A Head-to-Head Comparison of Ixekizumab and Adalimumab in Biologic-Naïve Patients with Active Psoriatic Arthritis: Efficacy and Safety Outcomes from a Randomized, Open-Label, Blinded Assessor Study Through 52 Weeks

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BACKGROUND

- Ixekizumab (IXE) is a high affinity monoclonal antibody against interleukin-17A[1] approved for the treatment of adult patients with active psoriatic arthritis (PsA) and moderate-to-severe plaque psoriasis (PsO)
- Efficacy and safety of IXE in patients with PsA were extensively evaluated in two phase 3, multicenter, double-blind studies: SPIRIT-P1 (NCT01695239)[2] and SPIRIT-P2 (NCT02349295)[3]
- TNF-inhibitors, such as adalimumab (ADA), have long been regarded the gold standard treatment for PsA, while IL-17 inhibition has been repeatedly shown in head-to-head (H2H) trials to have superior efficacy in PsO[4,5]
- Hitherto, no results of H2H clinical trials directly comparing different bDMARDs in patients with PsA have been published
- This question has been assessed in the present H2H trial in which IXE showed superiority to ADA for the simultaneous achievement of ACR50 and PASI 100 and PASI 100 and non-inferiority for ACR50 at week 24[6]
- Here we report the final efficacy and safety outcomes at week 52

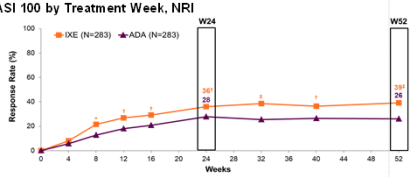
OBJECTIVE

- Primary Objective[6]:
  - To assess whether IXE is superior to ADA as measured by the proportion of patients simultaneously achieving ACR50 and PASI 100 at Week 24
- Key Secondary Objectives[6]:
  - To assess the non-inferiority on ACR50 response at Week 24 between IXE and ADA
  - To assess the superiority on PASI 100 response at Week 24 of IXE over ADA
- Other Secondary Objectives
  - Pre-specified endpoints covering all PsA domains at Week 52

KEY RESULTS

Note: NRI was used for imputation of all missing data, including drop-outs as non-responders.

Figure 1. Percentage of Patients Achieving Simultaneous ACR50 and PASI 100 by Treatment Week, NRI



*p<.01 vs. ADA; †p<.05 vs. ADA; ‡p<.001 vs. ADA.

Figure 2. ACR20/50/70 Response by Treatment Week, NRI

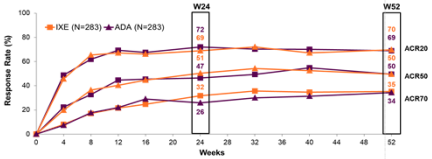
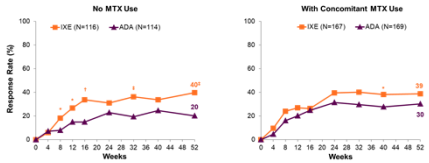
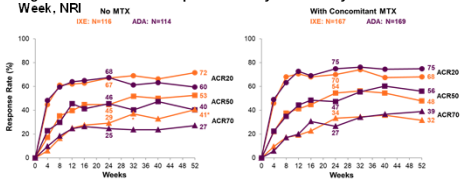


Figure 3. Simultaneous ACR50 and PASI 100 Response by MTX use by Treatment Week, NRI



*p<.05 vs. ADA; †p≤.001 vs. ADA; ‡p<.01 vs. ADA. p for IXE vs. ADA at Week 52 in concomitant MTX subgroup =.108. Subgroup-by-treatment interaction p-value at Week 16 = .019; all other time-points, NS.

Figure 4. ACR20/50/70 Response Rate by MTX use by Treatment Week, NRI



*p<.05 vs. ADA.

KEY RESULTS

Table 1. Safety Outcomes Through Week 52

Note: Patients with multiple occurrences of these categories are counted once for each category; patients may be counted in more than one category

	IXE N=283 n (%)	ADA N=283 n (%)
Treatment-emergent adverse events	209 (74)	194 (69)
Mild[a]	95 (34)	85 (30)
Moderate[a]	105 (37)	89 (31)
Severe[a]	9 (3.2)	20 (7.1)
TEAE related to study treatment[b]	98 (35)	87 (31)
Serious adverse events	12 (4.2)	35 (12)
Deaths	0	0
Discontinuation due to adverse event[c]	12 (4.2)	21 (7.4)

Table 2. Adverse Events of Special Interest Through Week 52

	IXE N=283 n (%)	ADA N=283 n (%)
Infections	119 (42)	111 (39)
Serious infections	5 (1.8)	8 (2.8)
Injection-site reactions[d]	30 (11)	10 (3.5)
Allergic reactions/hypersensitivity	11 (3.9)	13 (4.6)
Potential anaphylaxis	1 (0.4)[e]	0
Inflammatory bowel disease	2 (0.7)[f]	0
Ulcerative colitis	1 (0.4)[f,g]	0
Crohn's disease	1 (0.4)[f,h]	0
Cerebro-cardiovascular events	5 (1.8)	7 (2.5)
Malignancies	0	4 (1.4)
Depression	5 (1.8)	9 (3.2)
Cytopenias	9 (3.2)	12 (4.2)

[a]Patients with multiple occurrences of the same event are counted under the highest severity. [b]The TEAE's relationship to study treatment is judged by the investigator. [c]Including death.

[d]MedDRAHigh-level term. [e]Patient experienced mild injection site pain, cough, and dizziness at the baseline visit, which was resolved on the same day. [f]EPIdemiologique des Maladies de l'Appareil Digestif (EPIMAD) criteria for adjudication of suspected inflammatory bowel disease define "probable" and "definite" classifications as confirmed cases. Only 1 case met the EPIMAD criteria of confirmed inflammatory bowel disease. [g]Event was reported as colitis ulcerative and was adjudicated as possible ulcerative colitis and did not meet the EPIMAD criteria of confirmed inflammatory bowel disease. [h]Event was reported as colitis and was adjudicated as probable Crohn's disease.

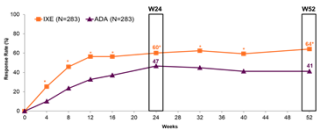
CONCLUSIONS

- IXE provided significantly greater simultaneous joint and skin improvement versus ADA as early as week 8 and through week 52
- IXE performed at least as well as ADA across multiple musculoskeletal PsA domains and showed superiority in the skin domain through week 52
- The efficacy of IXE was similar independently of MTX use. Moreover, in patients who did not use MTX, there was a trend toward better efficacy of IXE compared with ADA across the clinical responses
- Safety outcomes for IXE and ADA were consistent with previously established safety profiles for both drugs

Other Secondary Endpoints

- Arthritis: ≥20%/70% improvement in ACR criteria (ACR20, ACR70)
- Skin: ≥75%/90% improvement in PASI (PASI 75, PASI 90)
- Composite treat-to-target (T2T) measure in PsA: Minimal Disease Activity (MDA-18 entheseal points)
- Post-hoc (T2T): Very Low Disease Activity (VLDA-18 entheseal points), Disease Activity index for PSoriatic Arthritis (DAPSA) remission (score ≤4)
- Enthesitis: Spondyloarthritis Research Consortium of Canada (SPARCC) and Leeds Enthesitis Index (LEI)
- Dactylitis: Leeds Dactylitis Index Basic (LDI-B)
- Nail: Nail Psoriasis Severity Index (NAPSI)
- Physical function: Change in Health Assessment Questionnaire-Disability Index (HAQ-DI)
- Pre-specified endpoints based on concomitant MTX use
- Safety data

PASI 100 Response by Treatment Week, NRI



*p≤.001 vs. ADA. NRI was used for imputation of all missing data, including drop-outs as non-responders.

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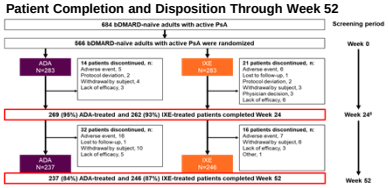
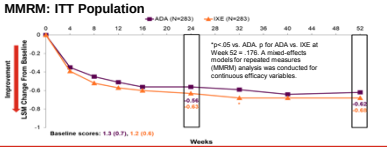
Patient Completion and Disposition Through Week 52



Note: Nine patients with active PsO and BSA ≥3% were assessed as PASI=0 at baseline, a medical inconsistency that was resolved using medical judgement. These patients were considered PASI 100 responders if PASI=0 and BSA=0 at post baseline visits

HAQ-DI Mean Change From Baseline by Treatment Week, MMRM: ITT Population



*p<.05 vs. ADA. p for ADA vs. IXE at Week 52 = .178. A mixed-effects models for repeated measures (MMRM) analysis was conducted for continuous efficacy variables.

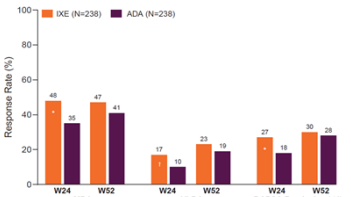
Baseline Demographics, Clinical Characteristics, and Disease Activity

	IXE N=283	ADA N=283
Age, years (mean ± SD)	47.5 ± 12.0	48.3 ± 12.3
Female, n (%)	121 (43)	133 (47)
BMI, kg/m² (mean ± SD)	30.0 ± 6.9	29.7 ± 8.3
Duration of symptoms since PsA diagnosis, years (mean ± SD)	6.6 ± 7.4	5.9 ± 6.4
Duration of symptoms since psoriasis diagnosis, years (mean ± SD)	16.1 ± 13.1	14.7 ± 12.6
Concomitant csDMARD use, n (%)	193 (68)	199 (70)
Concomitant MTX use, n (%)	167 (59)	169 (60)
Tender joint count (mean ± SD)	19.1 ± 12.7	21.3 ± 15.4
Swollen joint count (mean ± SD)	**10.1 ± 7.5**	**10.7 ± 8.1**
Patient pain VAS, mm (mean ± SD)	59.7 ± 21.9	62.4 ± 21.1
Patient's global assessment of disease activity VAS, mm (mean ± SD)	62.4 ± 20.3	65.2 ± 20.7
Physician's global assessment of disease activity VAS, mm (mean ± SD)	58.9 ± 17.5	59.4 ± 18.2
HAQ-DI (mean ± SD)	**1.2 ± 0.6**	**1.3 ± 0.7**
CRP, mg/L (mean ± SD) (ULN = 10 mg/L)	**9.8 ± 13.7**	**10.5 ± 19.3**
Leeds Enthesitis Index (LEI) >0, n (%)	**159 (56.4)**	**147 (51.9)**
SPARCC Enthesitis Index >0, n (%)	189 (67)	171 (60)
LDI-B >0, n (%)	42 (15)	58 (21)
DAPSA (mean ± SD)	**42.7 ± 20.6**	**45.8 ± 23.5**
Moderate-to-severe psoriasis, n (%)*	49 (17)	51 (18)
PASI (mean ± SD)	**7.9 ± 8.7**	**7.7 ± 7.3**
NAPSI fingernail score ≥0, n (%)	191 (68)	177 (63)

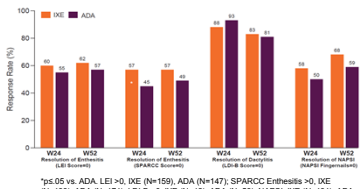
Data are n (%) or mean ± standard deviation. Values are mean ± SD unless otherwise indicated. *Criteria for moderate-to-severe psoriasis were PASI ≥12, sPGA ≥3, BSA ≥10%

Other Secondary Endpoints at Week 24 and Week 52, NRI

Note: NRI was used for imputation of all missing data, including drop-outs as non-responders.



*p<.05 vs. ADA.



*p≤.05 vs. ADA. LEI >0, IXE (N=159), ADA (N=147); SPARCC Enthesitis >0, IXE (N=189), ADA (N=171); LDI-B >0, IXE (N=42), ADA (N=58); NAPSI, IXE (N=191), ADA (N=171)

ABBREVIATIONS: ACR, American College of Rheumatology; ACR20/70, ≥20/70% improvement in ACR; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DAPSA, Disease Activity for Psoriatic Arthritis; DLQI, HAQ-DI, Health Assessment Questionnaire-Disability Index; IXE, ixekizumab; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; MDA, Minimal Disease Activity; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PASI75/90, 75/90% improvement in PASI; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation; SPARCC, Spondyloarthritis Research Consortium of Canada; T2T, treat-to-target; ULN; upper limit of normal; VAS, visual analogue scale; VLDA, Very Low Disease Activity

DISCLOSURES: JS: Research Grants: Abbvie, AstraZeneca, Lilly, Novartis and Roche; Honoraria for consultancies and/or speaking engagements: AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Gilead, ILTOO, Janssen, Eli Lilly and Company, Merck Sharp & Dohme, Novartis- Sandoz, Pfizer, Roche, Samsung, Sanofi, and UCB. PN: Received research grants and funding for clinical trials and honoraria for advice and lectures on behalf of Abbvie, BMS, Celgene, Eli Lilly and Company, Novartis, Roche, Sanofi, Gilead, Pfizer, Janssen, MSD. HT: Consultancies with Novartis, Abbvie, Eli Lilly and Company. HSK: Research Grants: Abbvie, Novartis; Honoraria for consultancies and/or speaking engagements: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Gilead, Janssen, Eli Lilly and Company, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, Roche, Sanofi, and UCB. LL, MH, AMG, SLL and SP are employees and shareholders at Eli Lilly and Company. PM: Grantsresearch support from: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Leo, Eli Lilly and Company, Merck, Novartis, Pfizer, Sun Pharmaceutical Industries, Inc., and UCB., Consultant for: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Leo, Eli Lilly and Company, Merck, Novartis, Pfizer, Sun Pharmaceutical Industries, Inc., and UCB., Speakers bureau: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech, Janssen, Leo, Merck, Novartis, Pfizer and UCB

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