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Efficacy and Safety of Guselkumab in Japanese Patients With Palmoplantar Pustulosis
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Palmoplantar pustulosis (PPP) causes erythematous, scaly plaques with recurrent sterile pustules refractory to treatment and with few randomized clinical trials conducted. Evidence points to involvement of interleukin 23 in the pathogenesis of PPP.

OBJECTIVE To determine the efficacy and safety of guselkumab, an anti–IL-23 monoclonal antibody, in Japanese patients with PPP.

DESIGN, SETTING, AND PARTICIPANTS A phase 3 randomized clinical trial was conducted from December 15, 2015, to December 12, 2017. A total of 159 enrolled patients (aged ≥20 years) had an inadequate response to conventional therapies, with a diagnosis of PPP for 24 or more weeks before screening. Intention-to-treat analysis was performed.

INTERVENTIONS Subcutaneous injections of guselkumab, 100 or 200 mg, at weeks 0, 4, and 12, and every 8 weeks thereafter were administered; placebo was given at weeks 0, 4, and 12.

MAIN OUTCOMES AND MEASURES Changes from baseline in PPP Area and Severity Index (PPPASI) score (possible score range, 0-72, with higher scores indicating greater area and severity), PPP severity index (PPSI) score (possible score range, 0-12, with higher scores indicating greater severity), and proportion of PPPASI-50 (≥50% reduction) responders at weeks 16 and 52 were assessed. Safety was monitored through week 52.

RESULTS A total of 159 patients (mean [SD] age at diagnosis, 46.8 [11.9] years; 126 women [79.2%]) were enrolled. Treatment groups comprised guselkumab, 100 mg (n = 54), guselkumab, 200 mg (n = 52), or placebo (n = 53). Both guselkumab groups demonstrated significant improvement in least-squares mean changes in PPPASI score compared with placebo: −15.3 and −11.7 in the guselkumab 100-mg and 200-mg groups, respectively, and −7.6 in the placebo group (difference [SE] vs placebo: −7.7 [1.7] in the 100-mg group, $P < .001$; 95% CI, −11.00 to −4.38; and −4.1 [1.7] in the 200-mg group, $P < .017$; 95% CI, −7.47 to −0.75]). Least-squares mean changes in PPSI score showed significant improvement in both guselkumab groups (100 mg: −2.0 [0.5]; $P < .001$; 95% CI, −2.96 to −0.95; 200 mg: −1.0 [0.5; $P = .04$; 95% CI, −2.06 to −0.03). A significantly higher proportion of patients in the guselkumab 100-mg group (31 [57.4%]) achieved a PPPASI-50 response at week 16 vs placebo (18 [34.0%]; $P = .02$); however, the result was not significant for the guselkumab 200-mg group (19 [36.5%]) vs placebo; $P = .78$). Each efficacy end point improved consistently through week 52. Health-related quality of life improved significantly as indicated by a reduction in the Dermatology Life Quality Index score (100 mg: −2.6; 95% CI, −4.0 to −1.2; $P < .001$; 200 mg: −1.6; 95% CI, −3.1 to −0.2; $P = .03$). Serious treatment-emergent adverse events were observed in 8 patients (placebo group, 2 of 53 [3.8%]; combined guselkumab group, 6/157≠10.5%). No serious infections were reported.

CONCLUSIONS AND RELEVANCE Targeting interleukin 23 with guselkumab may be an effective and safe treatment option for a recalcitrant disease such as PPP.

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Supplemental content

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Palmoplantar pustulosis (PPP) is a chronic, relapsing, inflammatory skin disease characterized by the presence of multiple sterile pustules subsequent to formation of vesicles along with erythematous scaling and is confined to the palms and soles.[1] Daily activities are impaired in patients with PPP compared with those with plaque psoriasis because PPP causes greater physical disability by restricting use of the palms and soles.[2] Although the pathogenesis of PPP is not fully understood, multiple factors that aggravate PPP are recognized; these include exaggerated production of proinflammatory cytokines[3] and stimulation induced by numerous triggers, such as smoking and infectious agents.[4,5] Palmoplantar pustulosis occurs more frequently in women[6,7] and is associated with smoking.[8] The prevalence of PPP in Japan is approximately 0.12%, which is comparatively higher than that in the Western population.[7]

Palmoplantar pustulosis shares common clinical features with other pustular psoriasis conditions and is often classified by its localized form in the West. However, its genetic features, such as frequent characteristic gene mutations, distinguish it from other pustular psoriasis subtypes.[1,9] Topical corticosteroids, vitamin D analogues, and phototherapy remain the most widely used PPP treatments. Eventually, most patients with PPP require systemic medications since topical therapies often lead to treatment failure.[10,11] Systemic treatment with oral retinoids, methotrexate, and cyclosporine is sometimes used in clinical practice, but the response varies from case to case.[12] Treatment with an interleukin (IL)-12/23 p40 antagonist (ustekinumab) and tumor necrosis factor antagonists have shown limited effects in PPP.[5,13] Owing to the lack of evidence for effective management, there is a need to develop improved treatment options for PPP.

Earlier studies have revealed that the IL-23/IL-17 pathway, through the proliferation of type 17 helper T cells in the skin, dendritic cells, and keratinocytes, activates chronic inflammation in PPP.[14-17] Guselkumab, a fully human immunoglobulin G1 λ monoclonal antibody, selectively blocks IL-23 signaling by targeting the p19 protein subunit of IL-23.[18] The efficacy of guselkumab in patients with psoriasis has been demonstrated in global studies.[18-22]

In a phase 2, proof-of-concept study,[23] subcutaneous administration of guselkumab, 200 mg, at weeks 0 and 4 in Japanese patients with PPP resulted in superior efficacy over placebo. The primary end point was achieved with a significant reduction in the mean PPP Severity Index (PPSI) score from baseline (possible score range, 0-12, with higher scores indicating greater severity). The 2 dose regimens, 100 and 200 mg, of guselkumab selected for the present study were based on clinical and pharmacokinetic and pharmacodynamic modeling results from the previous phase 2 study to explore the clinical response to different doses of guselkumab in PPP. In this confirmatory, placebo-controlled, phase 3 study, the efficacy and safety of 2 doses of guselkumab (100 and 200 mg) were evaluated in Japanese adults with PPP with an inadequate response to prior conventional treatment.

Key Points

Question Is guselkumab, an anti–interleukin 23 monoclonal antibody, efficacious and safe in Japanese patients with palmoplantar pustulosis?

Findings In this 60-week, randomized clinical trial of 159 patients with palmoplantar pustulosis, palmoplantar pustulosis area and severity index score was overall improved after subcutaneous injection of guselkumab, 100 mg and 200 mg or placebo; however, in the 200-mg group, the proportion of patients who achieved 50% or more reduction in palmoplantar pustulosis area and severity index score at week 16 was not significantly greater compared with placebo. Efficacy end points improved consistently through week 52, and health-related quality of life also improved significantly.

Meaning Guselkumab may be an effective and safe treatment option for management of palmoplantar pustulosis.

Methods

Trial Design and Participants

This phase 3, randomized, double-blind, multicenter, placebo-controlled trial was conducted to evaluate the efficacy and safety of guselkumab in patients with PPP across 40 sites in Japan from December 15, 2015, to December 12, 2017. Adults (aged ≥20 years) with a diagnosis of PPP[24] who had an inadequate response to conventional therapies for 24 or more weeks before screening were enrolled. Patients with a PPP Area and Severity Index (PPPASI) total score of 12 or higher (possible score range, 0-72, with higher scores indicating greater area and severity) and a PPPASI subscore of pustules or vesicles of 2 or higher at screening were included.

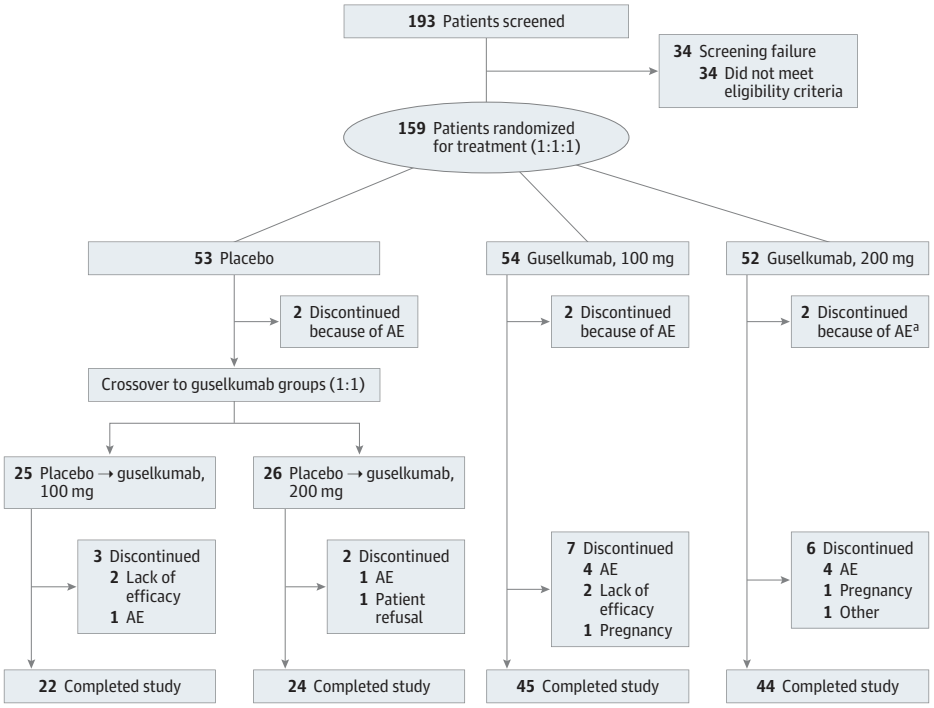
The study protocol was approved by an independent institutional review board at each of 40 study sites and was conducted in accordance with ethical principles outlined in the Declaration of Helsinki.[25] The protocol is available in Supplement 1. The study was consistent with International Conference on Harmonization and Good Clinical Practice guidelines and applicable regulatory requirements, and was in compliance with the protocol. Written informed consent was obtained from all patients before participating in the study. Participants received financial compensation.

Eligible patients were randomized centrally based on a computer-generated randomization schedule using randomly permuted blocks in a 1:1:1 ratio to receive subcutaneous injections of guselkumab, 100 or 200 mg, at weeks 0, 4, and 12, and every 8 weeks thereafter or placebo at weeks 0, 4, and 12. Patients were stratified by PPPASI total score range at baseline (≤20, 21-30, or ≥31) and smoking status (smoking or nonsmoking). Placebo group patients were rerandomized (1:1) to receive guselkumab, 100 or 200 mg, at weeks 16 and 20 and every 8 weeks thereafter through week 60.

Efficacy End Points

The primary efficacy end point was change from baseline in PPPASI total score at week 16. The PPPASI assesses severity of PPP lesions, and assessment details have been described

Figure. Study Design and Patient Disposition



AE indicates adverse event.

[a] One AE is not reported because it occurred before the first injection.

previously.[23] Major secondary end points were change from baseline in PPSI total score and proportion of patients who achieved a PPPASI-50 (≥50% improvement in PPPASI total score from baseline) response at week 16. The PPSI total score is the sum of individual subscores for each sign (erythema, pustules or vesicles, and desquamation or scale) on either of the palms or soles, whichever was observed during screening to have had the most severely affected areas.[23,26] Other secondary end points included change from baseline in PPPASI and PPSI score over time, proportions of patients who achieved PPPASI-50/75/90/100 response (ie, ≥50%, ≥75%, ≥90%, or 100% improvement in PPPASI score from baseline) and PPSI-50/75/90/100 responses (ie, ≥50%, ≥75%, ≥90%, or 100% improvement in PPSI score from baseline) over time, and change from baseline in the physician's global assessment (PGA) score for patient's overall (palms and soles) palmoplantar skin lesions status (0, clear; 5, very severe). Patient-reported outcomes included the Dermatology Life Quality Index (DLQI) (possible score range, 0-30: 0-1, no effect on the patient's life; 2-5, small effect; 6-10, moderate effect; 11-20, very large effect; and 21-30, extremely large effect),[27] 36-item Short-Form Health Survey (includes physical component summary score and mental component summary score),[28] and EuroQOL-5 Dimensions Questionnaire (possible score range of visual analog scale, 0 [worst imaginable health state] to 100 [best imaginable state]).[29]

Pharmacokinetics and Immunogenicity

Blood samples were collected every 4 weeks until week 28 and every 8 weeks thereafter through week 52 for measurement of serum guselkumab concentrations. Samples were collected at weeks 0, 4, and 16 for detection of guselkumab antibodies.

Safety Evaluations

Safety assessments included reporting of treatment-emergent adverse events (TEAEs), clinical laboratory test results, electrocardiogram findings, vital signs (axillary temperature, pulse rate, and blood pressure), physical examinations, injection-site evaluations, allergic reactions, and early detection of tuberculosis. In addition, concomitant medications were reviewed to identify any that may suggest the occurrence of TEAEs.

Concomitant Medications and Lifestyle Modification

Concurrent use of topical therapies (except for topical moisturizers) and use of phototherapy or systemic medications for PPP were prohibited during the study. Before the start of the study, all patients were assessed for the presence of any focal infection; however, treatment of an infection was not permitted except dental therapy for a newly recognized tooth abscess and/or tooth cavity. All patients were instructed to make an effort to stop smoking.

Statistical Analysis

A sample size of 150 patients was chosen to achieve 90% or greater power to detect treatment differences between the guselkumab and placebo groups (assuming a mean difference of 5.5 and a common SD of 8.1) for the primary end point at a significance level of .05 (2-sided). The assumptions for sample size and power calculations were based on the results of a phase 2 study in patients with PPP.[23]

Table 1. Demographic and Baseline Characteristics

Characteristic	Placebo (n = 53)	Guselkumab 100 mg (n = 54)	Guselkumab 200 mg (n = 52)	Guselkumab Combined (n = 106)	Total (n = 159)
Age, mean (SD), y	53.0 (8.14)	53.9 (10.88)	52.9 (13.39)	53.4 (12.13)	53.3 (10.94)
Women, No. (%)	44 (83.0)	46 (85.2)	36 (69.2)	82 (77.4)	126 (79.2)
Weight, mean (SD), kg	61.0 (9.78)	59.7 (10.31)	60.4 (12.02)	60.1 (11.13)	60.4 (10.68)
BMI, mean (SD)	24.0 (3.96)	23.7 (3.53)	23.5 (3.70)	23.6 (3.60)	23.7 (3.72)
Age at diagnosis, mean (SD), y	47.3 (9.49)	45.8 (12.90)	47.4 (13.20)	46.6 (13.01)	46.8 (11.9)
Disease duration, median (range), y	2.2 (0.5-37.5)	3.6 (0.6-42.4)	3.4 (0.5-27.2)	3.5 (0.5-42.4)	2.9 (0.5-42.4)
PPPASI total score, mean (SD)[a]	28.4 (10.80)	27.5 (11.77)	26.9 (10.76)	27.2 (11.23)	27.6 (11.07)
PPPASI score ≥40, No. (%)	11 (20.8)	8 (14.8)	4 (7.7)	12 (11.3)	NA
Mean (SD)	44.8 (3.61)	47.7 (5.71)	50.9 (8.21)	48.7 (6.45)	NA
PPSI total score, mean (SD)[b]	10.5 (1.55)	10.1 (1.84)	10.6 (1.40)	10.4 (1.65)	10.4 (1.61)
PGA score, No. (%)[c]					
2	1 (1.9)	0	0	0	1 (0.6)
3	18 (34.0)	24 (44.4)	16 (30.8)	40 (37.7)	58 (36.5)
4	27 (50.9)	25 (46.3)	29 (55.8)	54 (50.9)	81 (50.9)
5	7 (13.2)	5 (9.3)	7 (13.5)	12 (11.3)	19 (11.9)
DLQI score, mean (SD)[d]	8.7 (6.14)	9.3 (6.26)	7.9 (5.95)	8.6 (6.12)	8.7 (6.11)
EQ-5D VAS score, mean (SD)[e]	68.2 (21.28)	65.1 (21.54)	63.1 (20.00)	64.1 (20.73)	65.5 (20.93)
EQ-5D index score, mean (SD)[f]	0.7 (0.21)	0.7 (0.22)	0.7 (0.20)	0.7 (0.21)	
Smoking status, No. (%)					
Smokers	28 (52.8)	28 (51.9)	26 (50.0)	54 (50.9)	82 (51.6)
Nonsmokers	25 (47.2)	26 (48.1)	26 (50.0)	52 (49.1)	77 (48.4)
Nonbiologic systemic therapies, No. (%)[g]					
Never used	39 (73.6)	41 (75.9)	42 (80.8)	83 (78.3)	122 (76.7)
≥1	13 (24.5)	11 (20.4)	9 (17.3)	20 (18.9)	33 (20.8)
≥2	1 (1.9)	2 (3.7)	1 (1.9)	3 (2.8)	4 (2.5)
Biologics, No. (%)[h]					
Never used	51 (96.2)	53 (98.1)	52 (100.0)	105 (99.1)	156 (98.1)
Ever used	2 (3.8)	1 (1.9)	0	1 (0.9)	3 (1.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DLQI, Dermatology Life Quality Index; EQ-5D VAS, EuroQOL-5 Dimensions Questionnaire visual analog scale; NA, not applicable; PGA, Physician's Global Assessment; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PPSI, Palmoplantar Pustulosis Severity Index.

[a] Possible score range, 0 to 72, with higher scores indicating greater area and severity.

[b] Possible score range, 0 to 12, with higher scores indicating greater severity.

[c] Possible score range, 0 to 5: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe.

[d] Possible score range, 0 to 30: 0 to 1, no effect on the patient's life; 2 to 5, small effect; 6 to 10, moderate effect; 11 to 20, very large effect; and 21 to30, extremely large effect.

[e] Possible score range, 0 (worst imaginable health state) to 100 (best imaginable health state).

[f] The range of EQ-5D index score is from -0.025 to 1. Higher score indicates better health state.

[g] Includes psoralen UV A light, methotrexate, cyclosporine, etretinate.

[h] Includes etanercept and adalimumab.

Change from baseline in PPPASI score through week 16 was analyzed using a mixed model for repeated measures with treatment (guselkumab, 100 mg; guselkumab, 200 mg; or placebo); smoking status (smoking or nonsmoking); week 2, 4, 8, 12, and 16, and treatment-by-week interaction as fixed effects; and baseline PPPASI score as a covariate. Based on the mixed model for repeated-measures model, treatment effects for the guselkumab groups vs the placebo group at week 16 were estimated based on differences of least-squares (LS) means. Patients who discontinued the study owing to lack of efficacy or worsening of PPP or patients who received a protocol-prohibited medication or therapy from week 0 to week 16 were considered to have experienced treatment failure. After application of treatment failure rules, unimputed PPPASI data (without last observation carried forward) were used for mixed model for repeated measures analyses and data were assumed to be missing at random.

The change from baseline in PPSI through week 16 was also analyzed using the mixed model for repeated-measures model. The *P* values for LS mean differences along with 2-sided 95% CIs were calculated. Cochran-Mantel-Haenszel χ^2 testing stratified by baseline PPPASI total score (≤20, 21-30, and ≥31) and smoking status was applied for comparisons of responders who achieved PPPASI-50 at week 16. Additional details of the methods are described in the eMethods in Supplement 2. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc).

Results

Patients

A total of 159 patients were enrolled and randomized at week 0 to receive guselkumab, 100 mg (n = 54); guselkumab, 200 mg (n = 52); or placebo (n = 53). Through week 52, the study agent was discontinued in 24 of 159 patients (15.1%), mainly due to TEAEs (**Figure**).

Demographics were generally well balanced across treatment groups except for the lower proportion of women in the guselkumab 200-mg group. Baseline disease characteristics were generally comparable among groups except for the percentage of patients with a PPPASI score of 40 or greater

Table 2. Primary and Major Secondary Efficacy End Points at Week 16 in Intention-to-Treat Analysis Set[a]

End Point	Placebo (n = 53)	Guselkumab 100 mg (n = 54)	Guselkumab 200 mg (n = 52)
Primary[b]			
PPPASI total score, change from baseline			
LS mean (SE)	−7.6 (1.19)	−15.3 (1.17)	−11.7 (1.21)
LS mean difference (SE)		−7.7 (1.67)	−4.1 (1.70)
95% CI for difference		(−11.00 to −4.38)	(−7.47 to −0.75)
P value		<.001	.02
Major Secondary[c]			
PPSI total score, change from baseline			
LS mean (SE)	−2.0 (0.36)	−4.0 (0.36)	−3.1 (0.37)
LS mean difference (SE)		−2.0 (0.51)	−1.0 (0.51)
95% CI for difference		(−2.96 to −0.95)	(−2.06 to −0.03)
P value		<.001	.04
PPPASI-50 responders, No. (%)	18 (34.0)	31 (57.4)	19 (36.5)
P value[d]		.02	.78

Abbreviations: LS, least-squares; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PPPASI-50, 50% or greater reduction in PPPASI; PPSI, Palmoplantar Pustulosis Severity Index.

[a] Patients who discontinued the study agent owing to lack of efficacy or an adverse event of worsening of palmoplantar pustulosis or who started a protocol-prohibited medication/therapy that could improve palmoplantar pustulosis had their baseline PPPASI value carried forward to the postbaseline attending visits.

[b] Change from baseline in PPPASI total score at week 16; scoring presented in Table 1 footnote a.

[c] Change from baseline in PPSI total score and proportion of patients who achieved a PPPASI-50 response at week 16; scoring presented in Table 1 footnotes a and b.

[d] Based on Cochran-Mantel-Haenszel χ^2 test stratified by baseline PPPASI total score (≤20, 21-30, ≥31) and smoking status (smoking or nonsmoking).

(**Table 1**). The percentage of smokers at baseline was similar across the groups. Two patients quit smoking during the study; however, no obvious change in the amount of cigarette consumption was observed despite instruction to stop smoking.

Efficacy Assessment

At week 16, both guselkumab groups showed significant improvement in the PPPASI score compared with the placebo group. Least-squares mean change in PPPASI score from baseline was −15.3 (*P* < .001) for the guselkumab 100-mg group and −11.7 (*P* = .02) for the guselkumab 200-mg group vs −7.6 for the placebo group (**Table 2**).

At week 16, LS mean differences in PPSI score for the guselkumab groups vs the placebo group were significant (guselkumab 100 mg: −2.0, *P* < .001; 200 mg: −1.0, *P* = .04). A significantly higher proportion of patients in the guselkumab 100-mg group (31 [57.4%]) achieved a PPPASI-50 response at week 16 compared with the placebo group (18 [34.0%]) (*P* = .02); the PPPASI-50 response rate for the 200-mg group (19 [36.5%]) was similar to that for the placebo group (*P* = .78) (Table 2). Through week 16, higher proportions of patients in the guselkumab groups achieved a PPPASI-75 response (guselkumab 100 mg: 11 [20.4%], *P* = .01; 200 mg: 6 [11.5%], *P* = .12) compared with placebo (2 [3.8%]). Improvements in PPPASI and PPSI subscores of erythema and pustules/vesicles were observed as early as week 8 in the guselkumab groups (eFigure 1 in Supplement 2). At week 16, an improvement was noted for all 3 subscores of both the PPPASI and PPSI in the guselkumab 100-mg group.

The PPPASI and PPSI scores for the guselkumab groups continuously decreased (improved) after week 16 and reached almost similar levels before week 52 (eFigure 2A and B in Supplement 2). The proportions of patients achieving a PPPASI-50 response increased over time and at week 52 were 83.3% (n = 45) in the guselkumab 100-mg group and 84.6% (n = 44) in the 200-mg group (eFigure 2C in Supplement 2; **Table 3**). The proportions of PPSI-50 responders also increased over time in the guselkumab groups (Table 3). At week 52, the proportion of patients achieving a PPPASI-75 response reached 55.6% patients (n = 30) in the guselkumab 100-mg group and 59.6% (n = 31) in the 200-mg group (eFigure 2D in Supplement 2). A PPPASI-90 response was achieved by 29.6% of patients (n = 16) in the 100-mg group and 36.5% (n = 19) in the 200-mg group; PPSI subscores of none (0) or slight (1) were comparable between all groups (eFigure 1 and eFigure 3 in Supplement 2).

Through week 16, no significant treatment effect was observed based on the proportions of patients achieving a PGA score of cleared (0) or almost cleared (1). However, in a post hoc analysis assessing PGA 0/1/2 response, a higher response rate was observed for the guselkumab 100-mg group (25 [46.3%]) compared with the placebo group (11 [20.8%]). The proportions of patients who achieved a PGA 0/1/2 response at week 52 were comparable between guselkumab 100 mg (39 [72.2%]) and 200 mg (40 [76.9%]) (Table 3 and eTable 1 in Supplement 2).

At week 16, the guselkumab groups showed a significant decrease (improvement) in DLQI scores from baseline compared with the placebo group (LS mean differences: guselkumab 100 mg, −2.6; *P* < .001 and 200 mg, −1.6; *P* = .03) (Table 3). At week 52, generally similar improvements in DLQI

Table 3. Other Secondary End Points in Intention-to-Treat Analysis Set at 16 Weeks[a]

Week 16	Placebo (n = 53)	Guselkumab 100 mg (n = 54)	*P* Values	Guselkumab 200 mg (n = 52)	*P* Values	Guselkumab Combined (n = 106)
PPPASI-50/75/90/100 Responders, No. (%)						
PPPASI-50	18 (34.0)	31 (57.4)	.02[b]	19 (36.5)	.78[b]	50 (47.2)
PPPASI-75	2 (3.8)	11 (20.4)	.008[b]	6 (11.5)	.12[b]	17 (16.0)
PPPASI-90	0	1 (1.9)	.29[b]	2 (3.8)	.14[b]	3 (2.8)
PPPASI-100	0	0	NA	1 (1.9)	.32[b]	1 (0.9)
PPSI-50/75/90/100 Responders, No. (%)						
PPSI-50	6 (11.3)	19 (35.2)	.003[b]	10 (19.2)	.27[b]	29 (27.4)
PPSI-75	0	6 (11.1)	.01[b]	1 (1.9)	.31[b]	7 (6.6)
PPSI-90	0	1 (1.9)	.27[b]	1 (1.9)	.31[b]	2 (1.9)
PPSI-100	0	0	NA	1 (1.9)	.31[b]	1 (0.9)
PGA score, No. (%)						
0	0	0	NA	1 (1.9)	NA	1 (0.9)
1	3 (5.7)	4 (7.4)	NA	0	NA	4 (3.8)
2	8 (15.1)	21 (38.9)	NA	13 (25.0)	NA	34 (32.1)
3	23 (43.4)	24 (44.4)	NA	26 (50.0)	NA	50 (47.2)
4	15 (28.3)	5 (9.3)	NA	10 (19.2)	NA	15 (14.2)
5	4 (7.5)	0	NA	2 (3.8)	NA	2 (1.9)
Change from baseline in the SF-36, PCS	1.3 (9.18)	4.7 (13.76)	NA	3.3 (10.26)	NA	4.0 (12.13)
LS mean difference (95% CI) vs placebo	NA	2.29 (−1.62 to 6.20)	.25	2.13 (−1.83 to 6.08)	.29	NA
Change from baseline in the SF-36, MCS	1.2 (7.82)	0.6 (7.88)	NA	0.7 (7.06)	NA	0.7 (7.45)
LS mean difference (95% CI) vs placebo	NA	−0.62 (−3.45 to 2.20)	.66	−0.92 (−3.79 to 1.95)	.53	NA
EQ-5D index score, mean (SD)	0.8 (0.19)	0.8 (0.17)	NA	0.8 (0.18)	NA	0.8 (0.17)
Change from baseline in the EQ-5D index score	0.04 (0.17)	0.1 (0.19)	NA	0.1 (0.14)	NA	0.1 (0.17)
LS mean difference (95% CI) vs placebo	NA	0.07 (0.02 to 0.12)	.01	0.06 (0.01 to 0.11)	.02	NA
EQ-5D VAS score, mean (SD)	68.1 (21.23)	73.4 (19.86)	NA	71.6 (20.29)	NA	72.5 (19.99)
Change from baseline in the EQ-5D VAS score	−0.1 (14.33)	8.3 (21.25)	NA	8.5 (15.59)	NA	8.4 (18.60)
LS mean difference (95% CI) vs placebo	NA	6.2 (0.18 to 12.15)	.04	6.4 (0.37 to 12.53)	.04	NA
DLQI score, mean (SD)	6.9 (6.03)	4.3 (4.26)	NA	4.8 (4.95)	NA	4.6 (4.60)
Change from baseline in the DLQI score	−1.8 (4.71)	−5.0 (5.59)	NA	−3.1 (3.49)	NA	−4.1 (4.76)
LS mean difference (95% CI) vs placebo	NA	−2.6 (−4.04 to −1.19)	<.001	−1.6 (−3.06 to −0.17)	.03	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EQ-5D, EuroQOL-5 Dimensions Questionnaire; LS mean, least-squares mean; MCS, Mental Component Summary; NA, not applicable; PCS, Physical Component Summary; PGA, Physician's Global Assessment; PPPASI, Palmoplantar Pustulosis Area and Severity Index; PPPASI-50/75/90/100, ≥50%/75%/90%/100% reduction in Palmoplantar Pustulosis Area and Severity Index; PPSI, Palmoplantar Pustulosis Severity Index; PPSI-50/75/90/100, ≥50%/75%/90%/100% reduction in Palmoplantar Pustulosis Severity Index; SF-36, 36-Item Short-Form; VAS, visual analog scale.

[a] Changes in baseline scores over time; scoring presented in Table 1 footnotes.

[b] Based on Cochran-Mantel-Haenszel χ^2 test stratified by baseline PPPASI total score (≤20, 21-30, ≥31) and smoking status (smoking or nonsmoking).

scores were observed across treatment groups. Mean percent improvement in DLQI scores among patient subgroups with PPPASI improvement for the guselkumab groups combined were −2.20% for less than 25% improvement, 27.33% for 25% to 50% improvement, 55.67% for 50% to 75% improvement, and 69.36% for 75% or more improvement. Numerically greater 36-item Short-Form Health Survey physical component summary scores were observed for the guselkumab groups vs the placebo group, although the differences were not statistically significant. No notable difference in 36-item Short-Form Health Survey mental component summary scores was observed for the guselkumab groups vs the placebo group. Both guselkumab groups demonstrated significant improvements in EQ-5D (visual analog scale and index scores) compared with placebo (Table 3 and eTable 1 in Supplement 2).

Pharmacokinetic Assessment

The steady state median trough serum guselkumab concentration was achieved by week 20 and was 2-fold higher in the guselkumab 200-mg group (2.01 μg/mL) compared with the 100-mg group (0.86 μg/mL). Patients with body weight greater than 70 kg had lower median trough serum guselkumab concentrations compared with patients with body weight 70 kg or less.

Table 4. Overview of TEAEs Through Week 16 in All Treated Patients

Variable	No. (%)[a]			
		Guselkumab		
	Placebo (n = 53)	100 mg (n = 54)	200 mg (n = 52)	Combined (n = 106)
≥1 TEAE	40 (75.5)	33 (61.1)	40 (76.9)	73 (68.9)
Serious TEAEs	2 (3.8)	1 (1.9)	0	1 (0.9)
TEAEs that were reasonably related to study agent	11 (20.8)	10 (18.5)	8 (15.4)	18 (17.0)
TEAEs leading to discontinuation of study agent[b]	2 (3.8)	3 (5.6)	1 (1.9)	4 (3.8)
>5% TEAEs in any of the treatment arms				
Nasopharyngitis	9 (17.0)	7 (13.0)	13 (25.0)	20 (18.9)
Eczema	3 (5.7)	5 (9.3)	2 (3.8)	7 (6.6)
Urticaria	1 (1.9)	1 (1.9)	3 (5.8)	4 (3.8)
Erythema	0	0	3 (5.8)	3 (2.8)
Pustular psoriasis[c]	5 (9.4)	2 (3.7)	0	2 (1.9)
Injection-site erythema	0	2 (3.7)	4 (7.7)	6 (5.7)
Arthralgia	3 (5.7)	1 (1.9)	3 (5.8)	4 (3.8)
TEAEs of special interest				
Injection-site reaction	1 (1.9)	3 (5.6)	5 (9.6)	8 (7.5)
Infections	22 (41.5)	16 (29.6)	19 (36.5)	35 (33.0)
Infections that required oral or parenteral antibiotic treatment	13 (24.5)	8 (14.8)	7 (13.5)	15 (14.2)

Abbreviation: TEAE, treatment-emergent adverse event.

[a] Incidence is based on the number of patients experiencing at least 1 adverse event (ie, not the number of events).

[b] Includes pregnancy.

[c] Indicates palmoplantar pustulosis specifically.

Safety Assessment

Through week 16, the incidence rate of TEAEs was lower in the guselkumab 100-mg group (33 [61.1%]) vs the placebo group (40 [75.5%]), while the incidence rates of TEAEs between the 200-mg group (40 [76.9%]) and the placebo group were comparable (**Table 4**). Serious TEAEs were reported in 3 patients: 1 patient in the guselkumab 100-mg group (suspected lung carcinoma in situ) and 2 patients in the placebo group (large intestinal polyp and heat stroke). The proportion of patients with treatment-emergent infections was comparable between all groups. Injection-site reactions were more common in the guselkumab groups (guselkumab 100 mg: 3 [5.6%]; 200 mg: 5 [9.6%]) compared with the placebo group (1 [1.9%]) (Table 4). All injection-site reactions were nonserious and mild; none required dose interruption or withdrawal.

A few grade 3 laboratory abnormalities were reported, but none were persistent or led to clinical sequelae of concern, none were reported as serious TEAEs, and none led to study agent discontinuation. Through week 52, the proportions of patients reporting 1 or more TEAEs were 85.2% (46 of 54) in the guselkumab 100-mg group and 94.2% (49 of 52) in the 200-mg group (eTable in Supplement 2).

Serious TEAEs were observed in 8 patients (placebo before crossover to guselkumab: 2/53 patients [3.8%]; combined guselkumab groups: 6/157 patients [3.8%]). No deaths, opportunistic infections, cases of active tuberculosis, or major adverse cardiovascular events were reported. Gastric cancer was reported in 1 patient with multiple risk factors, including tobacco use, alcohol use, and *Helicobacter pylori* infection. No cases of anaphylactic, serum sickness-like, or hypersensitivity reactions were observed during the study. Through week 52, four patients were positive for antidrug antibodies against guselkumab in the guselkumab groups. Given the small number of patients with antibodies, a meaningful evaluation for the association between the development of antibodies to guselkumab and influence on efficacy could not be performed.

Discussion

The efficacy of guselkumab, through targeting IL-23 blockade, in PPP was demonstrated in this study based on improvements in both the PPPASI and PPSI disease activity indices. Both guselkumab dose regimens showed superior efficacy to placebo and better tolerability. These results corroborate findings from a proof-of-concept, phase 2 study, which met its primary end point by demonstrating a significantly greater PPSI response.[23]

The proportion of patients achieving a PPPASI-50 response was significantly higher with the guselkumab 100-mg dose vs placebo. Although the PPPASI-50 response rate for the guselkumab 200-mg group was lower than that for the 100-mg group at week 16, the rate continued to improve thereafter and reached the same level as the 100-mg group at week 52. The late PPPASI-50 response in the guselkumab 200-mg group could be related to the disproportionally smaller number of patients with a higher (≥40) baseline PPPASI score in the 200-mg group compared with the other treatment groups. At baseline, a larger proportion of patients showed a PPPASI score of 40 or higher in the 100-mg group vs the 200-mg group. This imbalance might have affected the PPPASI-50 result at week 16, as patients with higher disease activity tended to experience greater efficacy. Through week 52, most patients in the guselkumab groups achieved a PPPASI-50 response and 50% or more of patients achieved a PPPASI-75 response. As evaluated by the PPPASI and PPSI measures, clinical responses were sustained through week 52. Subscores for all 3 signs of PPP improved; however, the earliest responses observed were only for the erythema and pustules/vesicles subscores. This find-

ing suggests that responses for erythema and pustules/vesicles can be used as early indicators to evaluate treatment efficacy.

Treatment with guselkumab also showed significant improvement in health-related quality of life as indicated by decreases in DLQI score and increases in EQ-5D scores. There was correspondence between the results of PPPASI and DLQI analyses, which indicates a direct effect of disease severity on patients' daily life and suggests that improvement in PPP closely relates to improvement in quality of life. Through week 16, the incidence of TEAEs was comparable between the guselkumab and placebo groups. Most TEAEs reported, including infections and injection-site reactions, were mild. No new safety signals for guselkumab were identified in this study. Generally, low incidence rates of serious TEAEs were observed.

There is a lack of well-documented clinical studies for standard treatment options for PPP, with only a few randomized clinical trials conducted, and only limited cases or case series reported.[12,30] Evidence from initial studies with systemic therapies, such as cyclosporine and methotrexate, showed variable and unpredictable clinical responses.[10] Because PPP is often difficult to manage owing to limited available treatment options, results of this study provide robust evidence for guselkumab as an efficacious new potential treatment option of PPP.

Limitations

This study has some limitations. Placebo-controlled comparisons could not be made after week 16 as patients in the placebo group crossed over to receive guselkumab at week 16 and, since the concomitant use of topical corticosteroids or vitamin D_3 agents was not permitted, their use as a practical approach to combination therapy was not assessed. In addition, distribution of patients with severe PPP with relatively higher PPPASI scores (≥40) in the placebo group showed a slight imbalance.

Conclusions

Guselkumab demonstrated therapeutic potential in Japanese patients with moderate-to-severe PPP and improved their overall well-being and quality of life. A favorable benefit-to-risk profile for both the guselkumab 100- and 200-mg doses in PPP was demonstrated based on results through week 52 in this study.

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Concept and design: Terui, Kobayashi, Zheng.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Terui, Murakami, Morishima.
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