

## SHORT REPORT

# Ixekizumab improves secondary lesional signs, pain and sexual health in patients with moderate-to-severe genital psoriasis

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## Abstract

**Background** Epithelial surface disruption in genital psoriatic lesions may manifest as erosions, fissures and/or ulcers, causing pain and significantly impacting a patient's sexual health.

**Objective** To evaluate the impact of erosions, fissures and/or ulcers in genital psoriatic lesions on pain and sexual activity in patients with moderate-to-severe genital psoriasis (GenPs) and treatment responses to ixekizumab vs. placebo until Week 12.

**Methods** This *post hoc* subgroup analysis of patients presenting with and without erosions, fissures and/or ulcers in genital lesions from a phase IIIb multicentre, randomized, double-blind, placebo-controlled study (IXORA-Q; NCT02718898) in 149 adults with moderate-to-severe GenPs treated with subcutaneous ixekizumab (80 mg every 2 weeks;  $n = 75$ ) or placebo ( $n = 74$ ) evaluated outcomes for clinician-rated GenPs severity (static Physician's Global Assessment of Genitalia; sPGA-G) and patient-reported genital pain and itch (Genital Psoriasis Symptoms Scale; GPSS) and sexual health (Genital Psoriasis Sexual Frequency Questionnaire; GenPs-SFQ).

**Results** At baseline, 38% ( $n = 57$ ) of patients presented with genital erosions, fissures and/or ulcers independent of overall body surface area involvement (<10% or  $\geq 10\%$ ). These signs were associated with higher scores for disease severity (sPGA-G) and pain (GPSS) but not sexual health (GenPs-SFQ). Complete resolution of these signs was observed in 62% of ixekizumab-treated patients (25% for placebo) at Week 1 and 83% (21% for placebo) at Week 12. Patients treated with ixekizumab reported significant improvements in pain, itch, disease severity and sexual health over 12 weeks compared to placebo and irrespective of the presence/absence of genital erosions, fissures and/or ulcers at baseline.

**Conclusion** Ixekizumab led to rapid and sustained resolution of erosions, fissures and/or ulcers and significant improvements in GenPs severity, genital pain and sexual health. Ixekizumab may help to improve the well-being of patients with GenPs.

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## Conflicts of interest

J.F. Merola is a consultant and/or investigator for Biogen IDEC, AbbVie, Amgen, Eli Lilly and Company, Novartis, Pfizer, Jensen, UCB, Samumed, Celgene, Sanofi Regeneron, Merck and GSK; P.-D. Ghislain is consultant, speaker, investigator, for Schering-Plough/MSD, Abbott/AbbVie, Janssen-Cilag, Merck-Serono, Léo, Novartis, UCB, Amgen, Celgene, Eli Lilly and Company, Galderma, BMS, Meda, Maruho, Flen, Menarini, Almirall, PellePharm, Wyeth/Pfizer; J.N. Dauendorffer is an investigator and/or consultant for Eli Lilly and Company, Celgene, AbbVie; A. Potts Bleakman, A.J.M. Brnabic, R. Burge and E. Riedl are all employees and shareholders of Eli Lilly and Company.

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## Introduction

Up to 63% of patients with plaque psoriasis experience genital involvement at some time.<sup>1–4</sup> Genital skin is highly sensitive and prone to surface disruption, presenting clinically as erosions, fissures and/or ulcers. These signs of genital psoriasis (GenPs) typically are painful, often pruritic, and can impact a patient's sexual health and quality of life.<sup>2,5–7</sup> Still, GenPs is often under-reported, under-diagnosed and under-treated.<sup>6–8</sup>

Current therapies for GenPs are limited.<sup>4</sup> Systemic therapies are recommended when other treatment options fail,<sup>8,9</sup> but existing data on systemic treatments come from open-label trials or case reports.<sup>10</sup>

Ixekizumab, a high-affinity anti-interleukin-17A monoclonal antibody, is approved for the treatment of moderate-to-severe plaque psoriasis. In a randomized, placebo-controlled study (IXORA-Q; NCT02718898) in adults with moderate-to-severe GenPs, most patients achieved complete or nearly complete resolution of GenPs during 12 weeks of ixekizumab treatment as assessed by a static Physician's Global Assessment of Genitalia (sPGA-G)<sup>9</sup> score of 0 or 1.<sup>11</sup>

This *post hoc* analysis of the IXORA-Q study evaluated the impact of erosions, fissures and/or ulcers in GenPs lesions on genital pain and sexual health, as well as clinical responses to ixekizumab vs. placebo.

## Methods

Details of the IXORA-Q study have been reported.<sup>11</sup> Briefly, 149 adults with moderate-to-severe GenPs, sPGA-G score  $\geq 3$  and body surface area (BSA) involvement  $\geq 1\%$  were randomized to subcutaneous ixekizumab (80 mg every 2 weeks following an initial dose of 160 mg;  $n = 75$ ) or placebo ( $n = 74$ ) during a 12-week blinded treatment period. Patients with fungal genital infections or infective Koebner response at baseline were excluded.

### Outcome measures in the post hoc analysis

At each visit, investigators assessed the genital area (labia minora, labia majora and perineum in females and penis, scrotum and perineum in males) and rated the presence/absence of genital erosions, fissures and ulcers. They also rated disease severity using the sPGA-G<sup>6</sup> and the modified Genital Psoriasis Area and Severity Index (mGPASI).<sup>2,12</sup>

### Patient-reported outcomes

Patients rated their disease severity using the Patient's Global Assessment of Genital Psoriasis (PatGA-Genital), while pain and itch were assessed using the Genital Psoriasis Symptoms Scale (GPSS).<sup>13</sup> Genital pain and itch were assessed using the GPSS score, sum of GPSS pain, stinging and burning numeric rating scale (NRS) scores, and change in GPSS itch NRS score over 12 weeks.

The impact of GenPs on sexual health was assessed by evaluating the proportion of patients with little or no impact (0/1) on item 2 of the Genital Psoriasis Sexual Frequency Questionnaire

(GenPs-SFQ)<sup>14</sup> and item 9 of the Dermatology Life Quality Index (DLQI)<sup>15</sup> over 12 weeks.

Descriptions of all scales are provided in Appendix S1.

### Statistical analyses

All analyses were based on the intention-to-treat (ITT) population.

**Table 1** Baseline demographics and disease characteristics

	With genital erosions, fissures and/or ulcers <i>N</i> = 57	Without genital erosions, fissures and/or ulcers <i>N</i> = 92
Age, years	43.7 (11.46)	43.8 (13.51)
Male, <i>n</i> (%)	43 (75.4)	70 (76.1)
Weight, kg	90.2 (22.9)	95.6 (25.7)
Weight category, <i>n</i> (%)		
<80 kg	19 (33.3)	31 (33.7)*
$\geq 80$ to <100 kg	22 (38.6)	19 (20.7)
$\geq 100$ kg	16 (28.1)	42 (45.7)
Previous non-biologic systemic therapy†, <i>n</i> (%)	35 (61.4)	43 (46.7)
Time since psoriasis onset, years	16.6 (11.8)	16.5 (13.1)
Time since genital psoriasis onset, years	8.6 (8.1)	8.9 (9.8)
Percentage of BSA involved, <i>n</i> (%)		
1 to <10%	25 (43.9)	34 (37.0)
$\geq 10\%$	32 (56.1)	58 (63.0)
Overall sPGA score	3.6 (0.7)	3.5 (0.5)
sPGA-G score	3.6 (0.5)	3.3 (0.6)**
sPGA-G score category, <i>n</i> (%)		
3	24 (42.1)	62 (68.1)**
4	32 (56.1)	27 (29.7)
5	1 (1.8)	2 (2.2)
mGPASI score	32.8 (16.0)	23.9 (13.1)***
PatGA-Genital score	3.6 (1.1)	3.4 (1.1)
GenPs-SFQ item 2 score	2.0 (1.6)	1.8 (1.6)
DLQI item 9 score (0,1), <i>n</i> (%)	28 (49.1)	53 (57.6)
GPSS sum of symptom scores for pain, stinging and burning for each patient‡	17.6 (8.1)	14.5 (7.6)*

Data presented as mean (SD) unless indicated otherwise.

ANOVA, analysis of variance; BSA, body surface area; DLQI, Dermatology Life Quality Index; GenPs-SFQ, Genital Psoriasis Sexual Frequency Questionnaire; mGPASI, modified Genital Psoriasis Area and Severity Index; NRS, numeric rating scale; PatGA-Genital, Patient's Global Assessment of Genital Psoriasis; sPGA, static Physician's Global Assessment; sPGA-G, static Physician's Global Assessment of Genitalia.

As \* $P \leq 0.05$ , \*\* $P < 0.01$  and \*\*\* $P < 0.001$  for the difference between patients with and without genital erosions, fissures and/or ulcers. The asterisks at the weight category and the sPGA-G score category indicate that the two groups differed significantly across categories. *P*-values are based on Fisher's exact test (categorical data) or ANOVA (continuous data).

†Ever used, including methotrexate, cyclosporine, corticosteroids, acitretin, fumaric acid derivatives, apremilast and other systemic agents.

‡Score range 0–30 (each item on the GPSS NRS has score range 0–10).

**Table 2** Genital Psoriasis Symptoms Scale scores at baseline by body surface area involvement and presence/absence of genital erosions, fissures and/or ulcers

	1% to <10% BSA involvement N = 59		≥10% BSA involvement N = 90	
	With genital erosions, fissures and/or ulcers N = 25	Without genital erosions, fissures and/or ulcers N = 34	With genital erosions, fissures and/or ulcers N = 32	Without genital erosions, fissures and/or ulcers N = 58
GPSS total score†	48.6 (17.3)	36.3 (12.9)*	49.3 (21.3)	44.7 (20.0)
GPSS individual component scores [NRS]‡				
Itch	6.1 (2.3)	5.0 (1.9)*	6.5 (2.6)	6.2 (2.5)
Pain	6.1 (2.4)	4.1 (2.2)*	5.9 (2.8)	5.4 (2.7)
Discomfort	6.2 (2.4)	5.2 (2.0)	6.9 (2.7)	6.1 (2.5)
Stinging	5.7 (2.4)	4.2 (2.1)*	5.7 (3.2)	5.4 (2.7)
Burning	5.9 (2.5)	4.1 (2.0)*	5.8 (3.0)	5.2 (2.8)
Redness	6.6 (2.1)	5.4 (1.7)*	6.7 (2.6)	6.3 (2.4)
Scaling	5.8 (2.3)	4.3 (2.1)*	6.1 (2.8)	5.3 (2.8)
Cracking	6.1 (2.2)	4.1 (2.1)*	5.7 (3.0)	4.9 (3.0)
GPSS sum of symptom scores for pain, stinging and burning for each patient§	17.7 (7.3)	12.3 (6.1)*	17.4 (8.8)	15.9 (8.2)

Data are presented as mean (SD).

ANOVA, analysis of variance; BSA, body surface area; GPSS, Genital Psoriasis Symptoms Scale; NRS, numeric rating scale.

\* $P \leq 0.05$  for comparison between groups with and without genital erosions, fissures and/or ulcers (ANOVA with presence/absence of genital erosions, fissures and/or ulcers as a factor).

†Score range 0–80.

‡Each item on the GPSS NRS has a score range 0–10.

§Score range 0–30.

Baseline characteristics of the subgroups with and without genital erosions, fissures and/or ulcers were summarized and compared descriptively using Fisher's exact test for categorical data and analysis of variance (ANOVA) for continuous data.

For longitudinal analysis of treatment outcomes, missing data for categorical variables (binary outcomes) were imputed using non-responder imputation (NRI).

Change from baseline in binary outcome measures was analysed using a generalized linear model with logit link function. Continuous outcome variables were analysed using a mixed-effects model for repeated measures (MMRM) fitted with unstructured covariance matrix and compared for fit using Bayesian information criteria. The MMRM results are reported as least square (LS) means and standard error (SE), with between-group comparisons reported as LS mean difference, 95% confidence intervals (CIs) and  $P$ -values.

## Results

At baseline, 38% (57/149) of patients presented with genital erosions, fissures and/or ulcers. Specifically, of those patients, 75% ( $n = 43$ ) had genital fissures, 44% ( $n = 25$ ) genital erosions and 3.5% ( $n = 2$ ) genital ulcers. These secondary surface changes were associated with significantly higher baseline scores for sPGA-G and mGPASI (Table 1). Patients with these signs had significantly ( $P < 0.05$ ) higher mean baseline GPSS scores than patients without these changes, for pain (6.0 vs. 4.9), discomfort

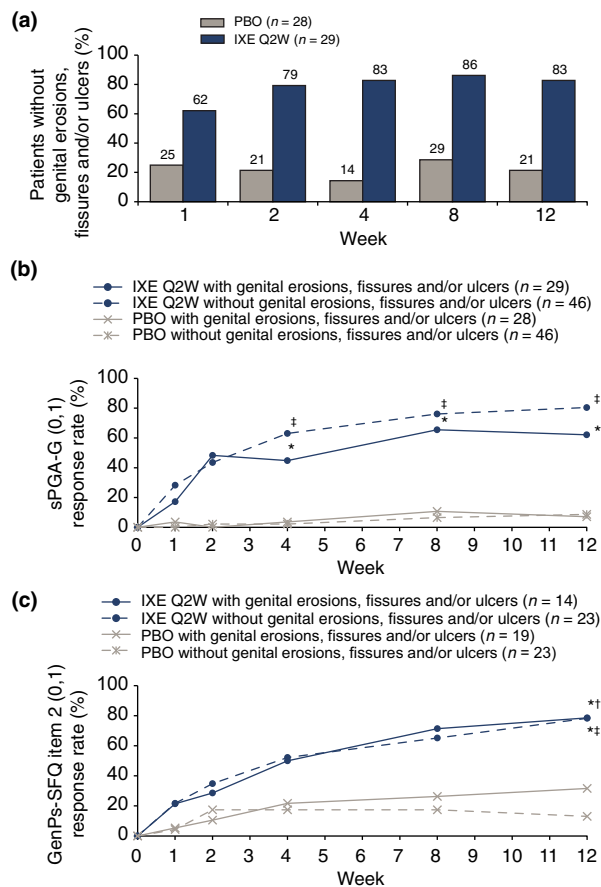
(6.6 vs. 5.7) and burning (5.9 vs. 4.8). However, GPSS itch NRS (6.3 vs. 5.7) and scores of sexual health (Table 1) did not differ between subgroups.

At baseline, 40% ( $n = 59$ ) of patients had 1% to <10% BSA involvement and 60% ( $n = 90$ ) had ≥10% BSA involvement. Genital erosions, fissures and/or ulcers were present at baseline in 42% ( $n = 25$ ) and 36% ( $n = 32$ ) of patients in these subgroups, respectively. In the subgroup with <10% BSA involvement, all baseline GPSS item scores with the exception of discomfort were significantly higher in patients with genital erosions, fissures and/or ulcers, whereas these scores were similar in patients with ≥10% BSA involvement, irrespective of the presence or absence of these signs (Table 2).

Patients with genital erosions, fissures and/or ulcers at baseline presented the lowest proportion in the category ≥100 kg (Table 1). Among patients with low BSA involvement (<10%), the subgroup of patients with genital erosions had significantly lower mean weight and body mass index (Table S1).

Among ixekizumab-treated patients, genital erosions, fissures and/or ulcers were resolved completely in 62% at Week 1 and in 83% at Week 12, compared with 25% and 21% of placebo-treated patients, respectively (Fig. 1a; see clinical images in Figure S1).

Irrespective of the presence or absence of genital erosions, fissures and/or ulcers at baseline, ixekizumab resulted in significantly greater improvements in the sPGA-G and mGPASI scores



**Figure 1** The graphs show (a) complete resolution of genital erosions, fissures and/or ulcers by treatment group over 12 weeks in the subgroup of patients with these signs at baseline (Week 0), (b) the Static Physician's Global Assessment of Genitalia (sPGA-G) (0,1) non-responder imputation response rate over 12 weeks.

\* $P < 0.01$  vs. PBO in patients with genital erosions, fissures and/or ulcers (solid grey line); † $P < 0.001$  vs. PBO in patients without genital erosions, fissures and/or ulcers (dashed grey line) from logistic regression analysis, and (c) the Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ) item 2 (0,1) response rate over 12 weeks in patients with and without genital erosions, fissures and/or ulcers at baseline by treatment group; non-responder imputation, intention-to-treat population with baseline GenPs-SFQ item 2 score  $\geq 2$ . \* $P < 0.01$  vs. PBO in patients with genital erosions, fissures and/or ulcers (solid grey line); † $P < 0.01$ ; ‡ $P < 0.001$  vs. PBO in patients without genital erosions, fissures and/or ulcers (dashed grey line) from generalized linear model. IXE Q2W, ixekizumab 80 mg every 2 weeks; PBO, placebo.

during 12 weeks of treatment vs. placebo; the differences vs. the placebo group with the same secondary surface changes were significant (Table 3). The sPGA-G (0,1) response rate with ixekizumab over 12 weeks was consistent, regardless of the presence/absence of these clinical signs at baseline, after adjustment for baseline variables (odds ratio [OR] 1.5; 95% CI 0.7, 3.6;

$P = 0.320$ ; Fig. 1b). At Week 12, the overall sPGA (0,1) response rate for patients with these clinical signs at baseline was 62.1% in the ixekizumab group and 0% in the placebo group.

### Patient-reported outcomes

The scores for GPSS total, GPSS sum of pain, stinging and burning, and GPSS itch NRS improved significantly over 12 weeks of ixekizumab treatment, regardless of the presence/absence of genital erosions, fissures and/or ulcers at baseline (Table 3). Significantly more patients achieved  $>50\%$  improvement in GPSS itch NRS during 12 weeks of treatment with ixekizumab vs. placebo, with or without secondary surface changes present (Figure S2).

At Week 12, significantly higher proportions of patients achieved GenPs-SFQ item 2 (0,1) responses with ixekizumab vs. placebo, irrespective of the presence/absence of secondary surface changes at baseline (Fig. 1c).

Results for the DLQI item 9 score (0,1) response rate were comparable (data not shown).

### Discussion

This *post hoc* analysis from the IXORA-Q study<sup>11</sup> showed that signs of surface disruption in GenPs lesions are common, occur independent of overall BSA involvement and are associated with higher scores for clinical severity of GenPs and with more severe pain-related symptoms.

According to our data, signs of surface disruption have a greater impact on patient-reported measures in patients with limited BSA involvement ( $<10\%$ ), highlighting the importance of assessing disease severity and treatment outcomes from both physician and patient perspectives. In patients with genital erosions, fissures and/or ulcers, genital pain was the lead symptom, especially in those with  $<10\%$  BSA involvement. This is consistent with previous reports highlighting that fissures and erosions are potential disease-aggravating factors in GenPs.<sup>2,16–18</sup>

Moderate genital itch at baseline was present in patients with and without signs of surface disruption. In line with Ryan *et al.*,<sup>11</sup>  $>50\%$  improvement rates in GPSS itch NRS during 12 weeks of treatment were significantly higher with ixekizumab vs. placebo, regardless of the presence/absence of secondary surface changes at baseline.

Consistent with reports of prevalence rates of obesity in GenPs, a relatively high proportion of patients in our study weighed  $\geq 100$  kg, but this was not associated with greater severity of GenPs or clinical signs of surface disruption.

Psoriasis affecting the genital area can cause emotional distress and sexual health problems.<sup>2,6,18</sup> In this analysis, the presence of epithelial surface disruption at baseline did not seem to cause greater worsening of sexual health problems. The improvements in sexual health observed with ixekizumab may be consequent to resolved genital lesions.

Previous research has shown that complete skin clearance in psoriasis is a clinically meaningful outcome for patients.<sup>19</sup> Thus,

**Table 3** Changes in outcome measures over 12 weeks of treatment with ixekizumab or placebo in subgroups with or without genital erosions, fissures and/or ulcers at baseline

Outcome measure†	Ixekizumab		Placebo		Between-group LS mean difference (95% CI), P value	With genital erosions, fissures and/or ulcers N = 28	Without genital erosions, fissures and/or ulcers N = 45	Ixekizumab vs. placebo LS mean difference (95% CI), P value	Without genital erosions, fissures and/or ulcers N = 46	With genital erosions, fissures and/or ulcers N = 29	Ixekizumab vs. placebo LS mean difference (95% CI), P value
	With genital erosions, fissures and/or ulcers N = 29	Without genital erosions, fissures and/or ulcers N = 46	With genital erosions, fissures and/or ulcers N = 28	Without genital erosions, fissures and/or ulcers N = 45							
sPGA-G score	-1.9 (0.2)	-1.9 (0.1)	-0.5 (0.2)	-0.6 (0.1)	-0.1 (-0.5, 0.3), P = 0.666			-1.4 (-1.9, -1.0), P < 0.001			-1.2 (-1.5, -0.8), P < 0.001
mGPASI score	-21.0 (1.8)	-16.6 (1.5)	-5.8 (1.9)	-6.2 (1.5)	-0.4 (-5.4, 4.6), P = 0.881			-15.4 (-21.6, -9.3), P < 0.001			-9.6 (-13.4, -5.8), P < 0.001
GPSS total score	-17.3 (2.1)	-14.8 (1.8)‡	-10.6 (2.1)	-9.2 (1.8)§	1.4 (-3.8, 6.6), P = 0.590			-10.0 (-15.3, -4.6), P < 0.001			-6.0 (-10.5, -1.5), P = 0.010
GPSS sum of pain, stinging & burning	-6.8 (0.8)	-5.4 (0.7)‡	-4.0 (0.8)	-3.2 (0.7)§	0.9 (-1.2, 2.9), P = 0.394			-3.9 (-6.1, -1.8), P < 0.001			-2.5 (-4.2, -0.7), P = 0.008
GPSS itch NRS	-2.0 (0.3)	-1.8 (0.2)‡	-1.3 (0.3)	-1.1 (0.3)§	0.3 (-0.4, 0.9), P = 0.413			-0.6 (-1.4, 0.1), P = 0.082			-0.9 (-1.5, -0.3), P = 0.006

CI, confidence interval; GPSS, Genital Psoriasis Symptoms Scale; LS, least square; MMRM, mixed-effects model for repeated measures; NRS, numeric rating scale; mGPASI, modified Genital Psoriasis Area and Severity Index; sPGA-G, static Physician's Global Assessment of Genitalia.

†Data presented as overall LS mean change (SE) from baseline over 12 weeks from MMRM model unless indicated otherwise. All models were adjusted for the following covariates: genital erosions, fissures and/or ulcers (yes vs. no), baseline score of variable of interest, visit, age, sex (male vs. female), weight category ( $\geq 100$  vs.  $< 80$  kg), sexual partner status (yes vs. no), baseline sPGA-G score, baseline mGPASI score, baseline GPSS total score, baseline Comprehensive Assessment of the Psoriasis Patient (CAPP)-Genital Severity Index score, and previous non-biologic systemic therapy (never used vs. ever used).

‡N = 42.

§N = 39.

our finding that most patients treated with ixekizumab achieved rapid and complete resolution of genital erosions, fissures and/ or ulcers can be considered clinically meaningful.

Limitations of this analysis are the limited study duration and number of patients in the respective subgroups and the potential for unmeasured confounding due to non-randomized comparison of subgroups.

Our data provide further evidence of the profound impact of GenPs on patients and may increase awareness and rates of diagnosis, monitoring and appropriate treatment of patients with this disease.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Details of outcome measures used in the *post hoc* analysis.

**Table S1.** Baseline characteristics of patients with and without genital erosions, fissures and/or ulcers by body surface area involvement (1% to <10%, ≥10%).

**Figure S1.** Clinical images illustrating a male patient at (a) baseline (Week 0) and (b) Week 12 of treatment with ixekizumab. IXE Q2W, ixekizumab 80 mg every 2 weeks.

**Figure S2.** Genital Psoriasis Symptoms Scale itch numeric rating scale >50% improvement from baseline (% patients).