



# Ixekizumab 80 mg Every 2 Weeks Treatment Beyond Week 12 for Japanese Patients with Generalized Pustular Psoriasis and Erythrodermic Psoriasis

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## ABSTRACT

**Introduction:** In 2018, ixekizumab (80 mg every 2 weeks [Q2W] beyond Week 12) received approval in Japan for patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP). This open-label study evaluated the efficacy and safety of ixekizumab (80 mg Q2W from Week 12 to Week 20) in Japanese patients with GPP and EP.

**Methods:** Seven patients with GPP and five patients with EP were enrolled. An initial dose of 160 mg (subcutaneous [SC] injection) was followed by 80 mg Q2W SC until Week 12. Primary endpoint assessed global improvement

score (GIS) by comparing psoriatic findings, Static Physician Global Assessment, Psoriasis Area and Severity Index score, and other evaluations with those at the baseline and were graded as 1 = resolved, 2 = improved, 3 = unchanged, and 4 = worsened. Patients who showed GIS = 1 (resolved) at Week 12 completed the study. Patients with GIS  $\geq$  2 continued to receive ixekizumab 80 mg Q2W until Week 20.

**Results:** At Week 12, four of seven patients with GPP showed “resolved,” two showed “improved,” and one showed “worsened.” Of five patients with EP, one showed “resolved” and four showed “improved.” Two patients with GPP and four patients with EP continued ixekizumab treatment until Week 20. At Week 20, one of the two patients with GPP showed “resolved” and one patient showed “improved.” All four patients with EP showed “improved.” One non-drug related serious adverse event was reported by one patient with EP at Week 12. From Week 12 to Week 20, no adverse events (AEs) were reported in patients with GPP, but two mild AEs were reported in one of the four patients with EP.

**Conclusions:** This study indicates that ixekizumab continuous Q2W dosing is efficacious and safe for patients with GPP and EP.

**Clinical Trial Registration:** NCT03942042.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s13555-021-00666-x>.

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## PLAIN LANGUAGE SUMMARY

Ixekizumab is an anti-interleukin-17 treatment for a skin condition with thick and scaly patches called psoriasis. Ixekizumab (initial dose of 160 mg followed by 80 mg administered every 2 weeks [Q2W] from Week 2 through Week 12 and thereafter 80 mg every 4 weeks [Q4W]) has been approved in Japan; people who have not achieved 100% clear skin after taking ixekizumab for 12 weeks can continue to receive ixekizumab Q2W rather than monthly. However, this approval partially lacked data from people with rare types of psoriasis, generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP). The aim of this study was to look at the effectiveness and safety of continuous Q2W dosing of ixekizumab in Japanese people with GPP and EP beyond Week 12. Researchers aimed to find out whether psoriasis symptoms in this population improved if they continued Q2W treatment for > 12 weeks. Seven people with GPP and 5 with EP participated in the study (12 in total). Participants initially received 160 mg under-the-skin injection of ixekizumab, followed by 80 mg injections Q2W. Two GPP and four EP participants continued to receive ixekizumab after 12 weeks up to Week 20. One GPP participant achieved 100% clear skin, and another GPP participant and all 4 EP participants showed improvement. No participants died, and safety findings were similar to previous ixekizumab studies from both Japanese and non-Japanese people. This study suggests that people with GPP and EP who continue to take ixekizumab Q2W after 12 weeks may show improvements in their psoriasis with a well-tolerated safety profile.

**Keywords:** Erythrodermic psoriasis; Generalized pustular psoriasis; Ixekizumab; Q2W

### Key Summary Points

#### Why carry out the study?

Ixekizumab (initial dose of 160 mg followed by 80 mg every 2 weeks from Week 2 through Week 12 and thereafter 80 mg every 4 weeks) has been approved for the treatment of psoriasis in various countries including Japan

Additionally, use of ixekizumab 80 mg every 2 weeks, continuing dosing beyond Week 12 for patients with psoriasis who have an inadequate response at Week 12, was approved in Japan in 2018, but lack of information existed on patients with rare types of psoriasis, generalized pustular psoriasis (GPP), and erythrodermic psoriasis (EP)

This study provided an opportunity to assess the efficacy and safety of ixekizumab 80 mg every 2 weeks beyond 12 weeks up to 20 weeks in patients with GPP and EP

#### What was learned from the study?

Ixekizumab 80 mg every 2 weeks proved to be efficacious and safe in patients with rare types of psoriasis beyond 12 weeks up to 20 weeks

## INTRODUCTION

Psoriasis is a common chronic skin disorder with an estimated prevalence of up to 3% worldwide [1–3], with lower rates of 1% observed in the Japanese population [4]. Generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) are rare diseases and account for 2.3% and 1.5% of all patients with psoriasis, respectively [5].

GPP is the most severe type of psoriasis characterized by multiple sterile pustules all over the body. GPP may be accompanied by systemic symptoms including fever, chills, severe itching, dehydration, rapid pulse rate, exhaustion,

anemia, weight loss, and muscle weakness [6]. GPP is designated as an “intractable disease” by the Japan Ministry of Health, Labor and Welfare (MHLW), and the estimated number of patients is approximately 1800–1900 nationwide [7]. EP is a severe, inflammatory type of psoriasis that can affect the whole body. Reddening and shedding of the skin are often accompanied by severe itching and pain, heart rate increase, fluid loss, and fluctuating body temperature [8].

Both psoriasis subtypes (GPP and EP) can sometimes be life-threatening without adequate treatment. Patients with these severe subtypes are known to experience frequent relapses [9] and require systemic treatment. However, since treatment options are limited, patients with GPP and EP experience an unmet medical need.

Interleukin (IL)-17A is a pro-inflammatory cytokine produced primarily by T helper 17 cells and is known to play a pivotal role in immunopathogenesis of psoriasis [10, 11]. Moreover, elevated serum IL-17 levels and elevated IL-17 mRNA expressions in skin lesions are reported in patients with GPP and EP [10, 11].

Ixekizumab (Taltz<sup>®</sup>) is a humanized immunoglobulin G subclass 4 monoclonal antibody (MAb) that binds to interleukin (IL)-17A with high affinity and specificity [12]. In 2016, it was approved in Japan for the treatment of psoriasis, PsA, GPP, and EP at an initial dose of ixekizumab 160 mg followed by ixekizumab 80 mg administered Q2W from Week 2 through Week 12 and thereafter 80 mg Q4W [12]. In August 2018, a new dosage and administration was approved in Japan to support 80 mg Q2W continued dosing beyond Week 12 for patients with psoriasis, PsA, GPP, and EP who have an inadequate response at Week 12 [13]. However, clinical studies consisting of the main data package in this new approval did not include the data from patients with GPP and EP who underwent treatment of ixekizumab 80 mg Q2W over 12 weeks.

The UNCOVER-J2 study (ClinicalTrials.gov: NCT03942042) was a multicenter, open-label, post-marketing, Phase 4 clinical trial designed to assess the efficacy and safety of ixekizumab administered Q2W beyond Week 12 until Week 20 in patients with GPP and EP. The study was

conducted to fulfill the requirements of the Pharmaceuticals and Medical Devices Agency (PMDA).

## METHODS

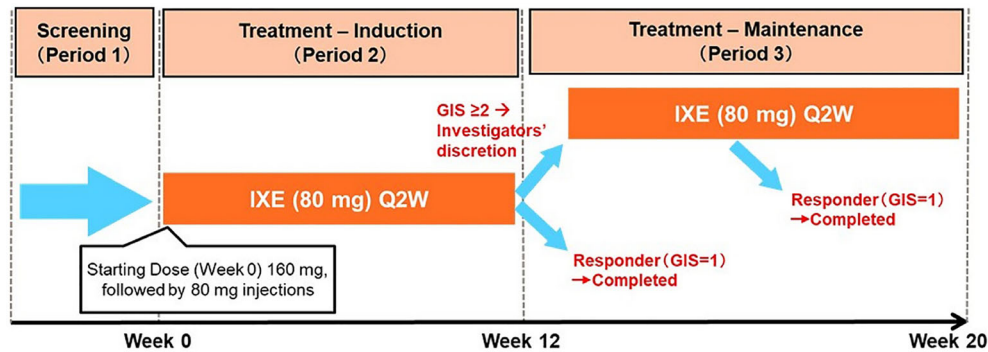
### Study Design and Treatment

Figure 1 demonstrates the study design. This open-label, post-marketing study consisted of 3 periods: screening period (Period 1), induction dosing period (Period 2), and maintenance dosing period (MDP; Period 3).

Induction dosing period lasted from Week 0 (Visit 2) to Week 12 (Visit 6). All eligible patients were administered 160 mg ixekizumab as two subcutaneous (SC) injections at Week 0 (baseline; Visit 2) followed by 80 mg as 1 injection at Week 2, 4, 6, 8, and 10. At Week 12, patients with global improvement score (GIS) = 1 (responders) completed the study, while patients with GIS  $\geq 2$ , and based on investigators' discretion, entered the MDP, which lasted from Week 12 (Visit 6) to Week 20 (Visit 10) and continued to use ixekizumab 80 mg given as one SC injection Q2W (Weeks 12, 14, 16, and 18).

Patients who either completed the study before Week 20 or discontinued study treatment after receiving at least one dose of ixekizumab had an early termination visit instead of the original scheduled visit. Once patients exited the study, they no longer had access to ixekizumab within the study.

The protocol was approved by Institutional Review Boards prior to patient recruitment, and each patient provided written informed consent before enrollment. The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Ethical Guidelines by the Council for International Organizations of Medical Sciences and the International Conference of Harmonization E6 Guidelines for Good Clinical Practice.



**Fig. 1** Study design. *IXE* Ixekizumab, *GIS* global improvement score, *Q2W* every 2 weeks

## Patient Population

The study included Japanese patients  $\geq 20$  years of age who presented with GPP or EP based on an investigator-confirmed diagnosis. Selected patients with GPP had to meet the criteria for GPP set by Ministry of Health, Labour, and Welfare at screening (Visit 1) and baseline (Week 0; Visit 2) regardless of IL-36 mutation status, whereas selected patients with EP had to be diagnosed to have body surface area (BSA)  $\geq 80\%$  involvement (with inflammatory erythema) at screening (Visit 1) and baseline (Week 0; Visit 2).

Some key exclusion criteria included manifestations of other skin conditions, serious infection (cellulitis or pneumonia) or intravenous antibiotic for an infection within 12 weeks prior to baseline, herpes zoster infection within 4 weeks of baseline, positive status for human immunodeficiency virus or hepatitis B or hepatitis C, prior treatment with ixekizumab, and live vaccination within 12 weeks prior to baseline.

Patients with GPP and EP were further classified, based on study period, into two population sets—Full Analysis Set (FAS) and MDP population. FAS included patients with GPP and EP separately who received at least one dose of study treatment in Period 2, and MDP population included the set of patients with GPP and EP separately who received at least one dose of study treatment in Period 3.

## Efficacy

Efficacy was assessed through the various endpoints at each scheduled visit after Week 12. The primary endpoint evaluated the number of patients who had improvement in their GIS by at least 1 point from Week 12 through Week 20 and with  $\leq 2$  of GIS. GIS grades were categorized as: 1 = resolved, 2 = improved, 3 = unchanged, and 4 = worsened. The GIS was assessed based on the comparison of the psoriatic findings, Static Physician Global Assessment (sPGA), Psoriasis Area and Severity Index (PASI) score, and other evaluations with those at the baseline. Other efficacy endpoints included number of patients who achieved static Physician Global Assessment (sPGA) (0, 1) and sPGA (0), Psoriasis Area and Severity Index (PASI) 75, PASI 90, and PASI 100, change from baseline and percent improvement from baseline in PASI, change from baseline in Psoriasis Scalp Severity Index (PSSI) in patients with scalp involvement at baseline, percent of BSA involvement of psoriasis, and change from baseline from GPP Severity Index score and who developed treatment-emergent anti-ixekizumab antibody (TE-ADA) and neutralizing anti-ixekizumab antibody (NAb). GPP Severity Index score was evaluated based on skin symptoms with an assigned score of 0–9 (erythematous area, erythematous area with pustule, edematous area) and systemic symptoms or laboratory findings with an assigned score of 0–8 (fever, white blood cell count, C-reactive protein, serum albumin). Severity was evaluated with

the total score of 0–17: 0–6 (mild), 7–10 (moderate), and 11–17 (severe) [14, 15].

### Health Outcomes

The study used two health outcome measures to assess quality of life: Itch NRS and DLQI. While both outcome measures are patient-administered, the Itch NRS is an 11-point horizontal scale anchored at 0 and 10, with 0 representing “no itch” and 10 representing “worst itch imaginable” [16], and the DLQI is a ten-question, validated, quality of life questionnaire that covers six domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include “not at all,” “a little,” “a lot,” and “very much,” with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (“not relevant”) responses scored as “0.” Totals ranged from 0 to 30 (the higher the score, the more quality of life is impaired), and a 5-point change from baseline was considered clinically relevant [17].

### Safety

Safety was assessed through clinical and laboratory evaluations that included electrocardiograms, vital signs, physical examinations, immunogenicity assessments, and Columbia-Suicide Severity Rating Scale (C-SSRS)/self-harm questionnaires. Adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) were coded to Medical Dictionary for Regulatory Activities preferred terms. The assessment of AEs included treatment-emergent adverse events (TEAEs). TEAE was defined as an event that first occurred or worsened in severity after baseline and on or prior to the date of the last visit within the treatment period.

### Statistical Analysis

All analyses were descriptive. For continuous variables, summary statistics included number of patients, mean, median, standard deviation, minimum, and maximum. Categorical binary

efficacy and health outcome variables were summarized using a non-responder imputation (NRI) method, and continuous efficacy and health outcomes variables were summarized using a last observation carried forward method.

## RESULTS

### Patient Disposition and Demographics

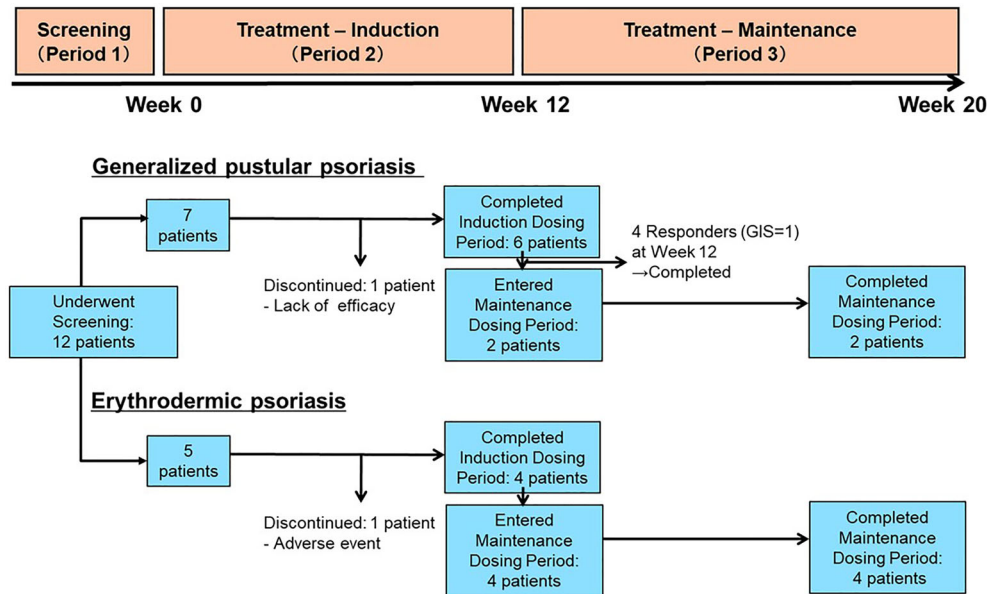
A total of 12 patients (7 with GPP, 5 with EP) were screened, and all 12 patients were enrolled in the trial at Week 0 and received treatment. Of the 12 patients in Period 2, 1 patient with GPP discontinued because of lack of efficacy and 1 with EP discontinued because of AE, resulting in 10 (83.3%) patients completing Week 12. Four patients with GPP achieved GIS = 1 at Week 12 and completed the study, resulting in six patients (50.0%; 2 patients with GPP and 4 patients with EP) entering Period 3 (MDP). All six patients completed Week 20 (Fig. 2).

The mean age of the total population was 43.8 years, and 50.0% of the patients were male (Table 1). The mean age at which GPP or EP was diagnosed was 43.0 years, and the mean duration since diagnosis was 1.1 years. All seven patients with GPP reported mild baseline GPP severity. The previous systemic psoriasis therapies included phototherapy, UVB (2 patients with GPP), non-biologic systemic agent (3 patients with GPP and 3 patients with EP), and biologic agents (1 patient with GPP and 2 patients with EP). All 12 patients in Period 2 and 5 patients in Period 3 received at least 1 concomitant therapy. Across Periods 2 and 3, all 12 patients received the planned dosage of ixekizumab—560 mg (80 mg × 2 starting dose at Week 2 followed by 80 mg Q2W until Week 10) and 320 mg (80 mg Q2W from Week 12 to Week 18), respectively.

### Efficacy

Overall, ten patients completed Week 12, of which two patients with GPP and four with EP continued the study beyond Week 12 and completed the study at Week 20. The primary





**Fig. 2** Patient disposition. GIS global improvement score

endpoint was met by one of six patients (GPP = 1/2; EP = 0/4) in the MDP population who showed improvement in their GIS by at least 1 point from Week 12 through Week 20 with GIS  $\leq$  2. Continuous administration of ixekizumab beyond Week 12 resulted in “resolved” or “improved” response (1 or 2 of GIS) in patients with GPP and in patients with EP.

Through the MDP, continuation of ixekizumab Q2W beyond Week 12 (Visit 6) up to Week 20 (Visit 10) allowed patients with GPP and patients with EP to maintain sPGA (0, 1). At Week 20, two patients with GPP and one patient with EP achieved sPGA (0, 1) while at the same week (Week 20), one patient with GPP achieved sPGA (0) (Supplementary Fig. 1).

At Week 12, 50% of patients with GPP and EP achieved PASI 75, and at Week 20, 100% and 75% of patients with GPP and EP achieved PASI 75, respectively, whereas PASI 90 was achieved by 50% of patients with GPP and 25% of patients with EP consistently at Week 12 and Week 20. At Week 20, 50% of patients with GPP achieved PASI 100 (Supplementary Fig. 2).

In addition, at Week 12 and Week 20, patients across both disease groups showed high average percent improvement from baseline in PASI. Similarly, improvements in patients with

scalp involvement in terms of PSSI and improvements in BSA involvement of psoriasis were observed. Furthermore, patients with GPP showed continuous improvement and reduction of GPP Severity Index total score upon Q2W ixekizumab administration beyond Week 12 up to Week 20. One patient with GPP scored 2 at baseline, 2 at Week 12, and 1 at Week 20, and another patient with GPP scored 4 at baseline, 1 at Week 12, and 0 at Week 20, respectively. Details of the changes from baseline and percent improvement from baseline results are provided in Table 2.

### Patient-Reported Outcomes

Continuous Q2W ixekizumab administration beyond Week 12 up to Week 20 resulted in maintained response for DLQI total score, DLQI (0,1), and DLQI (0) across patients in both disease cohorts (Supplementary Fig. 3). Similarly, maintained response was observed for the Itch NRS scores. Additionally, at Week 20, one patient with GPP and one patient with EP reported Itch NRS  $\geq$  4-point reduction. Data details are provided in Table 2.

**Table 1** Patient demographics and baseline disease characteristics

	<b>GPP</b> <i>N</i> = 7	<b>EP</b> <i>N</i> = 5	<b>Total</b> <i>N</i> = 12
Age, mean (SD) (years)	45.0 (19.10)	42.2 (14.39)	43.8 (16.63)
Sex			
Male, <i>n</i> (%)	3 (42.9)	3 (60.0)	6 (50.0)
Female, <i>n</i> (%)	4 (57.1)	2 (40.0)	6 (50.0)
Weight (kg)	67.9 (20.19)	77.6 (14.09)	71.9 (17.86)
Weight category, <i>n</i> (%)			
< 80 kg	5 (71.4)	3 (60.0)	8 (66.7)
≥ 80 and < 100 kg	2 (28.6)	2 (40.0)	4 (33.3)
≥ 100 kg	0	0	0
BMI, mean (SD) (kg/m <sup>2</sup> )	25.9 (5.73)	28.1 (2.76)	26.9 (4.68)
Previous systemic therapy, <i>n</i> (%)			
Never used	3 (42.9)	1 (20.0)	4 (33.3)
Non-biologic only	3 (42.9)	2 (40.0)	5 (41.7)
Biologic only	0	1 (20.0)	1 (8.3)
Biologic and non-biologic	1 (14.3)	1 (20.0)	2 (16.7)
Previous non-biologic systemic therapy <sup>a</sup> , <i>n</i> (%)			
Never used	3 (42.9)	2 (40.0)	5 (41.7)
Ever used	4 (57.1)	3 (60.0)	7 (58.3)
Previous biologic therapy <sup>a</sup> , <i>n</i> (%)			
Never used	6 (85.7)	3 (60.0)	9 (75.0)
Ever used	1 (14.3)	2 (40.0)	3 (25.0)
Previous IL-17 (secukinumab or broadalumab), <i>n</i> (%)			
Never used	7 (100.0)	4 (80.0)	11 (91.7)
Ever used	0	1 (20.0)	1 (8.3)
Age at GPP or EP diagnosis (years), mean	43.72	41.99	43.00
Duration since GPP or EP diagnosis (years), mean	1.55	0.44	1.09
Psoriasis vulgaris, <i>n</i> (%)	4 (57.1)	4 (80.0)	8 (66.7)
Psoriasis arthritis, <i>n</i> (%)	1 (14.3)	1 (20.0)	2 (16.7)
Baseline sPGA category, <i>n</i> (%)			
Number of patients with sPGA = 0	0	0	0
Number of patients with sPGA = 1	1 (14.3)	0	1 (8.3)

**Table 1** continued

	<b>GPP</b> <i>N</i> = 7	<b>EP</b> <i>N</i> = 5	<b>Total</b> <i>N</i> = 12
Number of patients with sPGA = 2	2 (28.6)	0	2 (16.7)
Number of patients with sPGA = 3	4 (57.1)	0	4 (33.3)
Number of patients with sPGA = 4	0	2 (40.0)	2 (16.7)
Number of patients with sPGA = 5	0	3 (60.0)	3 (25.0)
Baseline PASI score, mean	10.24	41.10	23.10
Baseline PSSI score	6.2 (7.40)	31.4 (10.90)	18.8 (15.92)
Baseline body surface area (%)	23.9 (22.38)	87.4 (7.99)	50.3 (36.97)
Baseline Itch NRS score	4.3 (2.69)	6.0 (1.41)	5.0 (2.34)
Baseline DLQI total score	6.9 (4.02)	14.0 (6.44)	9.8 (6.12)
Type of GPP (GPP only), <i>n</i> (%)			
GPP with preceding psoriasis vulgaris	2 (28.6)		2 (28.6)
Other	5 (71.4)		5 (71.4)
Baseline GPP Severity Index total score	3.1 (1.68)		3.1 (1.68)
Mutation of IL-36 RN (GPP only), <i>n</i> (%)			
Number of patients, <i>N<sub>x</sub></i>	1		1
No mutation <sup>b</sup>	1 (100.0)		1 (100.0)
Baseline GPP severity (GPP only), <i>n</i> (%)			
Mild (0–6 points)	7 (100.0)		7 (100.0)
Moderate (7–10 points)	0		0
Severe (11–17 points)	0		0

Data are mean (SD) unless otherwise stated

*n* number of patients in the specified category, *BMI* body mass index, *DLQI* Dermatology Life Quality Index, *EP* erythrodermic psoriasis, *GPP* generalized pustular psoriasis, *Itch NRS* Itch Numeric Rating Scale, *sPGA* static Physician Global Assessment, *PASI* Psoriasis Area and Severity Index, *PSSI* Psoriasis Scalp Severity Index

<sup>a</sup>Non-biologics are defined as: methotrexate, cyclosporine, retinoids, corticosteroids, fumaric acid derivatives, apremilast, other non-biologics, and psoralen and ultraviolet A (PUVA). Biologics are defined as: efalizumab, ustekinumab, infliximab, etanercept, alefacept, adalimumab, golimumab, certolizumab pegol, secukinumab, brodalumab, or other biologics

<sup>b</sup>Percentage is calculated as  $n/N_x * 100\%$

## Safety

There were no notable AEs, and the safety results of the study are aligned with the currently recognized safety profile of ixekizumab. A summary of AEs is presented in Table 3.

Treatment-emergent AEs (TEAEs) including nasopharyngitis, paronychia, pyrexia, and acne were reported in at least one of the six patients (GPP and EP) who entered the MDP. The incidence of all TEAEs reported during the MDP is presented in Table 3. All the TEAEs reported in the study were mild or moderate in severity, except the SAE of convulsive seizure reported by



**Table 2** Results of secondary efficacy endpoints during maintenance period for GPP and EP patients

Parameter	GPP (N = 2)		EP (N = 4)	
	Week 0 mean (min, max)	Week 12 mean (min, max)	Week 0 mean (min, max)	Week 12 mean (min, max)
PASI total score	11.9 (4.1, 19.7)	1.3 (1.2, 1.4)	39.4 (30.0, 56.1)	9.5 (1.1, 19.6)
Change from baseline		- 10.6 (- 18.5, - 2.7)		- 29.9 (- 55.0, - 13.4)
Percent improvement from baseline		79.9 (65.9, 93.9)		72.6 (40.6, 98.0)
PSSI <sup>a</sup> Total score	9.0	2.0	30.5 (20.0, 48.0)	9.0 (2.0, 16.0)
Change from baseline		- 7.0		- 21.5 (- 46.0, - 4.0)
Percent BSA (%)	45.0 (26.0, 64.0)	3.0 (2.0, 4.0)	88.0 (80.0, 100.0)	32.3 (3.0, 82.0)
Change from baseline		- 42.0 (- 62.0, - 22.0)		- 55.8 (- 87.0, 0.0)
GPP Severity Index total score	3.0 (2.0, 4.0)	1.5 (1.0, 2.0)		
Change from baseline		- 1.5 (- 3.0, 0.0)		
DLQI total score	6.5 (4.0, 9.0)	1.5 (0.0, 3.0)	12.8 (4.0, 20.0)	6.5 (0.0, 15.0)
Change from baseline		- 5.0 (- 9.0, - 1.0)		- 6.3 (- 18.0, 0.0)
DLQI <sup>b</sup> (0,1)		1 (50.0)		1 (25.0)
DLQI <sup>b</sup> (0)		1 (50.0)		1 (25.0)
Itch NRS	5.5 (3.0, 8.0)	1.0 (0.0, 2.0)	6.3 (5.0, 8.0)	5.0 (4.0, 7.0)
Change from baseline		- 4.5 (- 8.0, - 1.0)		- 1.3 (- 3.0, 2.0)
Itch NRS <sup>cb</sup> ≥ 4-point reduction		1 (100.0)		0 (0.0)

BSA body surface area, DLQI Dermatology Life Quality Index, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, Itch NRS Itch Numeric Rating Scale, PSSI Psoriasis Area and Severity Index,

PSSI Psoriasis Scalp Severity Index

<sup>a</sup>GPP N = 1

<sup>b</sup>Values represented in percentage (%)

**Table 3** Overview of adverse events

Assessment period	FAS population		Maintenance dosing period population	
	Period 2* (Week 0 to Week 12)		Period 2 and 3** (Week 0 to Week 20)	
	GPP ( <i>N</i> = 7) <i>n</i> (%)	EP ( <i>N</i> = 5) <i>n</i> (%)	GPP ( <i>N</i> = 2) <i>n</i> (%)	EP ( <i>N</i> = 4) <i>n</i> (%)
All TEAEs	4 (57.1)	3 (60.0)	1 (50.0)	3 (75.0)
Treatment-related AEs	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation of study	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Adverse events of special interest				
Hepatic, cytopenias, depressions and interstitial lung disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections	2 (28.6)	1 (20.0)	1 (50.0)	2 (50.0)
Nasopharyngitis <sup>†</sup>	1 (14.3)	1 (20.0)	1 (50.0)	1 (25.0)
Paronychia <sup>†</sup>	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Upper respiratory tract infection <sup>†</sup>	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic reactions/hypersensitivities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reactions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebro-cardiovascular events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inflammatory bowel disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse events				
Acne <sup>†</sup>	0 (0.0)	1 (20.0)	0 (0.0)	1 (25.0)
Dermatitis contact <sup>†</sup>	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia <sup>†</sup>	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
Seizure <sup>†</sup>	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Upper respiratory tract inflammation <sup>†</sup>	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)

*AE* adverse event, *EP* erythrodermic psoriasis, *FAS* full analysis set, *GPP* generalized pustular psoriasis, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

\*Period 2: induction dosing period, \*\*Period 3: maintenance dosing period, <sup>†</sup>preferred term

one male patient with EP. At Week 12, the patient was assessed as a responder and suffered from a convulsive seizure, subsequently discontinuing the study. Additionally, the AESIs

reported included upper respiratory tract infection and nasopharyngitis (1 patient each in GPP) and nasopharyngitis and paronychia (1

patient each in EP) (Table 3). No candidiasis or tuberculosis reactivation was reported.

No patients died or reported suicidal ideation or behavior on the C-SSRS during the study. Clinical laboratory evaluations including vital signs did not render any clinically significant results in patients with GPP or EP.

### Immunogenicity

All patients across both disease groups of GPP and EP showed TE-ADA-negative results.

## DISCUSSION

Psoriasis not only has a detrimental impact on quality of life but is also associated with various comorbidities, including PsA and psychological disorders [18, 19]. GPP and EP, in particular, are very severe and intractable types of psoriasis. This study was conducted to fulfill a regulatory commitment to the PMDA to evaluate the efficacy and safety of ixekizumab when dosed Q2W beyond Week 12 in patients with GPP and EP. The study design, including the number of patients and treatment duration of Week 20, was determined through the discussion with PMDA. The results of the study support the dosing of ixekizumab as a single agent at 80 mg Q2W beyond Week 12 for Japanese patients with GPP and EP who have an inadequate response at Week 12.

The primary endpoint measured by GIS was met by one patient with GPP. The continuation of ixekizumab Q2W beyond Week 12 up to Week 20 allowed patients with GPP and EP to maintain sPGA (0, 1). Most patients with GPP and EP achieved PASI 75 by Week 20. The pattern of improvement was shown by percent improvement in PASI, PSSI, and BSA involvement of psoriasis; other efficacy measures demonstrated maintained response throughout. Ixekizumab displayed robust efficacy against GPP and EP and sustained symptom improvement up to week 20. It has been observed that the GPP patients may often experience worsening of systemic and pustular signs and symptoms [6], but treatment with ixekizumab

through Week 20 mitigated such severe exacerbations.

Pustular symptoms observed in GPP could be assessed using the GIS and GPP Severity Index. The GPP Severity Index is an objective index that scores and evaluates pustular symptoms. In our study, patients with GPP showed continuous improvement and reduction of GPP Severity Index total score by Week 20. The GPP severity index total score is categorized into three ranges, all GPP patients were in the lowest category of mild at baseline, and their mild status was maintained at Week 20.

The reduction of DLQI total score and Itch NRS score is fundamental to augmenting a patient's satisfaction with treatment. Continuous Q2W treatment beyond Week 12 resulted in maintained response in both scores in patients with GPP and EP, which demonstrates that ixekizumab improved the quality of life of these patients.

Of six patients who continued ixekizumab Q2W beyond Week 12, five took systemic or topical concomitant therapy. These five patients took systemic or topical concomitant therapy both before and after Week 12. The therapy that first started after Week 12 was only bisphosphonate in one patient. Systemic therapies included oral steroid ( $n = 2$ ) and etretinate ( $n = 1$ ), and topical therapies included the strongest topical steroid ( $n = 1$ ).

Ixekizumab also demonstrated rapid improvement in GIS and secondary endpoints by Week 12 in patients with GPP and EP. The skin symptom or systemic manifestation cleared or improved after the start of ixekizumab as early as Week 2 in most of the patients. In the UNCOVER-J study [20], patients with GPP and EP had the same dosing regimen in Week 12 as in this study. Improvements across efficacy measures were observed in both the studies despite some differences seen in baseline characteristics such as disease duration. The effectiveness of ixekizumab by Week 12 was clearly replicated in the clinical trial.

There were no unexpected safety signals for ixekizumab in Japanese patients with GPP and EP. No deaths or serious infections were reported in the study. Ixekizumab was well tolerated in patients with GPP and EP with a variety of

baseline characteristics. One SAE (seizure) was reported by a patient with erythrodermic psoriasis. Finally, the patient was discontinued from the study. In the investigator's opinion, the event of seizure was not related to study medication because the patient had medical history of seizure. The overall safety results of this study in Japanese patients treated with ixekizumab were consistent with the previous studies conducted in the Japanese population [20, 21].

Potential background factors (age, disease duration, previous biologics therapy, IL36RN gene mutation, etc.) were examined, but predictive factors could not be found because of the small number of patients. The study limitations include small sample sizes for patients with GPP and EP, open-label study design, lack of a control group, and short study duration. The long-term efficacy and safety of the ixekizumab regimen in patients with GPP and EP will be assessed in the ongoing post-marketing surveillance study in Japan.

The duration of the trial (July 2019 to July 2020) included the period during which the COVID-19 pandemic was active in the country. When the pandemic disruption first occurred, while some of the patients had completed the study, enrollment was still ongoing and was continued without interruption. No pandemic-related SAEs were reported, and no compromises were made related to the statistical analyses. As such, the impact of the pandemic was minimal, and the study objectives were met.

## CONCLUSION

Overall, based on the results of this Phase 4 study in Japanese patients with GPP and EP, continuous Q2W administration of ixekizumab beyond Week 12 up to Week 20 appears to be an efficacious and tolerable regimen for Japanese patients. The safety profile was consistent with the known safety profile of ixekizumab.

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**Compliance with Ethics Guidelines.** Prior to patient recruitment, the protocol was approved by the Institutional Review Board of Nagoya City University Hospital and each of the participating sites. A list of Institutional Review Boards/Ethics Committees is provided as Table S1. Each patient provided written informed consent before enrollment. The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Ethical Guidelines by the Council for International Organizations of Medical Sciences and the International Conference of Harmonization E6 Guidelines for Good Clinical Practice.

**Data Availability.** Lilly provides access to all individual participant data collected during the trial, after anonymization, with the

exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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