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Efficacy and Safety of Guselkumab, an Anti–Interleukin 23 Monoclonal Antibody, for Palmoplantar Pustulosis
A Randomized Clinical Trial

Tadashi Terui, MD, PhD; Satomi Kobayashi, MD, PhD; Yukari Okubo, MD, PhD; Masamoto Murakami, MD, PhD; Keiichiro Hirose, MS; Hiroshi Kubo, MD, PhD

IMPORTANCE Palmoplantar pustulosis (PPP) is a recalcitrant skin disease with no biologics currently approved for treatment. The involvement of interleukin 23 (IL-23) and cytokines of the type 17 helper T cell lineage in the pathogenesis of PPP has been recently postulated.

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

DESIGN, SETTING, AND PARTICIPANTS This double-blind, randomized, placebo-controlled, parallel-group, 24-week trial was conducted between May 14, 2013, and September 27, 2014, at 11 centers in Japan. Participants were patients with moderate to severe PPP that did not respond adequately to conventional treatments.

INTERVENTIONS Patients were randomized 1:1 to receive guselkumab, 200 mg, by subcutaneous injection or matching placebo at weeks 0 and 4.

MAIN OUTCOMES AND MEASURES Changes in total scores of skin-related outcomes from baseline at the end of week 16 (primary clinical cutoff) and through week 24 were measured. Serum biomarker analyses were performed at baseline, week 4, and week 16, and safety was monitored through week 24.

RESULTS Of 49 randomized patients (35 [71%] women; median [range] age, 52 [28-77] years), 41 completed the study at week 24. Mean (SD) PPP severity index total scores (primary end point) improved significantly from baseline in guselkumab-treated patients (−3.3 [2.43]) vs placebo (−1.8 [2.09]) (least squares mean difference, −1.5; 95% CI, −2.9 to −0.2; $P = .03$). At week 16, PPP area and severity index scores (least squares mean difference, −5.65; 95% CI, −9.80 to −1.50; $P = .009$) and proportion of patients achieving 50% reduction in these scores (difference in proportion, 39.2; 95% CI, 14.0-64.3; $P = .009$) improved significantly. A numerically higher proportion of patients had a physician's global assessment score of 1 or less in the guselkumab group vs placebo. Improvement in efficacy scores was maintained through week 24 in the guselkumab group. Significant reductions from baseline in serum IL-17A and IL-17F cytokine levels were observed at weeks 4 and 16. Frequency of treatment-emergent adverse events was comparable between the guselkumab group (19 of 25 patients [76%]) and the placebo group (18 of 24 patients [75%]). Frequent adverse effects included nasopharyngitis (14 patients [29%]), headache (3 patients [6%]), contact dermatitis (3 patients [6%]), and injection site erythema (3 patients [6%]). No major safety concerns emerged during the study.

CONCLUSIONS AND RELEVANCE Targeting IL-23 and its associated immune cascade with guselkumab may be a safe and useful therapeutic option for treatment of PPP.

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Supplemental content

Author Affiliations: Department of Dermatology, Nihon University School of Medicine, Tokyo, Japan (Terui); Department of Dermatology, Seibo International Catholic Hospital, Tokyo, Japan (Kobayashi); Department of Dermatology, Tokyo Medical University, Tokyo, Japan (Okubo); Department of Dermatology, Ehime University School of Medicine, Ehime, Japan (Murakami); Janssen Pharmaceutical K.K., Tokyo, Japan (Hirose, Kubo).

Corresponding Author: Hiroshi Kubo, MD, PhD, Janssen Pharmaceutical K.K., 5-2, Nishikanda-3 chome, Chiyoda-Ku, Tokyo, Japan 101-0065 (hkubo1@its.jnj.com).

Palmoplantar pustulosis (PPP), a chronic, relapsing inflammatory skin disease, is characterized by the presence of multiple sterile pustules subsequent to the formation of vesicles along with erythematous scaling, particularly confined to the palms and soles.[1-5] It is a severe, recalcitrant disorder with a greater adverse impact on quality of life than other forms of inflammatory skin lesions located elsewhere on the body.[3,6] Tobacco smoking, focal infections (eg, tonsillitis), and seasonal conditions have been identified as common risk factors for triggering or worsening PPP, and middle-aged women are thought to be at a higher risk.[2,7-10] Data from a national health insurance claim database estimated the prevalence of PPP in Japan to be 0.12%, generally higher than in the Western population.[11]

Although PPP has been considered distinct from psoriasis because of differences in the pathogenesis and genetic divergence, most common treatments for psoriasis, including corticosteroids, retinoids, vitamin D analogues, and UV phototherapy, are used in patients with PPP.[12,13] However, most of these therapies are only modestly effective and require prolonged use to clear lesions. Systemic therapies for PPP, such as retinoids, cyclosporine, and methotrexate, lack controlled studies evaluating defined treatment regimens.[7,14-18] Among biologic therapies for PPP, variable results have been reported with tumor necrosis factor α (TNF-α) inhibitors (etanercept, adalimumab) and ustekinumab, a monoclonal antibody that targets interleukin 12 (IL-12) and IL-23; thus, more effective and reliable therapies are desirable.[19-22] Recently, secukinumab, an anti-IL-17A antibody, showed pronounced efficacy in palmoplantar psoriasis.[23] There are debatable differences between palmoplantar psoriasis and PPP; however, this finding suggests the effectiveness of blocking the IL-23 and IL-17 axis for PPP because of the similarity in the underlying molecular pathogenesis.[23]Although the pathogenesis of PPP is obscure, ongoing molecular disease profiling studies[24-28] indicate the dendritic cell–mediated production of IL-23 and resulting downward proliferation of type 17 helper T (T_H17) cells as the central pathway driving the phenotype of PPP. These studies have revealed increased expression of T_H17 cytokines, including IL-17A, IL-17F, and IL-22, in PPP lesions. Furthermore, the IL-17–induced IL-8 production and resulting neutrophil infiltration are linked to pustule formation in PPP. Thus, antibody therapies targeting IL-23 may provide beneficial clinical outcomes by disrupting key inflammatory regulators of PPP pathogenesis.

Guselkumab, a fully human IgG 1 λ monoclonal antibody, binds to the p19 subunit of IL-23 and antagonizes IL-23 without affecting IL-12. Binding of guselkumab to the p19 subunit blocks the binding of IL-23 to the receptor, thereby inhibiting downstream intracellular signaling and subsequent cytokine production via T_H17 cell differentiation.[29] In global phase 2 and phase 3 studies, guselkumab showed efficacy with acceptable tolerability in patients with moderate to severe plaque psoriasis.[30-33] The present report describes a phase 2 proof-of-concept study that was designed to assess the efficacy and safety of guselkumab in Japanese patients with moderate to severe PPP.

Key Points

Question Is guselkumab, a selective anti–interleukin 23 antibody, safe and effective in Japanese patients with moderate to severe palmoplantar pustulosis (PPP)?

Findings This 24-week, randomized clinical trial included 49 patients randomized to treatment with guselkumab (200 mg, subcutaneous injection) or placebo. Significant improvements from baseline were noted in PPP severity index total scores with guselkumab treatment vs placebo at week 16, and the positive treatment effects were maintained until week 24; no new safety concerns were identified.

Meaning Guselkumab may be a therapeutic option for patients with moderate to severe PPP.

Methods

Patients

The study protocol and amendments were reviewed and approved by an independent institutional review board at each study site: Asahikawa Medical College Hospital, Asahikawa Kosei Hospital, Tohoku University Hospital, Fukushima Medical University Hospital, Nihon University Hospital, Tokyo Medical University Hospital, Mano Medical Clinic, Shinshu University Hospital, Ehime University Hospital, Fukuoka University Hospital, and the Sapporo Skin Clinic. Written informed consent was obtained from each patient before enrollment. The study was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines, and other applicable regulatory requirements.

This multicenter, phase 2, randomized, double-blind, placebo-controlled study was conducted from May 14, 2013, to September 27, 2014, at 11 centers in Japan. The trial protocol, revised trial protocol, and statistical analysis plan are available in Supplement 1. Patients 20 years or older diagnosed with moderate to severe PPP with an inadequate response to prior conventional treatment (including topical corticosteroids, vitamin D_3 analogues, etretinate, and phototherapy) and with active lesions at screening and baseline (with a score of ≥7 on the palmoplantar pustulosis severity index [PPSI]) were included. Patients were excluded if they had previously received guselkumab at any time; any therapy targeting IL-6, IL-12, IL-17, or IL-23 within 6 months; any anti-TNF-α biologic therapy within 3 months or 5 half-lives; other PPP therapy (including phototherapy or any medications with systemic effects) within 4 weeks; or topical medications within 2 weeks prior to administration of the study agent.

Study Design and Treatment

This parallel-group study consisted of a screening period (6 weeks) and a double-blind period (24 weeks). A total of 49 patients were randomly assigned (1:1) to receive 200 mg of guselkumab (two 1-mL subcutaneous injections) or placebo at week 0 and week 4 (**Figure 1**). The 200-mg dose was selected based on the pharmacokinetic and pharmacodynamic modeling and simulation study for guselkumab (clinicaltrials.gov

identifier NCT00925574). Because PPP is considered a more difficult condition to treat, the maximal dose tested in the phase 2b plaque psoriasis study (dose range: 5-200 mg) was used in this PPP study.[31] Randomization was performed centrally based on a computer-generated randomization schedule using randomly permuted blocks and stratified by study site. After randomization (week 0), patients returned to the study site for 9 evaluation visits (weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24) during the double-blind period. Treatment assignment blinding was maintained for study site personnel, investigators, and randomized patients throughout the study. All efficacy assessments were conducted at week 16, the primary clinical cutoff for interim analysis, and week 24, the end of the study. Safety was monitored throughout the study.

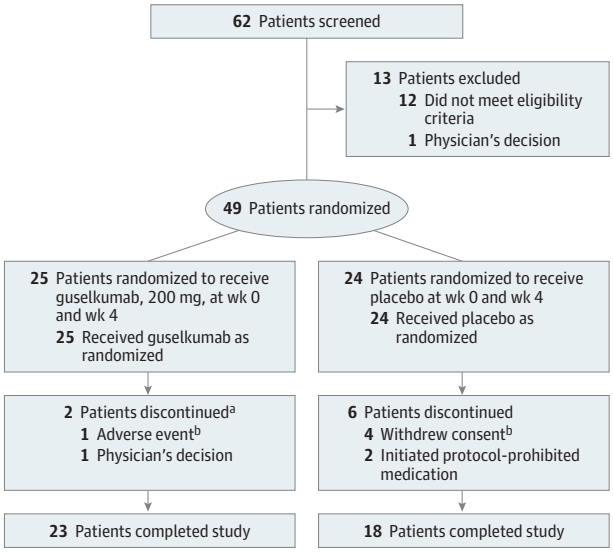
Efficacy

The primary efficacy end point was the change from baseline in the PPSI total score at week 16. The PPSI total score measures the severity of PPP lesions on palms or soles and their response to therapy on a scale of 0 to 12. The most severely affected areas on the palms and soles were identified during screening and assessed for individual findings (erythema, pustules or vesicles, and desquamation or scale) separately at each visit. The severity of each sign was rated on a scale of 0 to 4, with 0 indicating none; 1, minimal; 2, mild; 3, moderate; and 4, severe. The PPSI total score was the sum of the individual scores for each sign (erythema, pustules, and desquamation). Major secondary end points included change from baseline in PPSI total score and subscores at week 24 and PPP area and severity index (PPPASI) total score (severity assessed on a scale ranging from 0 to 72) at weeks 16 and 24. The PPPASI total scores were similar to PPSI but also assessed affected surface area by dividing the palms and soles into 4 regions. Other efficacy analyses included the proportion of patients with 50% or greater improvement from baseline of PPPASI score (PPPASI-50) at weeks 16 and 24 and the proportion of patients with a physician's global assessment (PGA) score of 1 or less (overall skin lesion status graded on a 0-5 scale, with 0 indicating clear skin and 5 indicating very severe lesions) at weeks 16 and 24. Assessment of PPSI subscores through week 24 was conducted post hoc and involved scoring of each PPP component (erythema, pustules or vesicles, and desquamation or scaling). Patients achieving scores of 0 or 1 for each component were classified as responders. Photographs of palms and soles were taken to assist visual observation. Proportion of patients with 75% or greater improvement from baseline of PPPASI score (PPPASI-75), change from baseline in physician's assessment, patient's visual analog scale assessment for PPP and pustulotic arthro-osteitis activity and pain, change in Dermatology Life Quality Index, and responses to the Short Form Health Survey were also investigated. However, these assessments are not included in the present report.

Serum Biomarker Assessment

Serum samples were collected at baseline (week 0), week 4, and week 16 from patients receiving guselkumab or placebo. Concentrations of cytokines such as IL-17A and IL-17F were analyzed using an ultrasensitive immunoassay system (Singulex Inc) to evaluate the effect of guselkumab treatment on the biology of T_H17 signaling.

Figure 1. Study Design Flow Diagram



A total of 49 patients were randomly assigned (1:1) to receive 200 mg of guselkumab (two 1-mL subcutaneous injections) or placebo at week 0 and week 4. After randomization (week 0), patients returned to the study site for 9 evaluation visits during the 24-week double-blind period.

[a] None had a disease flare on drug withdrawal.

[b] Received guselkumab or placebo only at week 0 and discontinued.

Safety

Safety assessments included reporting of treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, injection site reactions, and allergic reactions.

Statistical Analysis

Sample size calculation was based on the results from a phase 3 study[16] of topical vitamin D_3 analogue (maxacalcitol ointment) in Japanese patients with PPP. A sample size of 25 patients in each group (total of 50 patients) was required to detect a significant difference between the guselkumab and placebo groups with a power of 84% at an α level of .05 (2-sided), assuming a mean (SD) treatment difference in the change from baseline of PPSI total score of 1.8 (2.1) at week 16.

The primary and other efficacy end points were analyzed on the full analysis set (FAS) that consisted of all randomized patients who received at least 1 dose of study agent and had any postbaseline efficacy assessment. The change from baseline in PPSI and PPPASI was assessed using analysis of covariance with treatment as the factor and baseline PPSI total score as the covariate. The proportions of patients achieving PPPASI-50 and a PGA score of 1 or less were compared between the treatment groups using the Fisher exact test. Treatment difference between guselkumab and placebo was estimated based on least squares (LS) means of the difference and presented along with 95% confidence intervals. The last observation carried forward (LOCF) approach was used to

Table 1. Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	Guselkumab (N = 25)	Placebo (N = 24)	Total (N = 49)
Age, median (range), y	52.0 (28-67)	52.0 (32-77)	52.0 (28-77)
Women, No. (%)	18 (72)	17 (71)	35 (71)
Weight, mean (SD), kg	61.6 (10.99)	64.0 (14.43)	62.8 (12.72)
BMI, mean (SD)	23.4 (2.93)	25.0 (3.80)	24.2 (3.44)
Duration of PPP, median (range), y	7.3 (1.0-26.9)	2.7 (0.2-14.7)	4.6 (0.2-26.9)
Age at diagnosis, median (range), y	44.0 (27-59)	48.5 (27-75)	47.0 (27-75)
Baseline score, mean (SD)			
PPSI	8.9 (1.72)	9.8 (1.50)	9.3 (1.66)
PPPASI	19.1 (10.33)	24.8 (12.75)	21.9 (11.82)
PGA score, No. (%)			
Cleared	0	0	0
Minimal	0	0	0
Mild	1 (4)	1 (4)	2 (4)
Moderate	15 (60)	8 (33)	23 (47)
Severe	8 (32)	14 (58)	22 (45)
Very severe	1 (4)	1 (4)	2 (4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PGA, physician's global assessment; PPP, palmoplantar pustulosis; PPPASI, palmoplantar pustulosis area and severity index; PPSI, palmoplantar pustulosis severity index.

Table 2. Efficacy Outcomes (Full Analysis Set)

Outcome at wk 16, LOCF	Guselkumab (n = 25)	Placebo (n = 24)	Difference	*P* Value
PPSI total score, mean (SD) change from baseline	−3.3 (2.43)	−1.8 (2.09)	−1.5 (0.68) [−2.9 to −0.2][a]	.03[b]
PPPASI total score, mean (SD) change from baseline	−10.2 (8.07)	−6.4 (7.55)	−5.65 (2.06) [−9.80 to −1.50][a]	.009[b]
PPPASI-50 responders, No. (%)	15 (60)	5 (21)	39.2 (14.0 to 64.3)[c]	.009[d]
Patients with PGA scores ≤1, No. (%)	6 (24)	2 (8)	15.7 (−4.4 to 35.7)[c]	.25[d]

Abbreviations: LOCF, last observation carried forward; PGA, physician's global assessment; PPPASI, palmoplantar pustulosis area and severity index; PPPASI-50, proportion of patients with at least 50% improvement from baseline of PPPASI total score; PPSI, palmoplantar pustulosis severity index.

[a] Values are expressed as difference of least squares mean (standard error) [95% confidence interval].

[b] Based on the analysis of covariance with treatment as a factor and baseline scores as a covariate.

[c] Values are expressed as difference in proportion (95% confidence interval).

[d] Based on Fisher exact score.

impute missing data for all efficacy scores at week 16 and for PPSI and PPPASI total scores at week 24. Outcomes for PPPASI-50 and PGA score of 1 or less were analyzed in the FAS population with missing data imputed as nonresponse. The safety analysis set included all randomized patients who received at least 1 dose of the study agent. All safety results were descriptively summarized by treatment group.

Results

Demographics and Patient Disposition

Of the 62 patients screened, 49 were randomly assigned to guselkumab (n = 25) or placebo (n = 24). Median (range) age of the study population was 52 (28-77) years and 35 (71%) were women. A total of 41 patients completed the study at week 24 (Figure 1). Baseline demographic and disease characteristics were balanced between the groups, with the exception of median duration of disease, which was longer in patients randomized to guselkumab. Baseline PPSI and PPPASI scores were marginally lower (indicating lower disease activity) among patients receiving guselkumab vs placebo (**Table 1**).

Primary End Point

At week 16, there was a significant reduction in mean (SD) PPSI total scores from baseline in the guselkumab group (−3.3 [2.43]) vs placebo group (−1.8 [2.09]; difference in LS mean, −1.5; 95% CI, −2.9 to −0.2; *P* = .03) (**Table 2**).

Secondary End Points

Numerically greater reduction in mean (SD) PPSI total score was maintained from week 16 through week 24 in the guselkumab group (week 24: −3.9 [2.47]) vs placebo group (week 24: −2.5 [2.78]) (**Figure 2**A).

A significantly greater reduction in mean (SD) PPPASI total score from baseline was observed at week 16 for guselkumab (−10.2 [8.07]) vs placebo (−6.4 [7.55]) (difference in LS mean, −5.65; 95% CI, −9.80 to −1.50; *P* = .009) (Figure 2B). At week 24, mean (SD) reductions in PPPASI total scores continued to be numerically lower in the guselkumab group (−11.8 [8.99]) vs placebo group (−9.2 [9.72]).

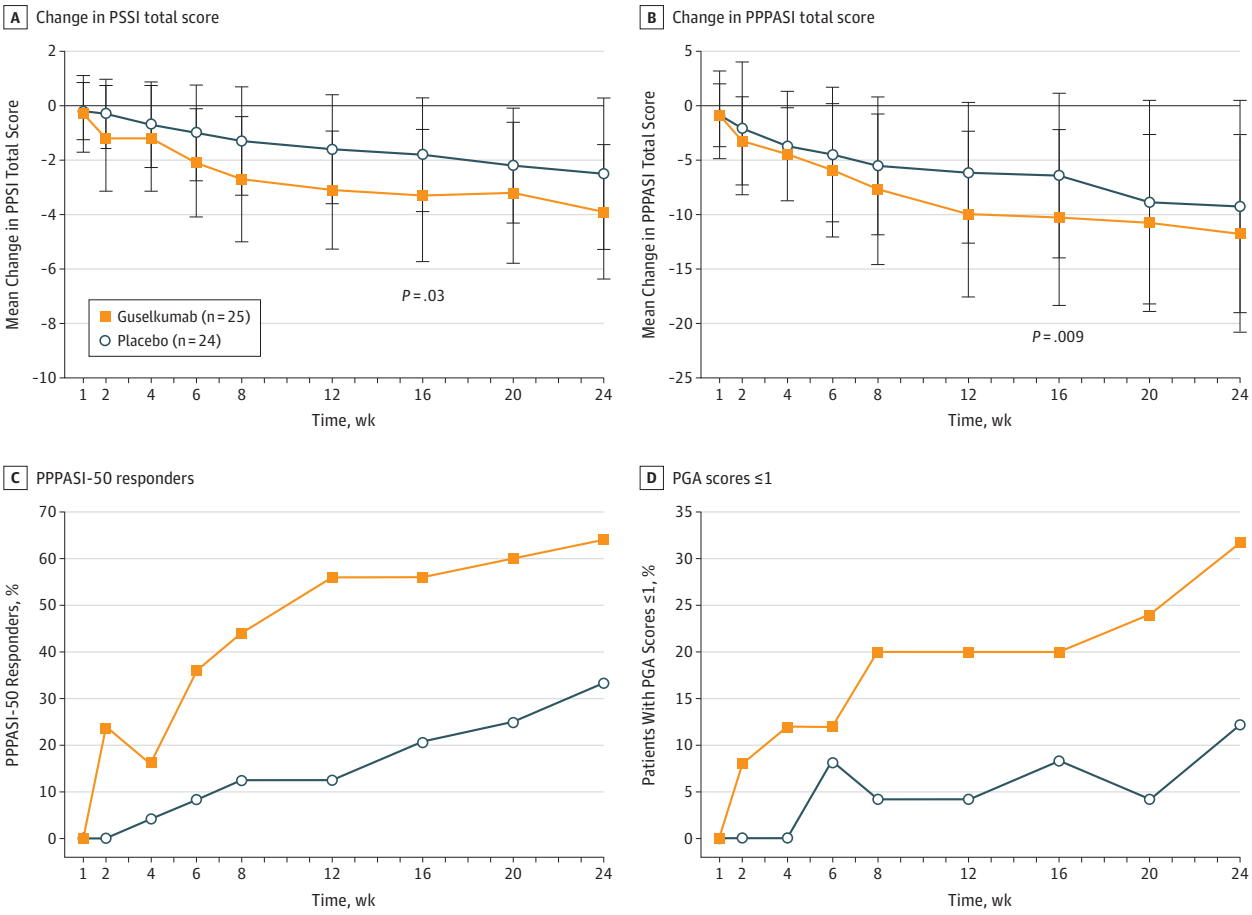
At week 16, the proportion of patients achieving PPPASI-50 (LOCF analysis) was significantly higher in the guselkumab group (15 of 25 [60%]) vs placebo group (5 of 24 [21%]) (difference in proportion, 39.2; 95% CI, 14.0-64.3; *P* = .009). Similarly, a greater proportion of patients receiving guselkumab achieved a PGA score (LOCF analysis) of 0 or 1 (indicating cleared or minimal PPP) at week 16 (6 of 25 [24%]) vs those receiving placebo (2 of 24 [8%]); however, the difference in proportion was not significant (difference in proportion, 15.7; 95% CI, −4.4 to 35.7; *P* = .25) (Table 2). Through week 24, a higher proportion of patients in the guselkumab group, as compared with the placebo group, were PPPASI-50 responders (guselkumab, 16 of 25 [64%]; placebo, 8 of 24 [33%]) and had a PGA score of 1 or less (guselkumab, 8 of 25 [32%]; placebo, 3 of 24 [13%]) (Figure 2C and D). No patients receiving guselkumab showed worsening of PPP while receiving treatment.

Disease activity at baseline and at week 16 for representative patients receiving placebo and guselkumab demonstrating clinical improvement is shown in eFigure 1 in Supplement 2.

Serum Biomarker Analysis

At baseline (week 0), mean (SD) serum concentrations of cytokines were 0.5 (0.20) pg/mL (IL-17A) and 3.2 (1.81) pg/mL (IL-17F). A significant reduction from baseline in circulating IL-17A levels was observed at weeks 4 and 16 for guselkumab-treated patients, while no significant changes were noted for

Figure 2. Efficacy Outcomes Through Week 24 (Full Analysis Set)



A, Mean change from baseline in palmoplantar pustulosis severity index (PPSI) total score through week 24 (last observation carried forward, full analysis set); guselkumab, n = 25; placebo, n = 24. B, Mean change from baseline in palmoplantar pustulosis area and severity index (PPPASI) total score through week 24 (last observation carried forward, full analysis set). Error bars indicate standard deviation. A and B, *P* values shown are for the least squares mean difference (guselkumab vs placebo) at week 16. C, Percentage of patients achieving proportion of patients with 50% or greater improvement from baseline of PPPASI total score (PPPASI-50) response through week 24 (nonresponder imputation, full analysis set). D, Percentage of patients with physician's global assessment scores of 1 or less through week 24 (nonresponder imputation, full analysis set).

the placebo group (eFigure 2A in Supplement 2). Serum levels of IL-17F also decreased significantly from baseline at weeks 4 and 16 for the guselkumab group and at week 16 for the placebo group (eFigure 2B in Supplement 2).

Post Hoc Analysis

The proportion of PPSI responders (achieving PPSI subscores of 0 or 1) was numerically higher for each component of PPP with guselkumab vs placebo (eAppendix in Supplement 2).

Safety Assessments

The proportion of patients experiencing 1 or more TEAEs was comparable between the guselkumab (19 of 25 [76%]) and placebo (18 of 24 [75%]) groups. Reported TEAEs were generally mild to moderate in severity. Common TEAEs (≥2 patients in any treatment group) included nasopharyngitis (14 patients [29%]), headache (3 patients [6%]), contact dermatitis (3 patients [6%]), injection site erythema (3 patients [6%]), and urticaria (2 patients [4%]) (**Table 3**). No deaths were reported during the study. Serious TEAEs were reported in 2 of 25 patients (8%) receiving guselkumab (1 case of pyelonephritis and 1 case of gastric cancer) and 1 of 24 patients (4%) receiving placebo (pustular psoriasis, exacerbation of the underlying disease). One patient (4%) in the guselkumab group prematurely discontinued the study because of urticaria. The frequency of infection was similar across both treatment groups (guselkumab, 13 of 25 [52%]; placebo, 14 of 24 [58%]). A higher proportion of patients receiving guselkumab (3 of 25 [12%]) experienced an injection site reaction of mild severity vs those receiving placebo (1 of 24 [4%]). Changes in vital signs, body weight, physical examination results, electrocardiogram results, or laboratory values were not clinically relevant.

Discussion

To our knowledge, this placebo-controlled, phase 2, proof-of-concept study is the first to demonstrate the clinical benefits of guselkumab, a selective anti-IL-23 antibody, in a cohort of

Table 3. Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

TEAEs	Patients, No. (%)		
	Guselkumab (n = 25)	Placebo (n = 24)	Total (N = 49)
Patients with ≥1 TEAE	19 (76)	18 (75)	37 (75)
Patients with ≥1 serious TEAE	2 (8)	1 (4)	3 (6)
Patients in whom study agent was discontinued because of ≥1 TEAE	1 (4)	0	1 (2)
TEAEs occurring in ≥2 patients overall			
Nasopharyngitis	7 (28)	7 (29)	14 (29)
Headache	2 (8)	1 (4)	3 (6)
Contact dermatitis	2 (8)	1 (4)	3 (6)
Injection site erythema	2 (8)	1 (4)	3 (6)
Urticaria	2 (8)	0	2 (4)
Cystitis	1 (4)	2 (8)	3 (6)
Pharyngitis	1 (4)	2 (8)	3 (6)
Eczema	0	3 (13)	3 (6)
Erythema	0	2 (8)	2 (4)
Folliculitis	0	2 (8)	2 (4)
TEAEs of clinical interest occurring in ≥1 patient overall			
Infections	13 (52)	14 (58)	27 (55)
Infections requiring treatment	7 (28)	6 (25)	13 (27)
Injection site reactions	3 (12)	1 (4)	4 (8)

Abbreviation: TEAEs, treatment-emergent adverse events.

patients with moderate to severe PPP. Treatment with guselkumab, 200 mg, given by subcutaneous injection at weeks 0 and 4 achieved significant improvement in PPSI total scores from baseline to week 16. Improvements in PPPASI total scores were significant, and the proportion of patients achieving PPPASI-50 was higher with guselkumab vs placebo.

Improvements in each PPSI component (based on frequency of score 0 or 1) support the efficacy of guselkumab in PPP. Onset of clinical response was rapid and apparent within 2 weeks as measured by PPSI, PPPASI, and response rates for PPPASI-50 and PGA less than or equal to 1, with a clear trend of improvement until the end of observation at week 24. Taken together, improvements using several efficacy measures suggest favorable response to guselkumab treatment.

The improvements in skin-related outcomes were noticeable after 2 systemic doses (at weeks 0 and 4) of guselkumab. Change from baseline in PPSI total scores measuring the qualitative features of skin findings for each pustule was regarded as the primary end point based on experience from a clinical study[16] evaluating topical vitamin D_3 analogue (maxacalcitol ointment) in patients with PPP. However, to evaluate the efficacy of a biological agent with systemic effects such as guselkumab, improvements in skin lesions based on PPPASI total scores that measure the severity of qualitative features along with extent of PPP based on involved surface area may be a more suitable primary end point for a phase 3 study.

The overall trend in clinical responses noted in the present study were consistent with the efficacy and safety findings in patients with moderate to severe plaque psoriasis, a related immune-mediated inflammatory skin disease.[30-33] In a small first-in-human study,[30] guselkumab (10, 30, 100, and 300 mg) was efficacious as measured by the proportion of patients with plaque psoriasis who achieved 75% improvement in the psoriasis area and severity index (PASI-75) scores at week 12 and maintained the improvement through 24 weeks. Furthermore, in a phase 2 study,[31] guselkumab significantly improved PASI score, and a higher proportion of patients in the treatment group achieved PGA scores of 0 or 1 compared with those in the placebo group (week 16) and those given the TNF-α antagonist adalimumab (week 40). In the more recent global phase 3 studies,[32,33] maintenance of guselkumab treatment demonstrated superior efficacy in improving the investigator global assessment and PASI scores vs placebo or adalimumab over a 48-week study period.

At week 24, the rate of TEAEs was similar between the guselkumab and placebo groups, and all TEAEs were of mild or moderate severity. The proportion of patients experiencing serious TEAEs was also small across both groups. Frequency of infections was similar between the groups and the occurrence of infections requiring treatment was low and comparable between the groups. Safety findings from this study were in accordance with observations from global phase 3 studies of guselkumab[32,33] and other available reports involving Japanese patients with plaque psoriasis.[30,31] No new safety signals were observed in these Japanese patients with PPP.

Evidence from molecular studies[24,27,30] supports the involvement of IL-23 in PPP and suggests that reductions in serum concentrations of IL-17A and IL-17F primarily drive the phenotypes of psoriasis and most likely PPP. By antagonizing IL-23 through targeting its p19 subunit, guselkumab selectively disrupts the inflammatory IL-23/T_H17 pathway and is therefore a viable biological therapy for these immune-mediated skin conditions.[19,29,34] Significant reductions in circulating levels of cytokines IL-17A and IL-17F in response to guselkumab observed in the present study were similar to responses observed in another Japanese study evaluating

guselkumab in patients with plaque psoriasis.[35] The mean (SD) baseline levels of IL-17A (0.7 [0.42] pg/mL) and IL-17F (6.4 [1.96] pg/mL) were higher in patients with plaque psoriasis as compared with those in the current study. This observation may be attributable to the differences in pathogenesis between plaque psoriasis and PPP.[12,13]

Overall, the efficacy of guselkumab highlights the role of the IL-23 and T_H17 axis in the pathogenesis of PPP and validates the approach of IL-23 inhibition in treating PPP. Further studies and comprehensive molecular characterization will be useful to ascertain the pathogenic immune pathways involved in PPP and their therapeutic significance.

Limitations

Limitations of the study include the small sample size and short treatment period. The use of descriptive statistics for the 24-week efficacy analyses may potentially restrict the interpretation of these results. Also, the full therapeutic benefit of guselkumab as seen with continued dosing could not be observed in this study as the patients received only 2 doses of guselkumab (at weeks 0 and 4).

Conclusions

Safety of guselkumab (200 mg given by subcutaneous injection) was consistent with earlier studies, and no new safety concerns specific to the Japanese population were identified. Overall, guselkumab demonstrated therapeutic potential in Japanese patients with moderate to severe PPP. Long-term phase 3 studies with a placebo crossover design and continued maintenance dosing in larger patient populations are required to further characterize the therapeutic benefit of guselkumab for the treatment of PPP.

ARTICLE INFORMATION

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Terui, Kobayashi, Okubo, Murakami, Kubo.
Drafting of the manuscript: Hirose, Kubo.
Critical revision of the manuscript for important intellectual content: Terui, Kobayashi, Okubo, Murakami.
Statistical analysis: Hirose.
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Study supervision: Terui, Kobayashi, Okubo, Murakami.

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