Efficacy and Safety of Ixekizumab Vs. Adalimumab (SPIRIT-H2H) With and Without Concomitant Conventional Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) in Biologic DMARD-Naïve Patients With Psoriatic Arthritis: 52-Week Results

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BACKGROUND

- Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A[1]
- SPIRIT-H2H was a Phase 3b/4 trial to evaluate the effectiveness and safety of IXE vs. adalimumab (ADA) in patients with psoriatic arthritis who were bDMARD naïve
  - IXE was superior to ADA at Week 24 for the primary endpoint of simultaneous achievement of ACR50 and PASI 100[2]
  - The 2 major secondary endpoints of SPIRIT-H2H were also achieved at Week 24[2]
    - Non-inferiority of IXE to ADA for ACR50
    - Superiority of IXE to ADA for PASI 100

OBJECTIVE

- To determine how concomitant csDMARD use affects the efficacy and safety of IXE and ADA, in subgroups defined by the presence or absence of csDMARD use at baseline, through Week 52 in SPIRIT-H2H
  - Additional analyses focusing on concomitant use with methotrexate (MTX) through Week 52 are also reported

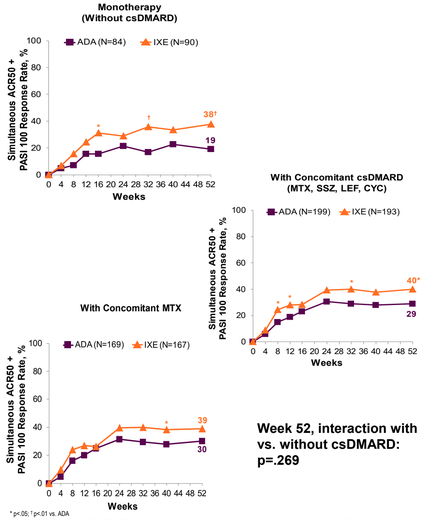
Abbreviations: ACR50=≥50% improvement from baseline in American College of Rheumatology criteria; bDMARD=biologic disease-modifying antirheumatic drug; IL=interleukin; PASI 100=100% improvement from baseline in the Psoriasis Area and Severity Index

References

1. Liu L, et al. *J Inflamm Res*. 2016;9:39-50.
2. Mease PJ, et al. *Ann Rheum Dis*. 2020;79:123-131.

KEY RESULTS

Percentage of Patients Achieving Simultaneous ACR50 and PASI 100 Response, NRI

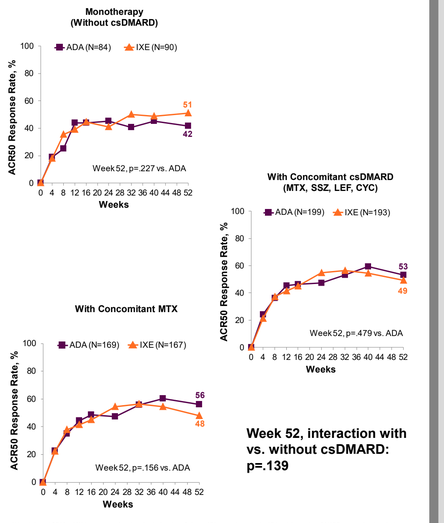


Week 52, interaction with vs. without csDMARD: p=.269

* p<.05; † p<.01 vs. ADA

Abbreviations: ACR50=≥50% improvement from baseline in American College of Rheumatology criteria; ADA=adalimumab; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; IXE=ixekizumab; LEF=leflunomide; MTX=methotrexate; N=number of patients; NRI=non-responder imputation; PASI 100=100% improvement from baseline in the Psoriasis Area and Severity Index; SSZ=sulfasalazine

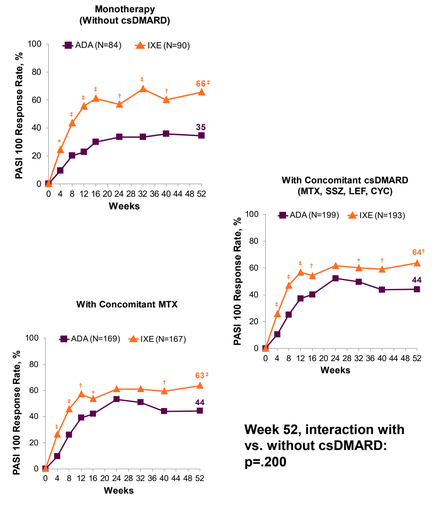
Percentage of Patients Achieving ACR50 Response, NRI



Week 52, interaction with vs. without csDMARD: p=.139

Abbreviations: ACR50=≥50% improvement from baseline in American College of Rheumatology criteria; ADA=adalimumab; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; IXE=ixekizumab; LEF=leflunomide; MTX=methotrexate; N=number of patients; NRI=non-responder imputation; SSZ=sulfasalazine

Percentage of Patients Achieving PASI 100 Response, NRI

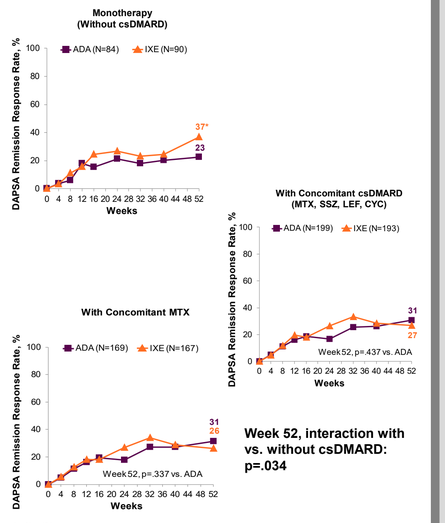


Week 52, interaction with vs. without csDMARD: p=.200

* p<.05; † p<.01; ‡ p<.001 vs. ADA

Abbreviations: ADA=adalimumab; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; IXE=ixekizumab; LEF=leflunomide; MTX=methotrexate; N=number of patients; NRI=non-responder imputation; PASI 100=100% improvement from baseline in the Psoriasis Area and Severity Index; SSZ=sulfasalazine

Percentage of Patients Achieving DAPSA Remission, NRI



Week 52, interaction with vs. without csDMARD: p=.034

* p<.05 vs. ADA

Abbreviations: ADA=adalimumab; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; DAPSA=Disease Activity Index for Psoriatic Arthritis; IXE=ixekizumab; LEF=leflunomide; MTX=methotrexate; N=number of patients; NRI=non-responder imputation; SSZ=sulfasalazine

CONCLUSIONS

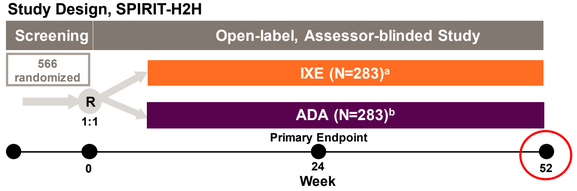
- The efficacy of IXE was sustained until Week 52 in the SPIRIT-H2H study with consistent difference from ADA in terms of the combined ACR50 and PASI 100 endpoint, in line with the data observed at Week 24[1]
- The safety results were consistent with the known safety profile of both drugs[1-3]
- ADA was associated with numerically lower response rates when used as monotherapy than in combination with csDMARDs
- The efficacy of IXE was similar regardless of whether it was taken as monotherapy or in combination with csDMARDs, with the difference to ADA especially visible in patients who did not take concomitant csDMARDs
- Results from the subset of patients taking MTX at baseline were consistent with those of the broader csDMARD group

References

1. Mease PJ, et al. Ann Rheum Dis. 2019;79:123-131.
2. Coates LC, et al. RMD Open. 2017;3:e000561.
3. Nash P, et al. RMD Open. 2018;4:e000692.

METHODS

Study Design, SPIRIT-H2H



- Randomization was stratified by concomitant use of csDMARDs and the presence/absence of moderate-to-severe plaque psoriasis (defined in the study as BSA ≥10% + PASI ≥12 + sPGA ≥3 at baseline)
- Dosing was based on the presence/absence of moderate-to-severe psoriasis at baseline[a,b]
- A citrate-free formulation of ADA was used
- 9 patients with active psoriasis 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

[a] IXE Q2W from Weeks 2 to 12 and IXE Q4W thereafter (N=49) for patients with study-defined moderate-to-severe psoriasis, and IXE Q4W for all other patients (N=234); [b]ADA 80 mg at Week 0, 40 mg at Week 1 and every 2 weeks thereafter for patients with study-defined moderate-to-severe psoriasis (N=51), and 40 mg every 2 weeks for all other patients (N=232). Abbreviations: ADA=adalimumab; BSA=body surface area; csDMARD=conventional synthetic disease-modifying antirheumatic drug; IXE=ixekizumab; IXE Q2W=80 mg ixekizumab every 2 weeks; IXE Q4W=80 mg ixekizumab every 4 weeks; N=number of patients; PASI=Psoriasis Area and Severity Index; R=randomization; sPGA=static Physician's Global Assessment

Key Eligibility Criteria

Inclusion Criteria

- Male or female ≥18 years years of age
- Diagnosis of PsA ≥6 months ago and fulfilling Classification Criteria for Psoriatic Arthritis
- Active PsA (≥3/68 tender and ≥3/66 swollen joints at screening and baseline)
- Active plaque PsO (BSA ≥3% at screening and baseline)
- Inadequate response to ≥1 csDMARD

Exclusion Criteria

- Prior/current bDMARD JAK inhibitor therapy for PsA or PsO
- Diagnosis of other inflammatory arthritic syndromes, such as rheumatoid arthritis, ankylosing spondylitis, reactive arthritis
- Diagnosis of or history of malignant disease within <5 years prior to randomization
- Active Crohn's disease, ulcerative colitis, or uveitis

Abbreviations: bDMARD=biologic disease-modifying antirheumatic drug; BSA=body surface area; csDMARD=conventional synthetic disease-modifying antirheumatic drug; JAK=Janus kinase; PsA=psoriatic arthritis; PsO=psoriasis

Subgroups and Assessments

Definition of subgroups by drug use:

- Presence or absence of csDMARD use at baseline (MTX, SSZ, LEF, CYC)
  - Presence or absence of MTX use at baseline

Prespecified subgroup analyses:[1]

- Simultaneous ACR50 and PASI 100
- ACR50
- PASI 100

Post hoc subgroup analyses:

- ACR70
- PASI 75/90
- MDA (18 entheseal points)
- DAPSA Remission
- LEI=0
- SPARCC=0
- LDI-B=0

Abbreviations: ACR50/70=≥50%/70% improvement from baseline in American College of Rheumatology criteria; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; DAPSA=Disease Activity Index for Psoriatic Arthritis; LDI-B=Leeds Dactylitis Index-Basic; LEF=leflunomide; LEI=Leeds Enthesitis Index; MDA=minimal disease activity; MTX=methotrexate; PASI 75/90/100=≥75%/90%/100% improvement from baseline in the Psoriasis Area and Severity Index; SPARCC=Spondyloarthritis Research Consortium of Canada Enthesitis Index; SSZ=sulfasalazine; ITT=intent to treat

Reference

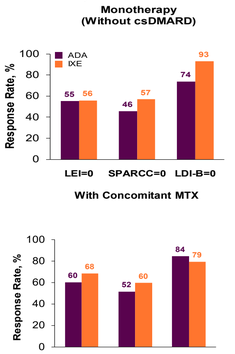
1. Smolen JS, et al. *Ann Rheum Dis*. 2020; under review.

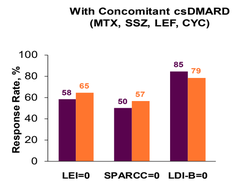
Statistical Analyses

- **Subgroup analysis was conducted using the ITT population**
- Logistic regression analysis was performed with treatment and baseline concomitant csDMARD use as factors and treatment-by-baseline concomitant csDMARD use as an interaction term
  - Interaction p-values were considered statistically significant using the 0.10 threshold
- Treatment group differences were evaluated within each category of the subgroup using the Fisher exact test
- **Missing data were imputed using non-responder imputation**

RESULTS

Percentage of patients Achieving LEI=0,[a] SPARCC=0,[b] and LDI-B=0[c] at Week 52, NRI





Week 52, interaction with vs. without csDMARD: LEI=0: p=.626; SPARCC= p=.672; LDI-B=0: p=.143

[a,b,c] Assessed in patients with LEI >0, SPARCC >0, and LDI-B >0 at baseline, respectively

Abbreviations: ADA=adalimumab; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; IXE=ixekizumab; LDI-B=Leeds Dactylitis Index-Basic; LEF=leflunomide; LEI=Leeds Enthesitis Index; MTX=methotrexate; NRI=non-responder imputation; SPARCC=Spondyloarthritis Research Consortium of Canada Enthesitis Index; SSZ=sulfasalazine

- The majority of patients treated with IXE or ADA had complete resolution of enthesitis or dactylitis following 1 year of treatment (being mindful of the low number of patients presenting dactylitis at baseline)
- There were no significant differences in responses between IXE and ADA treatment groups at Week 52 (p>.05)

Safety Summary

	Monotherapy (Without csDMARD)		With Concomitant csDMARD (MTX, SSZ, LEF, CYC)		With Concomitant MTX	
	ADA (N=84)	IXE (N=90)	ADA (N=199)	IXE (N=193)	ADA (N=169)	IXE (N=167)
All TEAEs	58 (69.0)	69 (76.7)	136 (68.3)	140 (72.5)	114 (67.5)	117 (70.1)
Mild	26 (31.0)	34 (37.8)	59 (29.6)	61 (31.6)	54 (32.0)	52 (31.1)
Moderate	24 (28.6)	30 (33.3)	65 (32.7)	75 (38.9)	50 (29.6)	61 (36.5)
Severe	8 (9.5)	5 (5.6)	12 (6.0)	4 (2.1)	10 (5.9)	4 (2.4)
Serious AEs	11 (13.1)	6 (6.7)	24 (12.1)	6 (3.1)	18 (10.7)	4 (2.4)
Deaths	0	0	0	0	0	0
Discontinuation owing to AE	7 (8.3)	4 (4.4)	14 (7.0)	8 (4.1)	12 (7.1)	4 (2.4)
Serious infections	5 (6.0)	3 (3.3)	3 (1.5)	2 (1.0)	3 (1.8)	1 (0.6)
Malignancies	0	0	4 (2.0)	0	3 (1.8)	0

- Frequencies of AEs were similar across the 3 subgroups for IXE and ADA
- Frequencies of AEs in the subgroup of patients using only MTX at baseline were similar to those from the "with concomitant csDMARD" group

Abbreviations: ADA=adalimumab; AE=adverse event; csDMARD=conventional synthetic disease-modifying antirheumatic drug; CYC=cyclosporine; IXE=ixekizumab; LEF=leflunomide; MTX=methotrexate; N=number of patients; SSZ=sulfasalazine; TEAE=treatment-emergent adverse event

Disclosures

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