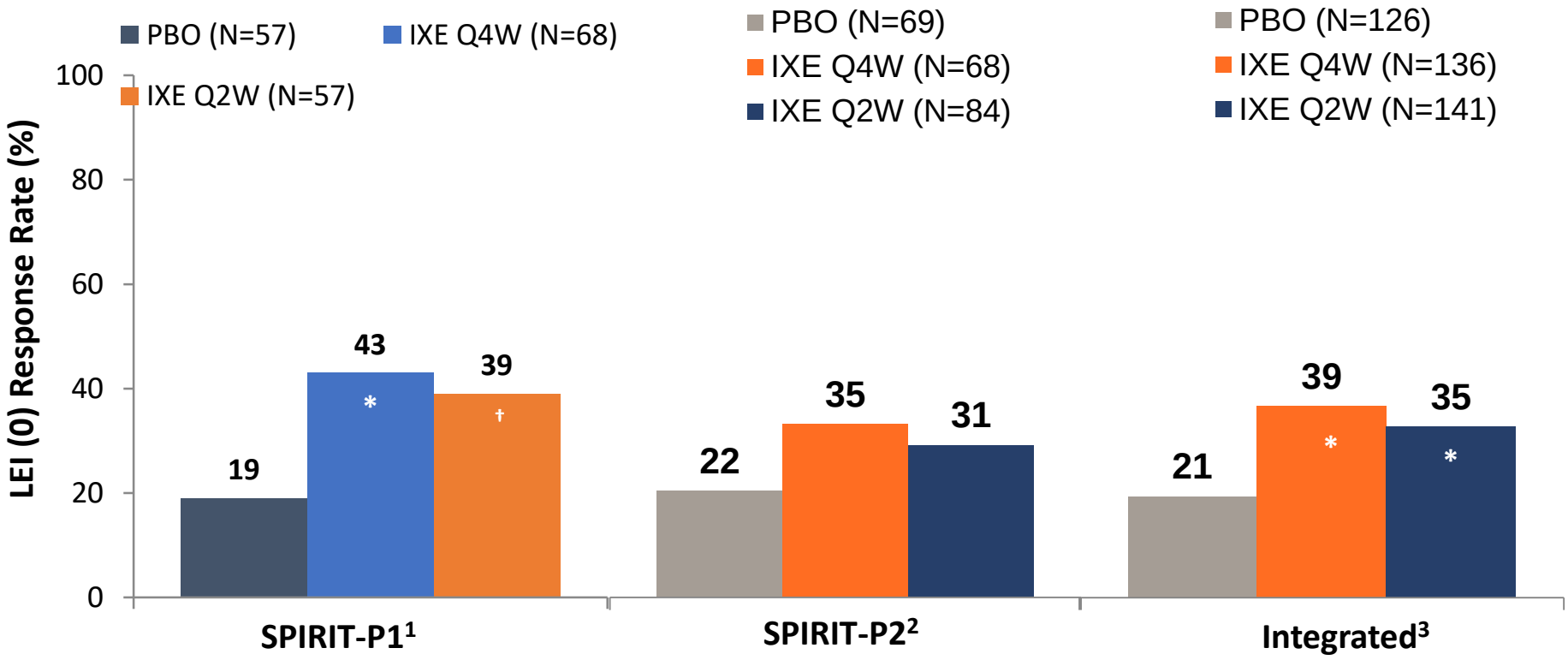
MMRM = mixed-effect model of repeated measure; mTSS = modified Total Sharp Score.

Nash P, et al. *Lancet*. 2017;389:2317-2327.

Resolution of Enthesitis (LEI=0) at Week 24, NRI

Double-Blind Treatment Period, ITT Population With Enthesitis at Baseline (LEI >0) (SPIRIT-P1 and SPIRIT-P2)

Patients treated with ixekizumab had higher frequency of resolution of enthesitis at Week 24



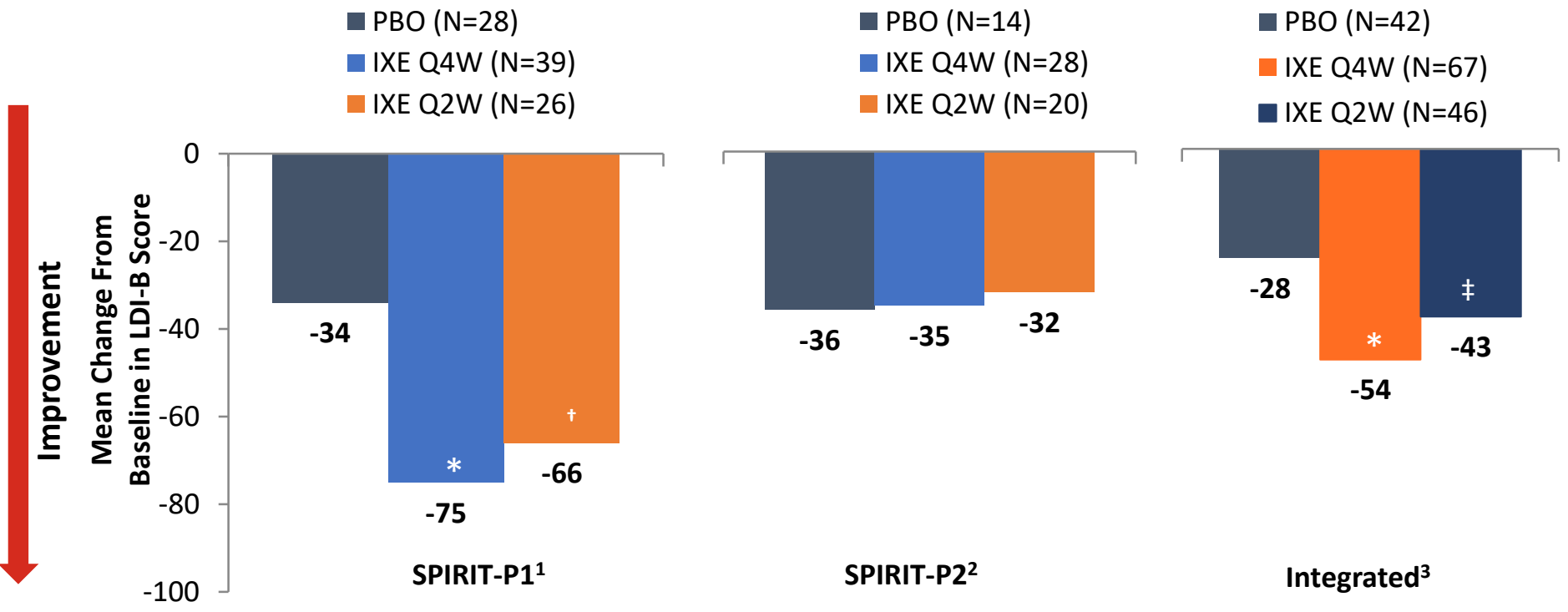
*p≤.01 vs. PBO; †p≤.05 vs. PBO.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327. 3. Combe B, et al. Poster presented at EADV 2017. Poster P0389.

Leeds Dactylitis Index Score-Basic at Week 24, MMRM

Double-Blind Treatment Period, ITT Population With Dactylitis at Baseline (LDI-B >0) (SPIRIT-P1 and SPIRIT-P2)

Patients treated with ixekizumab had significantly greater improvement in dactylitis compared with placebo at Week 24



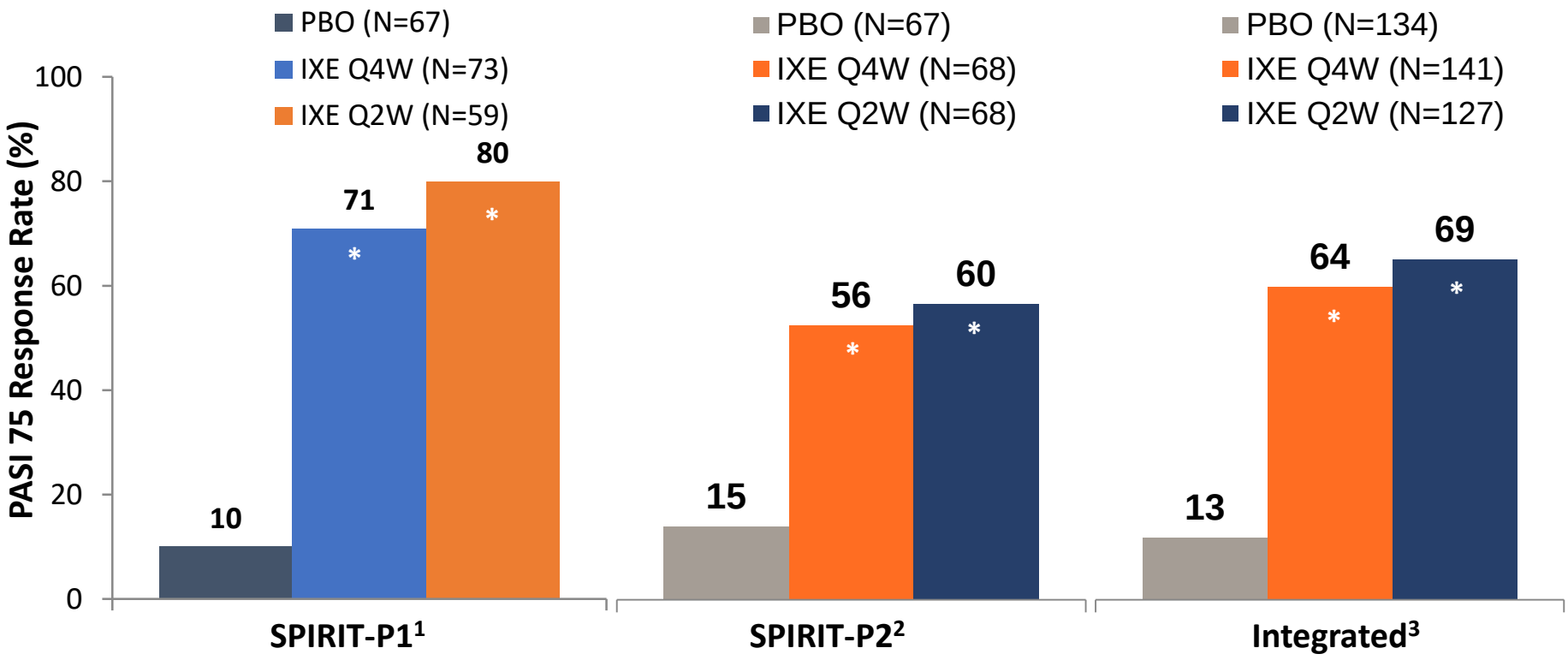
*p≤ .001 vs PBO. †p≤.01 vs. PBO. ‡p≤.05 vs. PBO.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327. 3. Combe B, et al. Poster presented at EADV 2017. Poster P0389.

PASI 75 Response Rate (%) at Week 24, NRI

Population With Baseline Ps ≥3% BSA (SPIRIT-P1 and SPIRIT-P2)

Approximately 65% of patients treated with ixekizumab had a PASI 75 response at **Week 24**



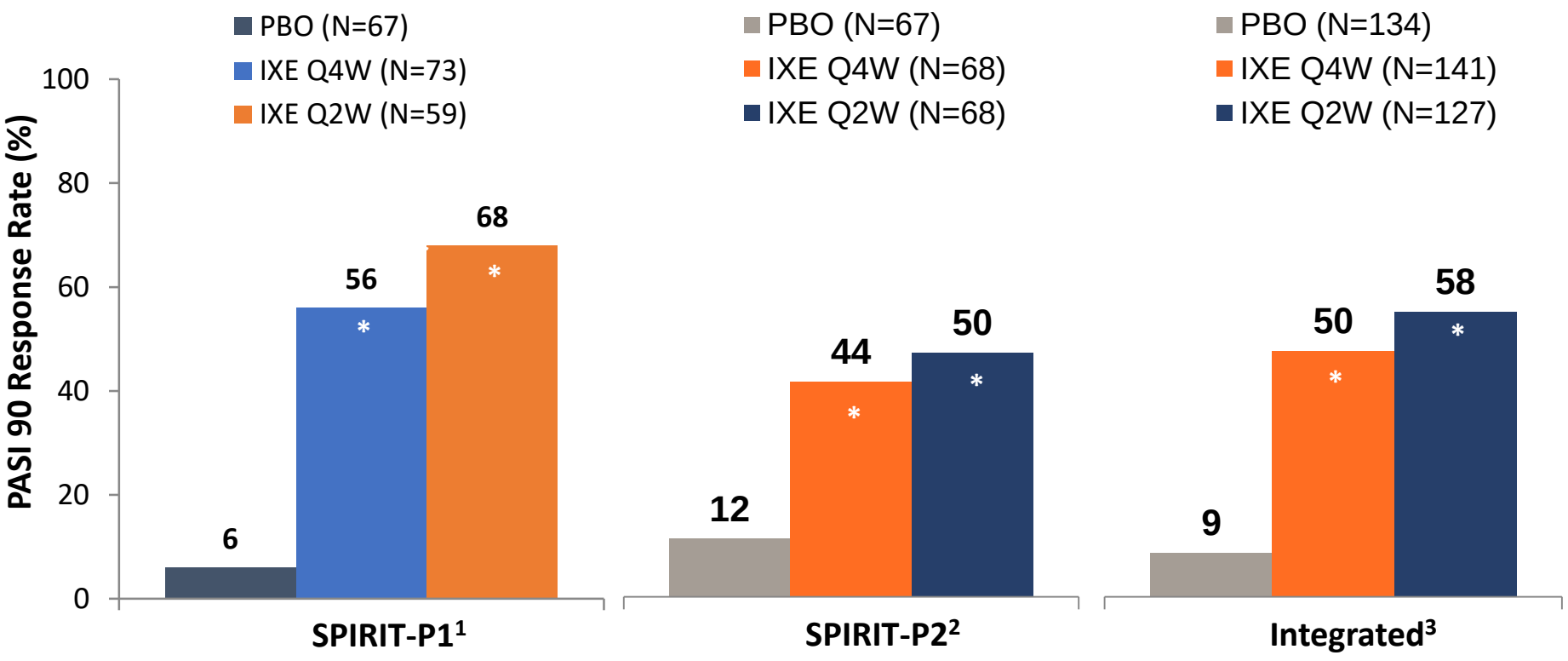
*p≤.001 vs. PBO.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327. 3. Combe B, et al. Poster presented at EADV 2017. Poster P0389.

PASI 90 Response Rate (%) at Week 24, NRI

Population With Baseline Ps ≥3% BSA (SPIRIT-P1 and SPIRIT-P2)

Approximately 60% of patients treated with ixekizumab had a PASI 90 response at **Week 24**



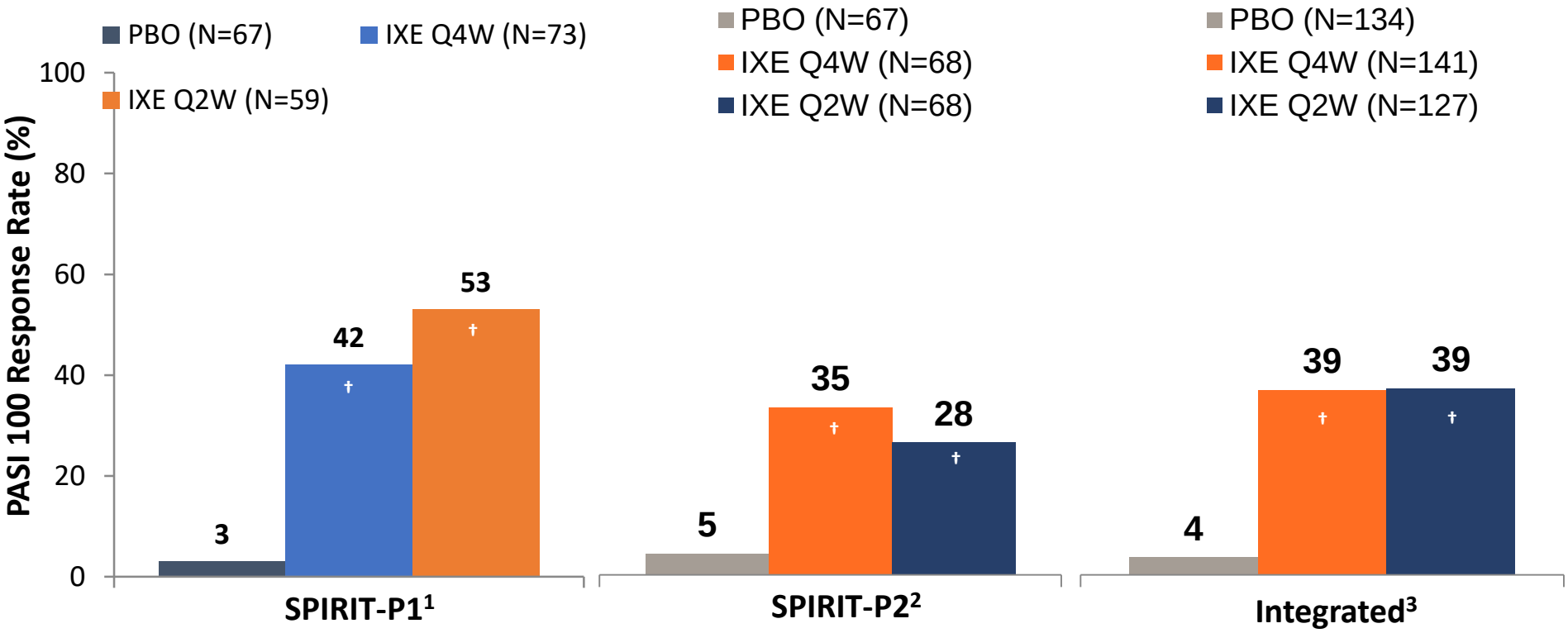
*p≤.001 vs. PBO.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327. 3. Combe B, et al. Poster presented at EADV 2017. Poster P0389.

PASI 100 Response Rate (%) at Week 24, NRI

Population With Baseline Ps ≥3% BSA (SPIRIT-P1 and SPIRIT-P2)

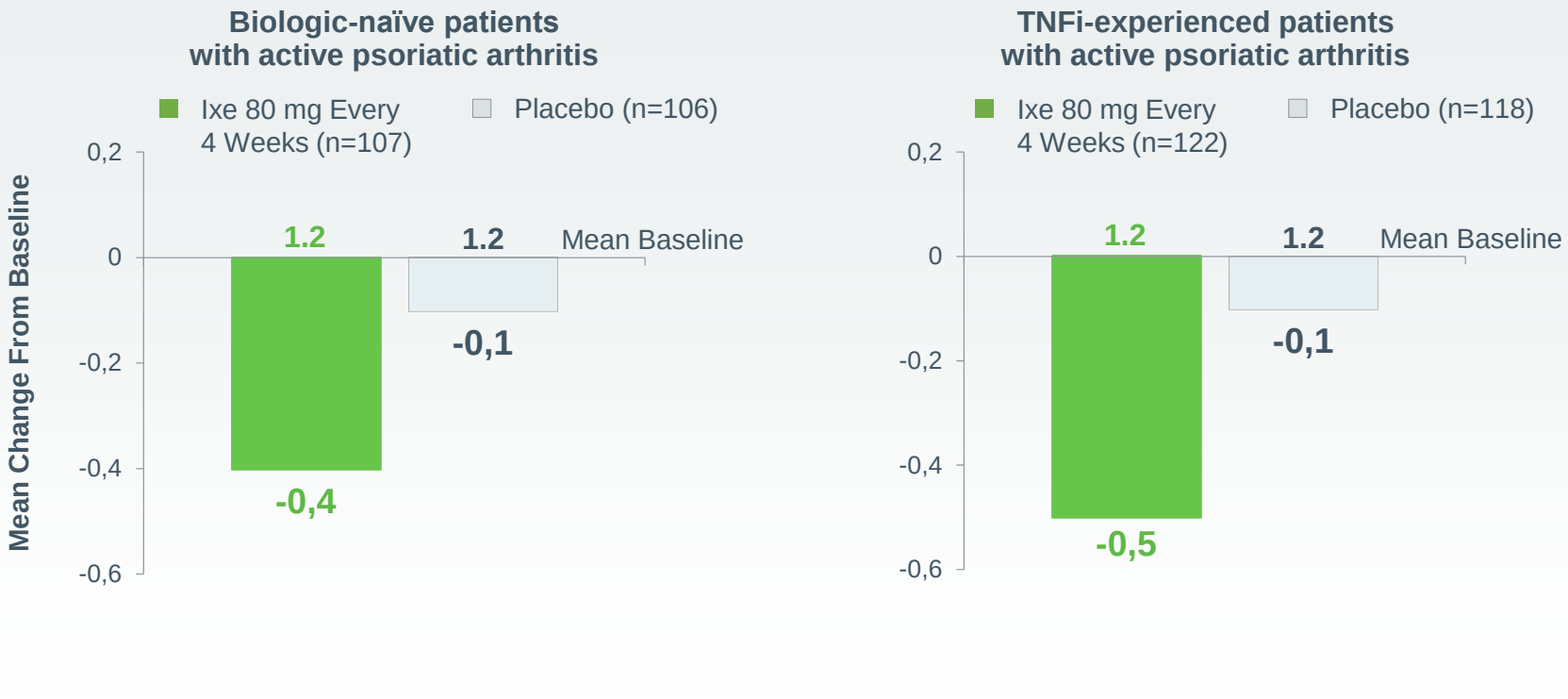
Approximately 40% of ixekizumab-treated patients had complete resolution of plaque psoriasis at **Week 24**



*p≤.01 vs. PBO; †p≤.001 vs. PBO.

1. Mease PJ, et al. *Ann Rheum Dis.* 2017;76:79-87. 2. Nash P, et al. *Lancet.* 2017;389:2317-2327. 3. Combe B, et al. Poster presented at EADV 2017. Poster P0389.

Clinically Significant Improvement in Physical Function as Early as Week 16



A ≥0.35 improvement from baseline is considered clinically meaningful in patients with PsA.[1]

Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

HAQ-DI = Health Assessment Questionnaire-Disability Index; MMRM = mixed-effects model for repeated measures analysis.

1. Mease PJ, et al. *J Rheumatol*. 2011;38:2461-2465.

Adverse Events of Special Interest Through Week 52

	Adverse Events of Special Interest Through Week 24		**Adverse Events of Special Interest Through Week 52**
	Ixekizumab 80 mg Every 4 Weeks (n=229) %	Placebo (n=224) %	Ixekizumab 80 mg every 4 weeks (n=229) %
Allergic reactions/hypersensitivities*	4.4%	1.8%	6.6%
Malignancy-related†	0.9%	0%	0.9%
Depression	1.7%	1.3%	2.6%
Candida infections	1.3%	0%	2.2%
Oral candidiasis	0.4%	0%	0.4%
MACE	0%	0%	0%
Crohn's disease/ulcerative colitis‡	0%	0%	0%

*No confirmed cases of anaphylaxis in clinical trials. All incidents of allergic reactions/hypersensitivity were non-anaphylactic.
†Includes all patients with ≥1 Treatment Emergent Adverse Event (TEAE), including nonmelanoma skin cancer (NMSC) and prostate cancer.
‡Incidents of inflammatory bowel disease events were reported in the plaque psoriasis trial safety population with Ixe. Patients with uncontrolled ulcerative colitis (UC) or Crohn's disease were excluded from the studies; however, patients with a personal or family history of UC/Crohn's were allowed in the study.

Certain adverse events, such as MACE and malignancy, require longer observation periods and larger patient exposure to ascertain risk. Lilly is conducting continued long-term safety studies, including post-marketing studies, to continue to evaluate the safety of Ixekizumab.

MACE = major adverse cerebrocardiovascular event.

Nash P, et al. *Lancet*. 2017;389:2317-2327. Supplementary appendix.

Integrated Safety Results

Double-Blind Treatment Period (SPIRIT-P1 and SPIRIT-P2)

Table 2. Safety Overview, Integrated Safety Dataset

n (%)	PBO (N=224)	IXE Q4W (N=229)	IXE Q2W (N=225)
≥1 TEAE	127 (56.7)	153 (66.8)*	156 (69.3)*
≥1 SAE	6 (2.7)	9 (3.9)	11 (4.9)
Deaths	0	0	0
Discontinuations due to AE	8 (3.6)	7 (3.1)	12 (5.3)
Infections	62 (27.7)	77 (33.6)	72 (32.0)
Serious infections	0	1 (0.4)	5 (2.2)*
Oral candidiasis	0	1 (0.4)	4 (1.8)*
Active tuberculosis	0	0	0
Hypersensitivities (non-anaphylaxis)	4 (1.8)	10 (4.4)	14 (6.2)*
Injection-site reactions	10 (4.5)	40 (17.5)*	57 (25.3)*†
Treatment-emergent neutropenia[a]	6 (2.7)	24 (10.6)*	19 (8.7)*
MACE	0	0	0
Inflammatory bowel disease	0	0	1 (0.4)

* p<.05 vs. PBO, † p<.05 vs. IXE Q4W using logistic regression analysis; [a] Based on laboratory assessment

AE=adverse event; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 4 weeks; MACE=major adverse cerebro-cardiovascular events; PBO=placebo; SAE=serious adverse event; TEAE=treatment-emergent adverse events

Combe B et al Poster EADV 2017 P0389.pdf

Ασφάλεια

- Ixekizumab therapy was well tolerated as the rate of discontinuation due to an adverse event was **3-5%**
- The most common treatment-emergent adverse events were **injection-site reactions**, of which the majority were mild or moderate
- While numbers were small, some adverse events of special interest tended to be numerically more frequent in the Q2W versus the Q4W group
- The observed adverse events were consistent with the mechanism of action of IL-17A inhibition
- The safety profile of ixekizumab for PsA is comparable to the profile observed in patients with psoriasis

IL=Interleukin; IXE Q2W=80 mg of Ixekizumab Every 2 Weeks; IXE Q4W=80 mg of Ixekizumab Every 4 Weeks; PsA=Psoriatic Arthritis.

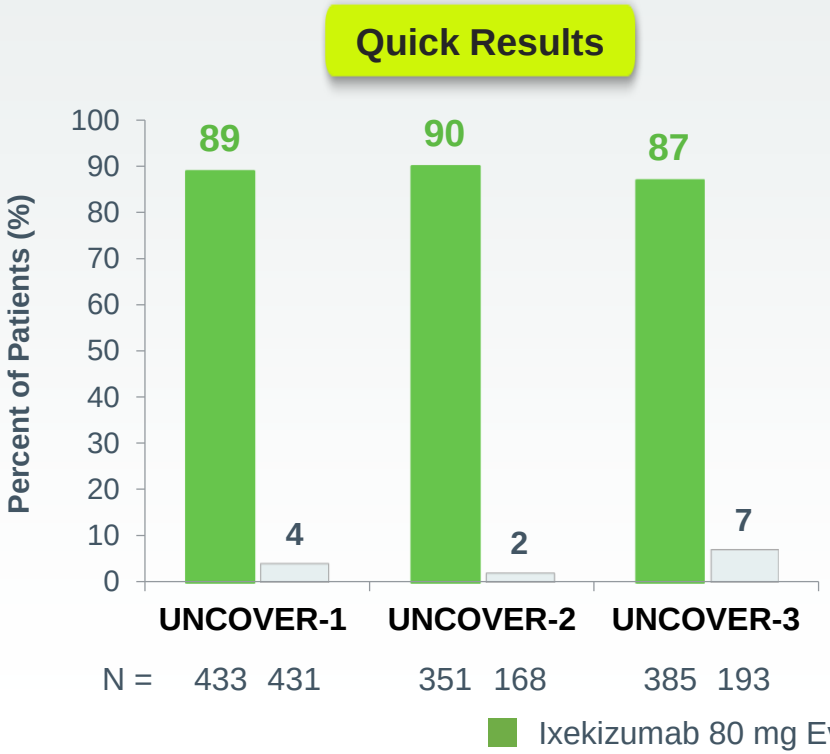
1. Taltz SPC 2. Langley RG, et al. Poster presented at: *EADV 2017*; Poster P1311. 3. Strober B, et al. J Am Acad Dermatol. 2017;76:432-440.e17 4. van der Heijde et al. *The Journal of Rheumatology; e-pub ahead of print: DOI: 10.3899/jrheum.170429*

Ixekizumab

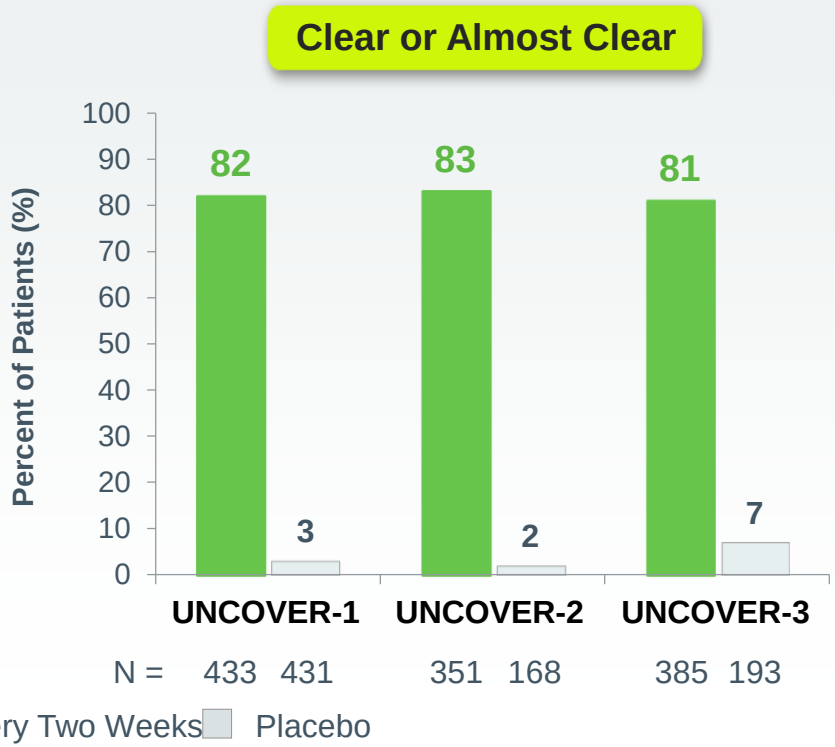
Δερματική Ψωρίαση

PASI 75 and sPGA 0,1 Response at Week 12, NRI Analysis

Up to 90% of Ixekizumab-treated Patients Achieved PASI 75 at Week 12



Up to 83% of Ixekizumab-treated Patients Achieved Clear or Almost Clear Skin (sPGA 0,1) at Week 12

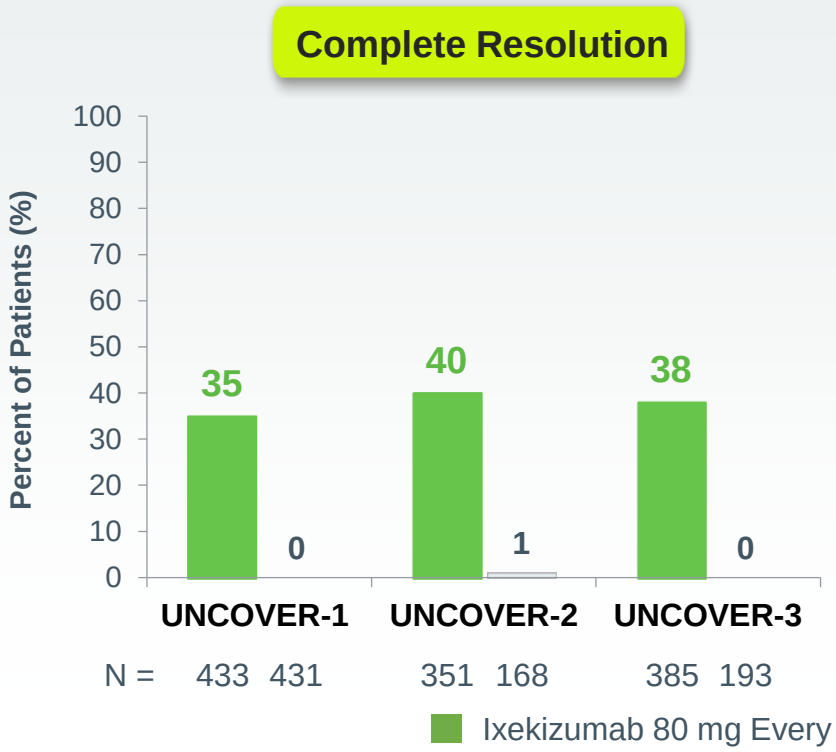


Ixekizumab 80 mg Every Two Weeks Placebo

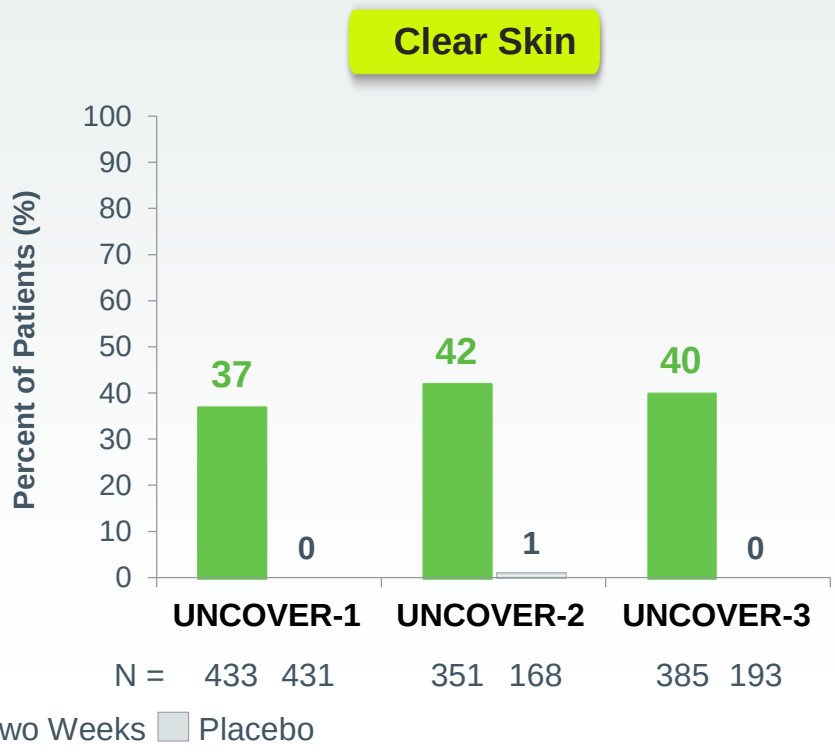
Taltz SPC

PASI 100 and sPGA 0 Response at Week 12, NRI Analysis

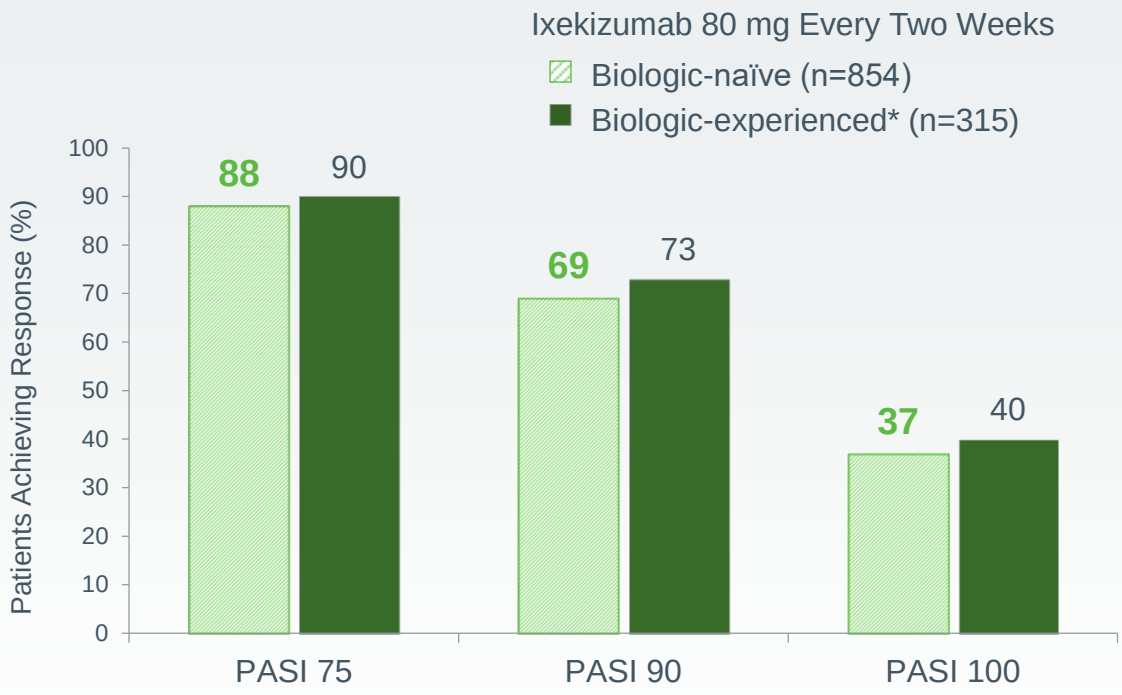
Up to 40% of Ixekizumab-treated Patients Achieved
Complete Resolution (PASI 100) at Week 12



Up to 42% of Ixekizumab-treated Patients Achieved
Clear Skin (sPGA 0) at Week 12



Efficacy Compared to Placebo at Week 12 Regardless of Previous Treatment With a Biologic



NRI analysis

- In these trials, 83% of biologic-naïve and 80% of biologic-experienced patients receiving Ixekizumab achieved sPGA 0,1 vs 5% and 2%, respectively, for patients receiving placebo.
- In the placebo group, biologic-naïve (n=535) and biologic-experienced (n=257) patients achieved PASI 75 rates of 5% and 3%, PASI 90 rates of 2% and 0%, and PASI 100 rates of 0% and 0%, respectively.

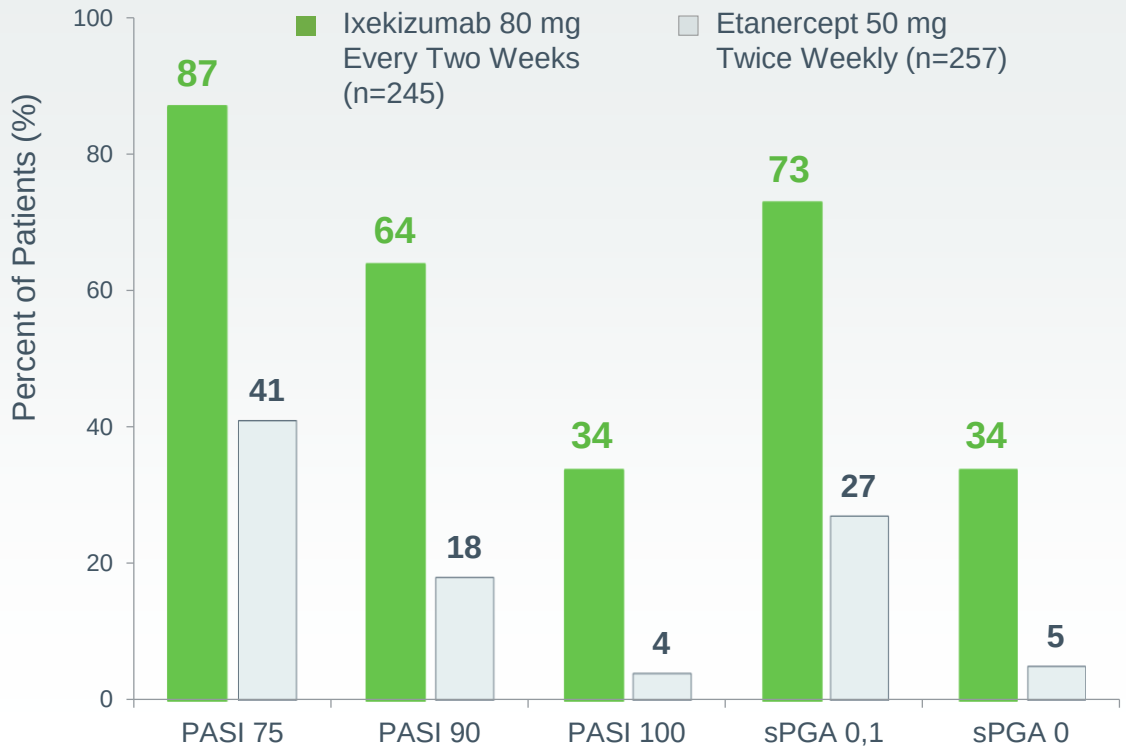
*Patients were classified as biologic-experienced if they had received prior treatment with at least 1 biologic agent. Previous biologic therapy included anti-TNFs (15%), anti-IL-12/23 (9%), and other biologic agents.

IL = interleukin; TNF = tumor necrosis factor.

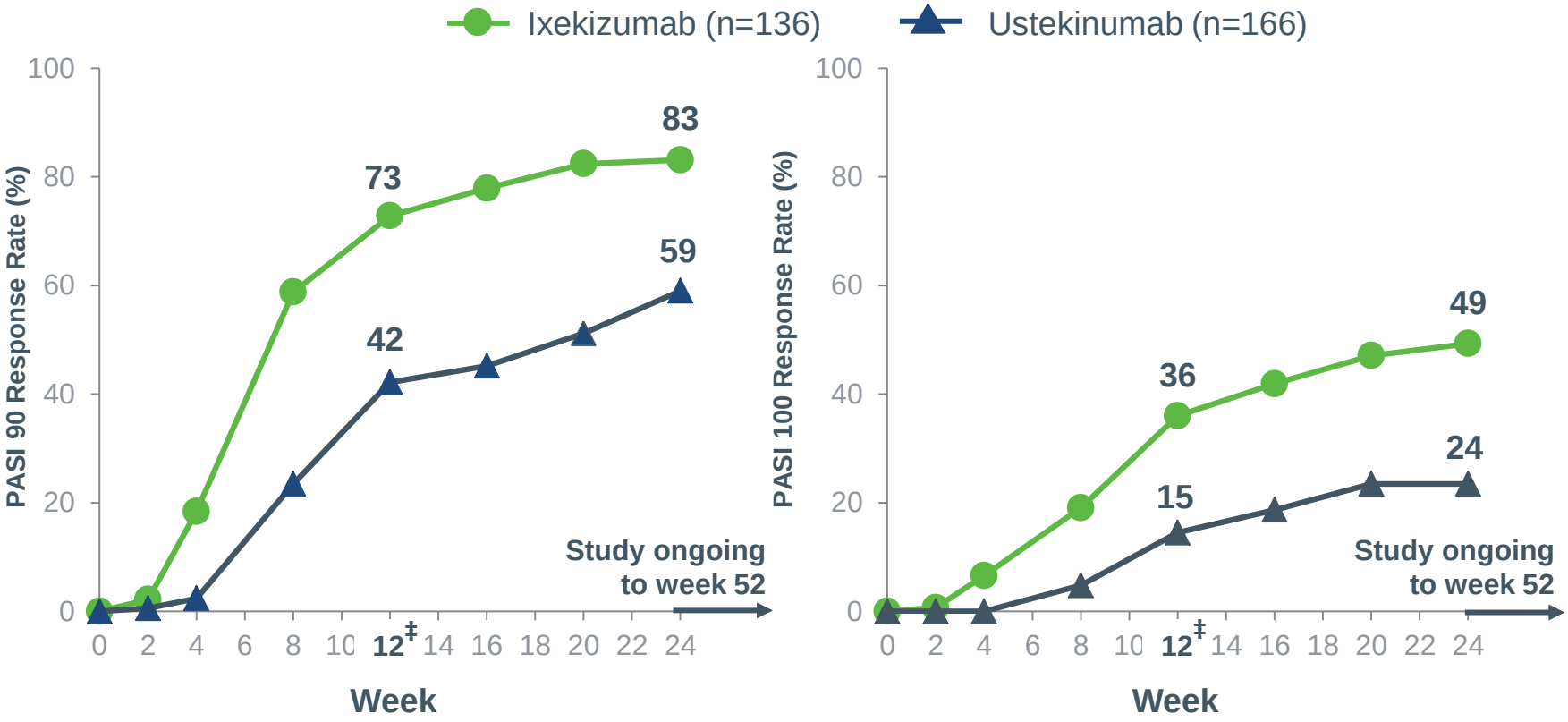
Gottlieb et al. JEADV 2017, 31, 679–685

Ixekizumab Showed Superiority in Two Head-to-Head Trials vs Etanercept at Week 12

NRI analysis



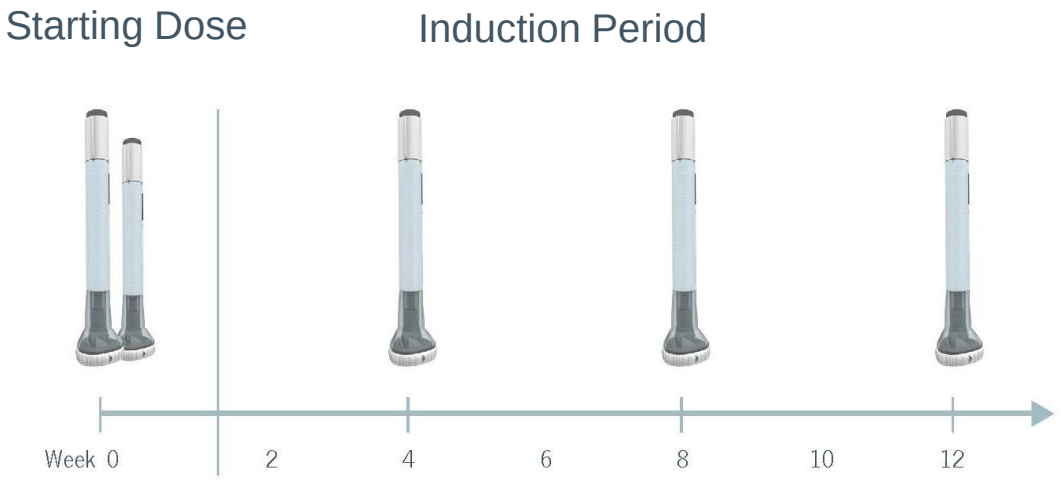
Ixekizumab vs Ustekinumab: PASI 90* and PASI 100† Response by Treatment Week, NRI



*Primary efficacy measure; †Key secondary efficacy measure; ‡Week 12 was the primary endpoint.

Reich et al. Br J Dermatol. 2017 Oct;177(4):1014-1023.

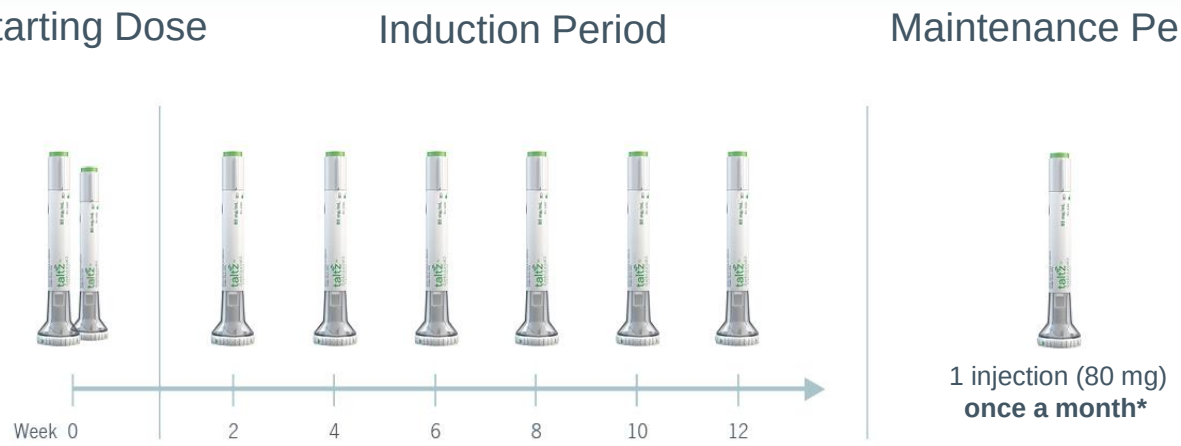
Ixekizumab Dosing for Patients With Psoriatic Arthritis



Starting dose: 2 injections (80 mg each)
Subsequent doses: 1 injection (80 mg) every 4 weeks

If patients forget to take their Ixekizumab dose, instruct them to inject a dose as soon as they remember; then to take their next dose at the regularly scheduled time.

Ixekizumab Dosing for Patients With Psoriasis



Starting dose: 2 injections (80 mg each)
First 12 weeks: 1 injection (80 mg) every 2 weeks (then every 4 weeks thereafter)

*Every 4 weeks.

The dosing regimen for adult patients with moderate to severe plaque psoriasis, and for adult patients with psoriatic arthritis and coexistent moderate to severe plaque psoriasis

Ixekizumab: ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

COMPLETELY CLEAR SKIN + JOINT SYMPTOM IMPROVEMENT

Completely Clear Skin in Patients With Moderate to Severe Plaque Psoriasis*

UNCOVER-2 Week 12

90% PASI 75 vs 2% placebo | **71**% PASI 90 vs 1% placebo | **40**% PASI 100 vs 1% placebo | **83**% sPGA 0,1 vs 2% placebo

*Defined as BSA ≥10%.

■ Ixe 80 mg Every 2 Weeks (n=351) ■ Placebo (n=168)

Joint Symptom Improvement in Patients With Psoriatic Arthritis

SPIRIT-P1 (BIOLOGIC-NAÏVE) WEEK 24

58% ACR20 vs 30% placebo | **40**% ACR50 vs 15% placebo | **23**% ACR70 vs 6% placebo

■ Ixe 80 mg Every 4 Weeks (n=107) ■ Placebo (n=106)

SPIRIT-P2 (TNFi-Experienced) Week 24

53% ACR20 vs 20% placebo | **35**% ACR50 vs 5% placebo | **22**% ACR70 vs 0% placebo

■ Ixe 80 mg Every 4 Weeks (n=122) ■ Placebo (n=118)

Taltz SPC