Efficacy of Ixekizumab and Guselkumab in Histopathologic Changes in Psoriasis: Results from a Randomized, Double-Blind, Head-to-Head Trial (IXORA-R)

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BACKGROUND

- Although not fully elucidated, the pathogenesis of plaque PsO has been attributed to increased proliferation and poor differentiation of keratinocytes, resulting in the thickening of the epidermis[1]
- Ixekizumab, an IL-17A inhibitor,[2] and guselkumab, an IL-23p19 inhibitor,[3] are highly effective drugs approved for the treatment of moderate-to-severe plaque PsO[4-7]
- IXORA-R, a Phase 4, randomized, double-blind, head-to-head, multicenter trial (NCT03573323) comparing the efficacy and safety of ixekizumab with guselkumab for patients with moderate-to-severe plaque PsO, demonstrated that significantly more patients receiving ixekizumab achieved PASI 50 at Week 1, PASI 75 at Week 2, and PASI 100 at Week 4 compared with those receiving guselkumab[8]

OBJECTIVE

- This analysis was conducted to examine epidermal normalization as measured by epidermal thickness and keratinocyte proliferation in a subset of patients from IXORA-R who consented to participate in a biopsy addendum

SUMMARY OF KEY FINDINGS

In this substudy of IXORA-R, IXE was associated with greater reductions in keratinocyte proliferation and epidermal thickness in the first 4 weeks of treatment, suggesting that IXE can deliver more rapid PsO resolution compared with GUS

	Time (Weeks)			
	0	1	2	4
Keratinocyte proliferation[a] (Ki-67 staining)	-		↓	↓
Epidermal thickness[a] (H&E staining)	-	↓	↓	↓

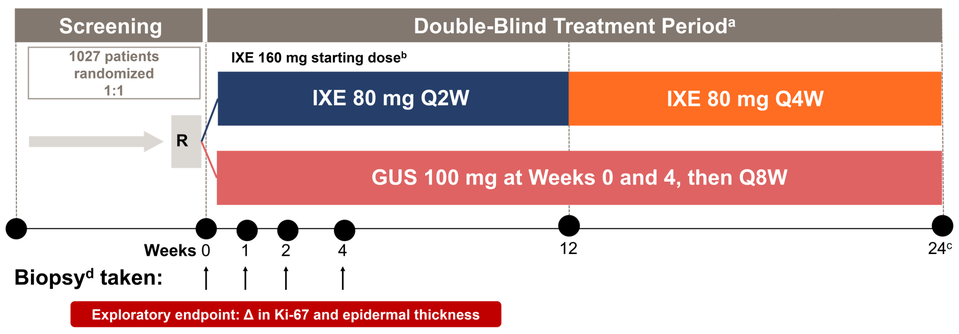
[a] Arrows represent significant reductions from baseline observed with IXE compared with GUS

CONCLUSIONS

- In this substudy, greater epidermal normalization was shown with ixekizumab than with guselkumab in the first 4 weeks of treatment, with significant reductions observed as early as Week 1 in epidermal thickness and Week 2 in Ki-67 expression
- These immunohistochemistry results further support the clinical observation that ixekizumab can deliver more rapid PsO resolution compared with guselkumab

METHODS

Study Design: IXORA-R



[a] Patients received the approved-label dose for PsO for both IXE and GUS; to maintain blinding, patients randomized to GUS received 1 placebo injection at Weeks 0, 2, 6, 8, 10, and 16; [b] Administered as two 80-mg subcutaneous injections at Week 0; [c] After Week 24, patients entered a post-treatment follow-up period for a minimum of 12 weeks (maximum follow-up of 24 weeks to Week 48); [d] For patients who provided consent for this substudy, skin biopsies were taken from the same target lesion

Analysis Population and Assessments

Patients Included in Analysis

- **Subset of all randomized patients[a] (IXE: N=41; GUS: N=31)**

Outcomes Assessed (Weeks 1, 2, and 4)

- **Treatment disposition**
- **Changes from baseline in keratinocyte proliferation marker Ki-67 and epidermal thickness**
  - Treatment comparison between IXE and GUS was conducted using an MMRM analysis, with treatment, pooled site, baseline value, visit, treatment-by-visit, and baseline value-by-visit as fixed factors

[a] Only patients who provided consent to participate in the biopsy addendum were included. Missing data were not imputed

RESULTS

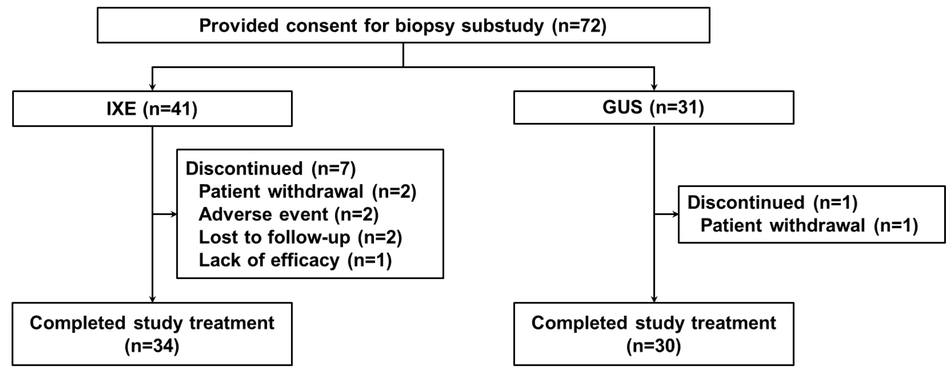
Patient Demographics and Other Baseline Characteristics

- Baseline characteristics were relatively well balanced between the 2 arms

	IXE (N=41)	GUS (N=31)
Age, years	46.6 (11.8)	49.1 (14.5)
Male, n (%)	33 (80.5)	17 (54.8)*
BMI, kg/m²	34.2 (7.7)	33.7 (9.1)
Race, n (%)		
White	34 (82.9)	29 (93.5)
Black	4 (9.8)	1 (3.2)
Other/not reported	3 (7.3)	1 (3.2)
Time since PsO diagnosis, years, median (range)	14.1 (2.2-42.8)	10.9 (0.7-51.2)
PASI score	19.2 (8.9)	19.7 (10.1)
BSA % involvement	23.7 (16.0)	27.0 (19.7)
sPGA score, n (%)		
Moderate	20 (48.8)	18 (58.1)
Severe	16 (39.0)	12 (38.7)
Very severe	5 (12.2)	1 (3.2)
DLQI	13.2 (7.0)	14.1 (7.4)
Prior systemic therapy, n (%)		
Non-biologics	11 (26.8)	5 (16.1)*
Biologics	6 (14.6)	7 (22.6)
Both	5 (12.2)	0

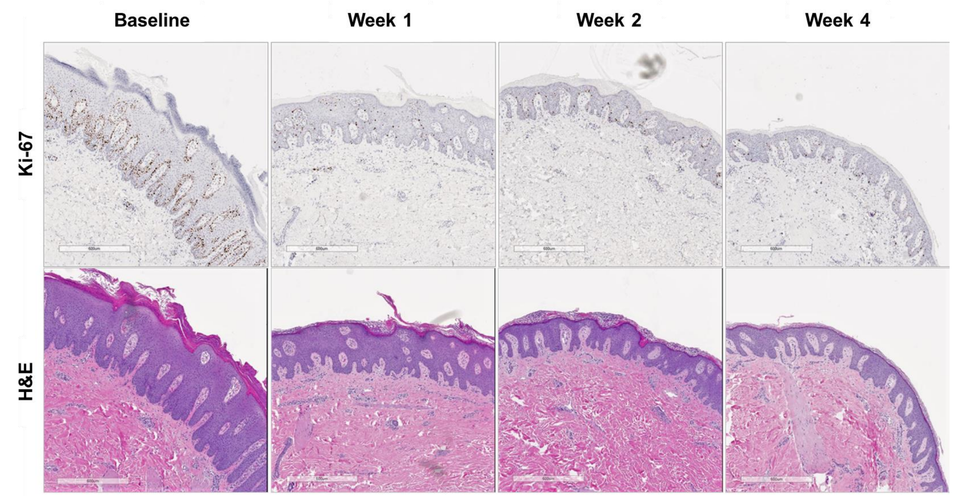
* Differences in the proportion of patients between IXE vs. GUS were statistically significant (p≤.05)
Note: Data are presented as mean (SD) unless otherwise indicated

Treatment Disposition in Substudy



Histopathologic Imaging From A Representative Ixekizumab-treated Patient From Baseline to Week 4

- Ki-67 immunostaining showed a time-dependent decrease in keratinocyte proliferation concomitant with a decrease in epithelial thickness demonstrated by H&E staining



Notes: Histopathological changes in Ki-67 immunostaining and epidermal thickness were assessed at Weeks 0, 1, 2, and 4 of a psoriatic plaque from a representative IXE-treated patient. Magnification ×20
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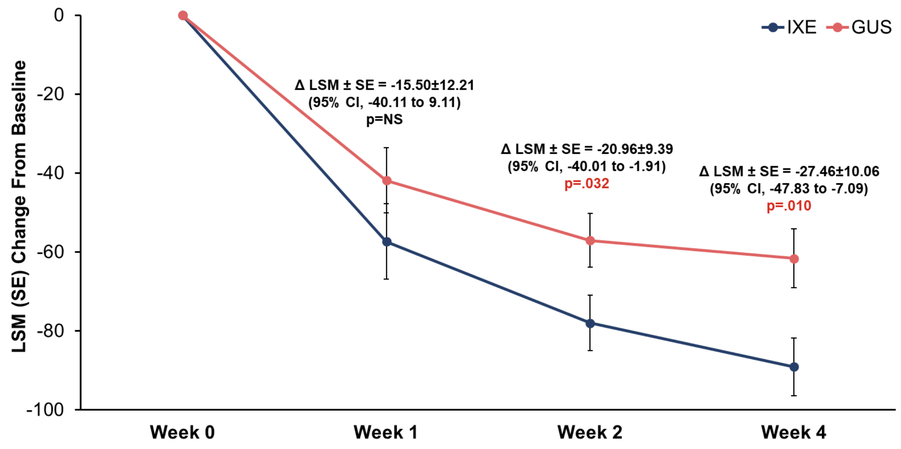
Histopathologic Changes From Baseline to Week 4

- Significantly reduced Ki-67 expression and epidermal thickness were observed in patients treated with ixekizumab compared with those treated with guselkumab
  - Difference in Ki-67 levels was statistically significant as early as Week 2 (p=.032)
  - Difference in epidermal thickness was statistically significant as early as Week 1 (p=.022)

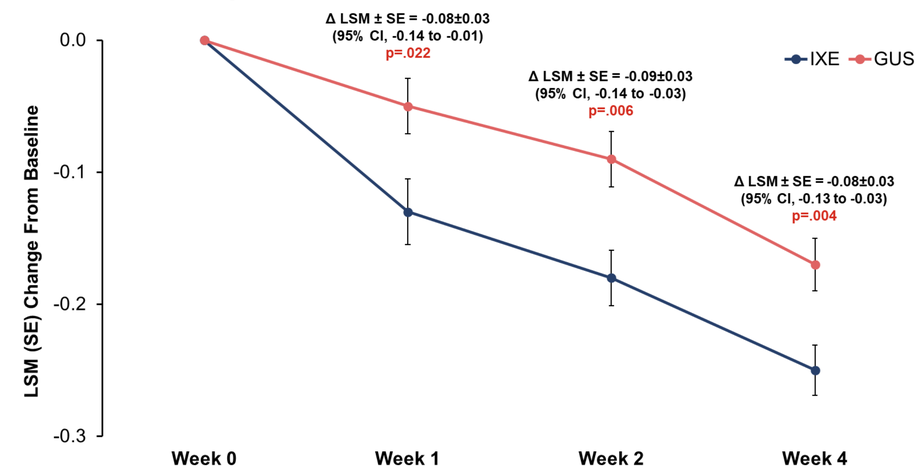
Change From Baseline in Ki-67 From Baseline to Week 4



	Week 1		Week 2		Week 4	
	IXE	GUS	IXE	GUS	IXE	GUS
Number of patients with evaluable samples	29	19	27	20	25	20
LSM ± SE	-57.33±8.28	-41.83±9.52	-77.99±6.84	-57.03±7.02	-89.05±7.41	-61.59±7.29

Notes: Changes from baseline in Ki-67 were analyzed using an MMRM analysis, with treatment, pooled site, baseline value, visit, treatment-by-visit, and baseline value-by-visit as fixed factors. One patient with CTCL was excluded from the analysis. Error bars represent SE of LSM of each treatment arm

Change From Baseline in Epidermal Thickness From Baseline to Week 4



	Week 1		Week 2		Week 4	
	IXE	GUS	IXE	GUS	IXE	GUS
Number of patients with evaluable samples	29	18	27	20	25	20
LSM ± SE	-0.13±0.02	-0.05±0.03	-0.18±0.02	-0.09±0.02	-0.25±0.02	-0.17±0.02

Notes: Changes from baseline in epidermal thickness were analyzed using an MMRM analysis, with treatment, pooled site, baseline value, visit, treatment-by-visit, and baseline value-by-visit as fixed factors. One patient with CTCL was excluded from the analysis. Error bars represent SE of LSM of each treatment arm

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ABBREVIATIONS

BMI=body mass index; BSA=body surface area; CI=confidence interval; CTCL=cutaneous T-cell lymphoma; DLQI=Dermatology Life Quality Index; GUS=guselkumab; H&E=hematoxylin and eosin; IL=interleukin; IXE=ixekizumab; LSM=least squares mean; MMRM=mixed-effects model for repeated measures; NS=not significant; PASI=Psoriasis Area and Severity Index; PASI 50/75/100=≥50%/≥75%/100% improvement from baseline in PASI; PsO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; R=randomization; SD=standard deviation; SE=standard error; sPGA=Static Physician's Global Assessment

DISCLOSURES

- **S. Forman** has served as a speaker, consultant, advisory board member, and/or investigator for: AbbVie, Aclaris Therapeutics, Asana BioSciences, AstraZeneca, Athenex, Celgene, Cutanea, Eli Lilly and Company, Incyte Corporation, Innovaderm Research, Novartis, Pfizer, Promius Pharma, Regeneron, UCB Pharma, Valeant Pharmaceuticals, and XBiotech; **A. Pinter** has served as an investigator and/or speaker and/or advisor for: AbbVie, Almirall, Amgen, Biogen, BioNTech, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma, GlaxoSmithKline, Hexal, Janssen, LEO Pharma, MC2 Therapeutics, Medac, Merck Serono, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Pascoe Natural Healthcare, Pfizer, Regeneron, Roche, Sandoz, Sanofi Genzyme, Schering-Plough, Tigercat Pharma, and UCB Pharma; **K. A. Papp** has served as a speaker and/or adviser for and/or has received grant/research support from: AbbVie, Akros Pharma, Amgen, Anacor Pharmaceuticals, Arcutis, Astellas, AstraZeneca, Baxalta, Baxter International, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite BioPharma, Coherus BioSciences, Dermira, Dow Pharmaceutical Sciences, Eli Lilly and Company, Forward Pharma, Galderma, Genentech, Gilead Sciences, GlaxoSmithKline, InflaRx, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck Serono, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Takeda, UCB Pharma, and Valeant Pharmaceuticals/Bausch Health; **L. Renda**, **B. Konicek**, **R. Higgs**, **G. Gallo**, **H. Elmaraghy**, and **S. Y. Park** are employees and minor shareholders of: Eli Lilly and Company; **C. Maari** has served as an advisory board member, investigator, and/or speaker for: AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma, GlaxoSmithKline, Janssen, Novartis, and Pfizer
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