ORIGINAL ARTICLE

Efficacy of guselkumab in a subpopulation with pustulotic arthro-osteitis through week 52: an exploratory analysis of a phase 3, randomized, double-blind, placebo-controlled study in Japanese patients with palmoplantar pustulosis

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Abstract

Background Previous studies of guselkumab have demonstrated clinical benefits in patients with plaque-type psoriasis, generalized pustular psoriasis, erythrodermic psoriasis and palmoplantar pustulosis (PPP).

Objective The aim of this exploratory analysis of a double-blind, multicenter, placebo-controlled, phase 3 study in Japanese patients with PPP was to evaluate the efficacy of guselkumab in the subset of patients with pustulotic arthro-osteitis (PAO).

Methods Patients were randomized to receive guselkumab 100 or 200 mg at weeks 0, 4, 12 and every 8 weeks, or placebo with cross-over to guselkumab 100 or 200 mg at week 16 (placebo group). Efficacy endpoints were changes from baseline in magnetic resonance imaging (MRI) score, EuroQOL-5 dimensions (EQ-5D) index score, EQ-5D pain/discomfort dimension score and C-reactive protein (CRP, mg/L) level in all PAO patients through week 52. Data from both guselkumab groups were combined and presented as results for a single overall guselkumab group.

Results Among 159 patients with PPP, 66 with PAO were randomized across treatment groups. For patients with MRI data for all regions assessed, the proportion of patients in the guselkumab group with PAO characterized as severe decreased from 23.8% (10/42) at baseline to 5.4% (2/42) at week 52. The mean (SD) change from baseline at week 52 in EQ-5D index score was 0.20 (0.17) among PPP patients with PAO and 0.15 (0.17) among those without PAO in the guselkumab group. Among all PAO patients, the proportions with an EQ-5D pain/discomfort dimension score of no or slight pain/discomfort in the guselkumab group increased from baseline to week 52 [33.3% (7/21) vs. 87.5% (35/40)]. The mean (SD) CRP levels decreased in all PAO patients in the guselkumab group at week 52 compared to baseline [−1.71 (8.16) mg/L].

Conclusion Guselkumab treatment showed beneficial outcomes for PAO signs and symptoms in Japanese patients with PPP.

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Conflict of Interest

TY, KF, AM and TT received grants from Janssen Pharmaceutical K.K. TK, RZ, HM and RG declare a conflict of interest on the basis that they are full-time employees of Janssen Pharmaceutical K.K. of Johnson & Johnson. The material presented in this paper reflects authors own personal views and should not be interpreted as being representative of the views of their employers or institutions.

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Introduction

Palmoplantar pustulosis (PPP) is a skin disease characterized by recurrent eruptions of sterile pustules, erythema and exfoliation.[1,2] Lesions are located exclusively, and often symmetrically, on the palms and/or soles. Association of PPP with bone and joint pain was first reported in Japan by Ishibashi et al.[3] Pustulotic arthro-osteitis (PAO), first described by Sonozaki et al. and alternatively termed Sonozaki syndrome,[2,4] is a chronic disease characterized by an inflammatory osteitis of the sternoclavicular joint associated with PPP.[2,5] Other clinical manifestations of PAO include inflammation of the spine, the sacroiliac joint and peripheral joints.[2,5,6] PAO develops in approximately 20%–30% of patients with PPP[2] and has a significant impact on patients' quality of life.[7] The frequency of occurrence of arthritis in Japanese PPP patients is similar to that reported in non-Asian countries (13%–64.7%).[8]

Treatment for PAO is usually pursued for symptomatic relief and consists of non-steroidal anti-inflammatory drugs and systemic cyclosporine.[4,9–12] Given that PAO may be associated with focal infection, treatment of underlying focal infection such as tonsillectomy may be considered.[2,5] However, currently available treatment options are of limited benefit and early recurrence of symptoms or treatment failure are common; hence, there is a substantial need for the development of effective therapeutic options that target the underlying pathogenic mechanism for PAO.

The pathogenesis of PPP is believed to involve dendritic cell-mediated interleukin (IL)-23 production and subsequent downstream proliferation of T helper cell 17 (Th17).[13–16] Furthermore, IL-17 induced IL-8 production and resulting neutrophil infiltration are linked to pustule formation in PPP.[17–21] Although its pathogenesis is not well understood, considering the association between PPP and PAO, IL-23-mediated inflammation may be involved in causing PAO as well. However, the role of IL-23 in the pathogenesis of PAO has not been well investigated to date.

Guselkumab (CNTO 1959), a fully human immunoglobulin G1λ monoclonal antibody, selectively binds to the p19 subunit of IL-23[22,23] and blocks the binding of IL-23 to its receptor, thereby inhibiting downstream intracellular signalling and subsequent cytokine production via Th17 cell differentiation.[24] Guselkumab is approved for the treatment of plaque psoriasis in the United States[25], EU[26] and Japan[27] based on results derived from a large phase 3 clinical trial development programme.[17,19,20,23,28] Clinical improvement with guselkumab treatment was also demonstrated in previous global studies of psoriasis[17,19] and psoriatic arthritis (PsA),[29] and in the Japanese studies with plaque-type psoriasis,[28,30] generalized pustular psoriasis, erythrodermic psoriasis and PPP.[1,20,31]

Recent data from the phase 3, randomized, double-blind, placebo-controlled study (parent study for this exploratory analysis) demonstrated the efficacy and safety of guselkumab in Japanese patients with PPP based on improvements in measures of disease severity, including the PPP area and severity index (PPPASI) and PPP severity index (PPSI).[31] To date, the evidence for the effect of guselkumab in patients with PAO is lacking. The objective of this exploratory substudy was to evaluate the efficacy of guselkumab treatment for PAO in Japanese PPP patients with both conditions.

Methods

The study protocol was approved by the local Institutional Review Board, and the study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki. The study was conducted in a manner consistent with International Conference on Harmonization and Good Clinical Practice guidelines, applicable regulatory requirements, and was in compliance with the study protocol. Written informed consent was obtained from all patients to participate in the study. The study was registered at ClincalTrials.gov as NCT02641730.

Patient population

Detailed methodology for this study has been published previously.[1,31] Briefly, patients 20 years of age who were diagnosed with PAO, based on clinical judgement of the investigators, at the time of screening for PPP in the primary study[31] were included in this analysis. Patients were enrolled if they had a PPPASI total score of ≥12, and a PPPASI severity score of pustules/vesicles on the palms or soles ≥2 at screening. Patients who had an inadequate response to conventional therapies, such as topical treatment, phototherapy and/or systemic treatment, were included.

Patients with plaque-type psoriasis, evidence of current or history of recurrent infectious disease, drug-induced PPP, malignancy (≤5 years before screening) or active tuberculosis were excluded. Patients who received treatment for a focal infection (within 24 weeks), anti-TNFα biologic therapy (within 12 weeks or 5 half-lives), any therapeutic agent directly targeting IL-12/23, IL-17 or IL-23 (within 24 weeks) or any other PPP therapy were also excluded.

Study design and medication

This exploratory substudy of a double-blind, multicenter, placebo-controlled, phase 3 study (conducted across 40 sites in Japan) was performed to evaluate the efficacy of guselkumab in Japanese PPP patients with PAO. The study was comprised of three phases: a screening phase (up to 6 weeks), a blinded treatment phase (placebo-controlled phase: week 0 to week 16 and cross-over phase: week 16 to week 60) and an observation phase (week 60 to week 84). Eligible patients underwent central randomization (1 : 1 : 1) using a stratified block randomization method at week 0 to receive either guselkumab 100 mg or guselkumab 200 mg (at weeks 0, 4, 12 and every 8 weeks thereafter) or placebo (at weeks 0, 4, and 12) by subcutaneous

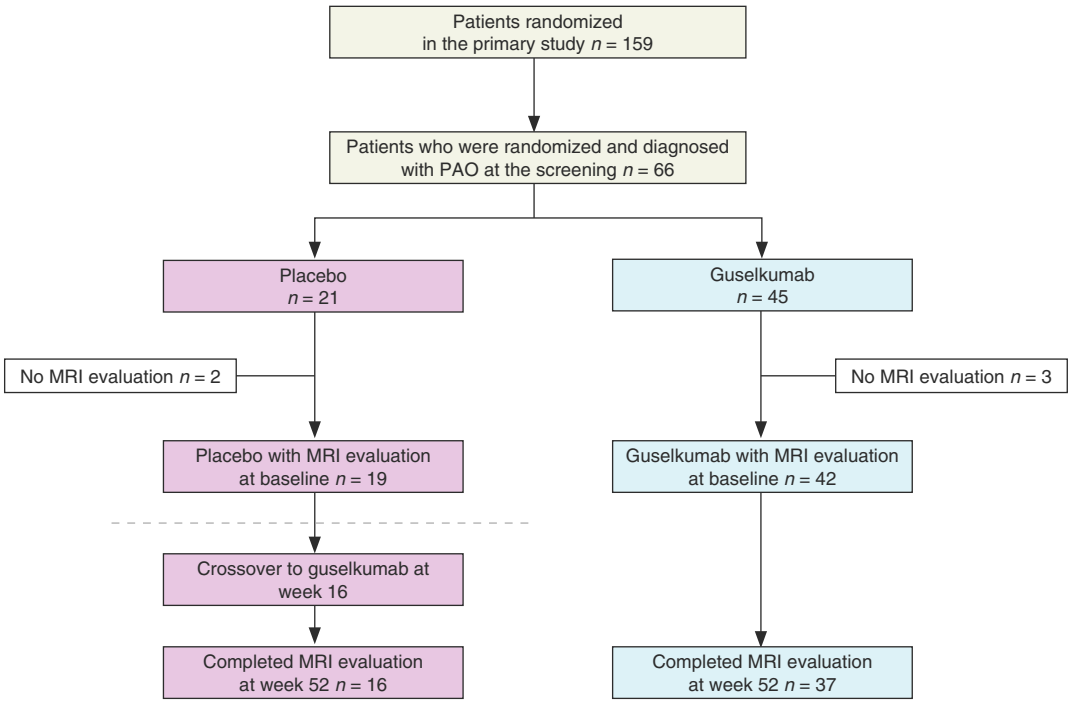

Figure 1 Study design and patient disposition. MRI, magnetic resonance imaging; *n*, number of patients.

injection. At week 16, patients in the placebo group were re-randomized (1 : 1) to receive either guselkumab 100 or 200 mg at weeks 16, 20 and every 8 weeks thereafter until week 60. Patients initially randomized to guselkumab 100 or 200 mg were administered placebo at week 16 to maintain blinding.

Concomitant and prohibited medications

Patients were permitted to use non-steroidal anti-inflammatory drugs. However, the use of systemic corticosteroids for patients with PAO was limited to situations for which there were no adequate alternatives in the opinion of the treating physician and was to be used on a short-term basis (preferably for ≤2 weeks). Use of any other therapies that could affect PPP or the efficacy evaluation including topical therapies, phototherapy, systemic medications (e.g., bisphosphonates or immunosuppressants) and treatments for focal infection for PPP were prohibited throughout the study.

Efficacy endpoints

The efficacy endpoints used for assessment of PAO in the substudy were the change in magnetic resonance imaging (MRI) score, EuroQOL-5 dimensions (EQ-5D) score and C-reactive protein (CRP, mg/L) level at week 52 compared to baseline.

Efficacy assessments

The MRIs for subset of patients with PAO were obtained at baseline and at week 52 and were evaluated according to a prespecified procedure by a central reviewer, a qualified radiologist with >30 years of experience in reading musculoskeletal MRIs. Briefly MRIs of the anterior chest wall, spine, sacroiliac joint and peripheral joint regions were obtained with T1-weighted spin echo (T1W-SE) and either short-tau inversion recovery (STIR) or fat-suppressed T2-weighted turbo-spin echo (FS-T2W-TSE), and MRI scores were assigned to pathological features of each region. If activity scores and symptoms were similar among the regions assessed, the anterior chest region was prioritized for analyses. In addition, the Psoriatic Arthritis Magnetic Resonance Imaging Scoring (PsAMRIS) system created by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group was used as a reference for the MRI scoring.[32–35] Based on their MRI scoring, the central MRI reviewer made a global assessment of PAO severity (absent, mild, moderate, severe, not applicable). Patients with any contraindication to MRI scanning (e.g., claustrophobia, implantation of electric device) and with metallic implant in the area of interest were excluded from MRI assessments.

The EQ-5D was used as a patient-reported measure of overall health status and QoL. The EQ-5D consists of five dimensions:

mobility, self-care, usual activities, pain/discomfort and anxiety/depression. An exploratory evaluation of the impact of guselkumab on pain associated with PAO was performed using the 'pain/discomfort,' dimension/domain of the EQ-5D. The 5 levels of 'pain/discomfort' scoring used in the EQ-5D were consolidated into 2 categories, 'absent (1) + mild (2)' and 'moderate (3) + severe (4) + extreme (5)' for this exploratory analysis. The scores for each of the EQ-5D dimensions/domains were also converted into a single overall summary EQ-5D index score.

CRP levels were assessed by nephelometry, using blood samples collected at screening, every 2 weeks through week 4, every 4 weeks through week 28 and every 8 weeks through week 52. The lowest detectable level of CRP was 0.020 mg/dL.

Statistical methods

Descriptive statistical methods were used for this exploratory subset analysis to assess the magnitude of the treatment effect. Efficacy was analysed based on the intent-to-treat (ITT) population that included all the PAO patients who were randomized in the CNTO1959PPP3001 study.[31] Data from the guselkumab 100 mg and guselkumab 200 mg groups were combined and presented as results for a single overall guselkumab group. Patients who were initially randomized to placebo at week 0 are referred to as placebo-guselkumab group for visits after week 16 despite crossing over to receive guselkumab 100 mg or guselkumab 200 mg at week 16 and thereafter. For characterizing the improvement in QoL in PAO patients as compared to non-PAO patients, analyses were also performed for non-PAO subpopulation in EQ-5D. No statistical methods were used to impute missing data for this exploratory analysis.

Results

Patient disposition and characteristics

In the primary study, a total of 159 patients with PPP were enrolled. Among these, 66 patients diagnosed with PAO at screening were randomized at week 0 to receive either placebo (n = 21) or guselkumab (n = 45; Fig. 1). Among these patients, n = 19 in placebo group and n = 42 in guselkumab group had MRI evaluations; 48 patients underwent MRI for assessment of the anterior chest region and 13 patients underwent MRI for evaluation of regions other than the anterior chest.

Treatment duration for the guselkumab group was 52 and 36 weeks for the placebo-guselkumab (cross-over) group. At baseline, the mean (standard deviation [SD]) age was 51.0 (7.4) years for the placebo group and 53.6 (11.2) years for the guselkumab group. Demographic characteristics were generally well balanced across treatment groups and comparable to whole PPP population of this study.[31] At baseline, median PPP disease duration was 2.5 years for the placebo group and 3.7 years for the guselkumab group, mean (SD) PPPASI score was 29.9 (11.3) for the placebo group and 27.2 (10.3) for the guselkumab group, and mean (SD) dermatology life quality index (DLQI) score was 8.0 (5.9) for the placebo group and 10.6 (6.3) for the guselkumab group (Table 1). Among patients who completed week 52 MRI evaluation, the proportions of patients who ever used systemic NSAIDs for PAO through week 52 were 75% (12/16) in the placebo group and 83.8% (31/37) in the guselkumab group. No patients used systemic corticosteroid for PAO through week 52.

Efficacy

MRI score Among PAO patients in the guselkumab group with MRI evaluations across all regions imaged, the proportion with disease activity characterized as moderate or severe was 71.4% (30/42) at baseline and 56.8% (21/37) at week 52 (Table 2). The proportions of patients in the guselkumab group with a change in MRI score at week 52 compared to baseline of a ≥2 grade improvement, 1 grade improvement or no change were 5.4% (2/37), 37.8% (14/37) and 54.1% (20/37), respectively. Worsening

Table 1 Demographics and baseline disease characteristics in pustulotic arthro-osteitis patients

	Placebo n = 21	Guselkumab n = 45
Age, years	51.0 (7.38)	53.6 (11.15)
Women, n (%)	19.0 (90.50)	39.0 (86.70)
Weight, kg	58.78 (8.75)	58.59 (9.66)
BMI, kg/m^2	22.95 (3.18)	23.61 (3.28)
Age at diagnosis, years	44.0 (10.69)	45.0 (12.70)
PPP disease duration, median (range), years	2.46 (0.5; 37.5)	3.74 (0.6; 42.4)
PPPASI total score (0–72)*	29.91 (11.26)	27.24 (10.25)
Anterior chest	28.29 (11.48)	28.29 (10.52)
Non-anterior chest	34.44 (10.37)	23.88 (8.97)
PPSI total score (0–12)	10.50 (1.69)	10.50 (1.41)
PGA score, n (%)		
Mild (2)	0	0
Moderate (3)	8 (38.10)	14 (31.10)
Severe (4)	9 (42.90)	26 (57.80)
Very severe (5)	4 (19.00)	5 (11.10)
DLQI score (0–30)	8.0 (5.91)	10.6 (6.25)
EQ-5D index score	0.73 (0.20)	0.64 (0.21)

Values are presented as mean (SD) unless specified. Patients in placebo group crossed over to receive guselkumab 100 or 200 mg starting at week 16.

BMI, body mass index; DLQI, Dermatology Life Quality Index; EQ-5D, EuroQOL-5 dimensions questionnaire; MRI, magnetic resonance imaging; n, number of patients; PAO, pustulotic arthro-osteitis; PPP, palmoplantar pustulosis; PPPASI, PPP area and severity index; PPSI, PPP severity index; PGA, physician's global assessment; SD, standard deviation.

*Analysis set was the group of PAO patients with MRI score assessments; n = 19 in the placebo group and n = 42 in the guselkumab group.

Table 2 Change from baseline in MRI score at week 52 in pustulotic arthro-osteitis patients

PAO severity as measured by MRI		Placebo	Guselkumab
All regions			
Baseline	*n*	19	42
	None	0	2 (4.8)
	Mild	4 (21.1)	10 (23.8)
	Moderate	12 (63.2)	20 (47.6)
	Severe	3 (15.8)	10 (23.8)
Week 52	*n*	16*	37
	None	1 (6.3)	5 (13.5)
	Mild	7 (43.8)	11 (29.7)
	Moderate	8 (50.0)	19 (51.4)
	Severe	0	2 (5.4)
Change from baseline at week 52	*n*	16*	37
	≥2 grades improvement	0	2 (5.4)
	1 grade improvement	7 (43.8)	14 (37.8)
	Unchanged	9 (56.3)	20 (54.1)
	Worsening	0	1 (2.7)
Region: Anterior chest			
Baseline	*n*	16	32
	None	0	1 (3.1)
	Mild	4 (25.0)	9 (28.1)
	Moderate	10 (62.5)	17 (53.1)
	Severe	2 (12.5)	5 (15.6)
Week 52	*n*	14*	29
	None	1 (7.1)	4 (13.8)
	Mild	5 (35.7)	10 (34.5)
	Moderate	8 (57.1)	13 (44.8)
	Severe	0	2 (6.9)
Change from baseline at week 52	*n*	14*	29
	≥2 grades improvement	0	1 (3.4)
	1 grade improvement	5 (35.7)	8 (27.6)
	Unchanged	9 (64.3)	19 (65.5)
	Worsening	0	1 (3.4)
Region: Other than anterior chest			
Baseline	*n*	3	10
	None	0	1 (10.0)
	Mild	0	1 (10.0)
	Moderate	2 (66.7)	3 (30.0)
	Severe	1 (33.3)	5 (50.0)
Week 52	*n*	2*	8
	None	0	1 (12.5)
	Mild	2 (100.0)	1 (12.5)
	Moderate	0	6 (75.0)
	Severe	0	0
Change from baseline at week 52	*n*	2*	8
	≥2 grades improvement	0	1 (12.5)
	1 grade improvement	2 (100.0)	6 (75.0)
	Unchanged	0	1 (12.5)
	Worsening	0	0

Region other than the anterior chest included the foot, thumb, clavicle, cervical spine 2, lumber spine and sacroiliac joint 7. Values are presented as *n* (%).
MRI, magnetic resonance imaging; n, number of patients; PAO, pustulotic arthro-osteitis.
*Patients in placebo group crossed over to receive guselkumab 100 or 200 mg starting at week 16.

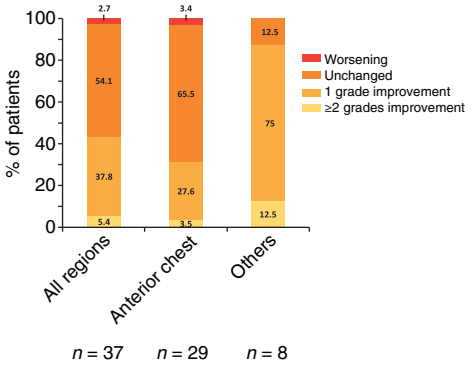

Figure 2 Change from baseline in MRI score at week 52 in the guselkumab group. MRI, magnetic resonance imaging; *n*, number of patients.

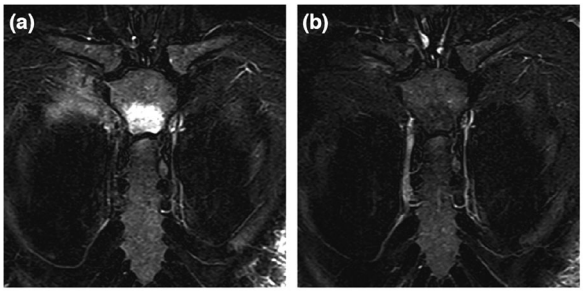

Figure 3 MRI images of anterior chest region of a patient with improvement in pustulotic arthro-osteitis from guselkumab group at week 0 and week 52: short-tau inversion recovery (STIR) sequence. MRI, magnetic resonance imaging.

of the MRI score was observed only in 2.7% (1/37) patient in the guselkumab group (Table 2, Fig. 2).

The baseline PPPASI scores were comparable between PAO patients and all PPP patients.[1] Mean change from baseline in PPPASI score at week 52 in PAO patients who completed MRI evaluation was −23.6 (8.21), which was comparable to that in all PPP patients [−19.7 (11.41)]. Among PAO patients, there was difference in baseline PPPASI score between those with improved MRI score and those with unchanged or worsening MRI score at week 52 [23.7 (8.12) and 32.1 (9.90), respectively]. Clinical response to skin lesion was observed in both subpopulations regarding mean change from baseline in PPPASI score at week 52 [−20.8 (7.65) and −25.8 (8.13), respectively] though there is no evident correlation between response to PPP lesion and that to PAO lesion.

Among patients with MRI assessments of the anterior chest region, the proportions of patients in the guselkumab group with PAO disease activity classified as moderate and severe were 53.1% (17/32) and 15.6% (5/32) at baseline and 44.8% (13/29) and 6.9% (2/29) at week 52, respectively. The proportions of patients in the guselkumab group with a change in MRI score in anterior chest region at week 52 compared to baseline of a ≥2 grade improvement, 1 grade improvement or no change were 3.4% (1/29), 27.6% (8/29) and 65.5% (19/29), respectively (Table 2). Figure 3 shows representative MRI scans of anterior chest region of a patient with improvement in PAO from the guselkumab group at baseline (week 0) and week 52.

All individual pathological features of the anterior chest region MRI assessments evaluated were improved at week 52 compared to baseline except for synchondrosis-bone erosion. Among these items, inflammatory features including bone marrow oedema/osteitis and soft tissue swelling/oedema have shown relatively better improvement. For regions other than the anterior chest, overall MRI features showed a trend towards improvement, except for bone proliferation (Table 3).

EQ-5D The mean (SD) change at week 52 from baseline in EQ-5D index score was 0.14 (0.13) among PPP patients with PAO and 0.16 (0.22) among those without PAO in the placebo-guselkumab group. The mean (SD) change at week 52 from baseline in EQ-5D index score was 0.20 (0.17) among PPP patients with PAO and 0.15 (0.17) among those without PAO in the guselkumab group (Table 4). The change in EQ-5D index score was comparable between PPP patients with PAO and those without PAO in the guselkumab group (Table 4). In all PPP patients, baseline EQ-5D index score and change from baseline in EQ-5D index score at week 52 were 0.7 (0.21) and 0.15 (0.19), respectively, which were comparable to scores of PAO patients.

The proportion of PPP patients with an EQ-5D pain/discomfort dimension score of moderate or above was higher among those with PAO compared to those without PAO at baseline. Among all PAO patients, the proportions with an EQ-5D pain/discomfort dimension score of no or slight pain/discomfort were 33.3% (7/21) in the placebo group and 28.9% (13/45) in the guselkumab group at baseline. At week 16, higher proportion of patients in the guselkumab group 73.3% (33/45) had no or slight pain/discomfort in comparison with the placebo group 47.4% (9/19); improvement in pain/discomfort dimension scores continued through week 52 [guselkumab: 87.5% (35/40); placebo-guselkumab: 94.4% (17/18)] (Table 5, Fig. 4). An overall shift in EQ-5D pain/discomfort dimension scores from moderate or greater pain/discomfort to no or slight pain/discomfort was observed for both PAO and non-PAO patients through week 52 (Table 6, Fig. 5). Among PAO patients in the guselkumab group with an improved MRI score at week 52, the proportions with an EQ-5D pain/discomfort dimension score of moderate or above were 75% (12/16) at baseline and 0% (0/16) at week 52. However, PAO patients with no change in their MRI score at

Table 3 Summary of MRI assessment items by MRI improvement status at week 52 and MRI measured region in pustulotic arthro-osteitis patients

		Placebo	Guselkumab
Region: Anterior chest			
Baseline			
n		16	32
Synchondrosis			
Inflammation of synchondrosis	Present	10 (62.5)	16 (50.0)
	Absent	6 (37.5)	16 (50.0)
Bone marrow oedema/osteitis	Present	15 (93.8)	26 (81.3)
	Absent	1 (6.3)	6 (18.8)
Soft tissue swelling/oedema	Present	14 (87.5)	23 (71.9)
	Absent	2 (12.5)	9 (28.1)
Bone erosion	Present	8 (50.0)	14 (43.8)
	Absent	8 (50.0)	18 (56.3)
Bone proliferation	Present	4 (25.0)	3 (9.4)
	Absent	12 (75.0)	29 (90.6)
Week 52			
n		14*	29
Inflammation of synchondrosis	Present	5 (35.7)	12 (41.4)
	Absent	9 (64.3)	17 (58.6)
Bone marrow oedema/osteitis	Present	9 (64.3)	19 (65.5)
	Absent	5 (35.7)	10 (34.5)
Soft tissue swelling/oedema	Present	9 (64.3)	13 (44.8)
	Absent	5 (35.7)	16 (55.2)
Bone erosion	Present	7 (50.0)	13 (44.8)
	Absent	7 (50.0)	16 (55.2)
Bone proliferation	Present	2 (14.3)	2 (6.9)
	Absent	12 (85.7)	27 (93.1)
Region: Other than anterior chest			
Baseline			
n		3	10
Spine			
Spondylodiscitis	Present	0	4 (40.0)
	Absent	1 (33.3)	3 (30.0)
	NA	2 (66.7)	3 (30.0)
Bone marrow oedema/osteitis	Present	1 (33.3)	6 (60.0)
	Absent	0	1 (10.0)
	NA	2 (66.7)	3 (30.0)
Paravertebral soft tissue swelling/oedema/mass	Present	0	2 (20.0)
	Absent	1 (33.3)	5 (50.0)
	NA	2 (66.7)	3 (30.0)
Bone proliferation	Present	1 (33.3)	1 (10.0)
	Absent	0	6 (60.0)
	NA	2 (66.7)	3 (30.0)
Week 52			
n		2*	8
Spondylodiscitis	Present	0	1 (12.5)
	Absent	1 (50.0)	5 (62.5)
	NA	1 (50.0)	2 (25.0)
Bone marrow oedema/osteitis	Present	0	3 (37.5)
	Absent	1 (50.0)	3 (37.5)
	NA	1 (50.0)	2 (25.0)

Table 3 *Continued*

		Placebo	Guselkumab
Paravertebral soft tissue swelling/oedema/mass	Present	0	0
	Absent	1 (50.0)	6 (75.0)
	NA	1 (50.0)	2 (25.0)
Bone proliferation	Present	1 (50.0)	2 (25.0)
	Absent	0	4 (50.0)
	NA	1 (50.0)	2 (25.0)

Region other than the anterior chest included the foot, thumb, clavicle, cervical spine 2, lumber spine and sacroiliac joint 7. Values are presented as *n* (%).
MRI, magnetic resonance imaging; *n*, number of patients; NA, not applicable.
*Patients in placebo group crossed over to receive guselkumab 100 or 200 mg starting at week 16.

Table 4 Change from baseline in EQ-5D index score at week 52 in pustulotic arthro-osteitis patients and non-pustulotic arthro-osteitis patients

	Placebo	Guselkumab
PAO patients		
Baseline, *n*	21	45
	0.73 (0.20)	0.64 (0.21)
Week 52, *n*	18*	40
	0.92 (0.09)	0.84 (0.14)
Change from baseline at week 52	0.14 (0.13)	0.20 (0.17)
Non-PAO patients		
Baseline, n	32	61
	0.72 (0.22)	0.75 (0.19)
Week 52, n	29*	51
	0.86 (0.13)	0.93 (0.09)
Change from baseline at week 52	0.16 (0.22)	0.15 (0.17)

Values are presented as mean (SD). Patients in placebo group crossed over to receive guselkumab 100 mg or 200 mg starting at week 16. Data were analysed based on the observed data by randomized treatment group at week 0.
EQ-5D, EuroQOL-5 dimensions questionnaire; *n*, number of patients; PAO, pustulotic arthro-osteitis.
*Patients in placebo group crossed over to receive guselkumab 100 or 200mg starting at week 16.

week 52 showed relatively mild improvements in their EQ-5D pain/discomfort dimension scores (Table 5, Fig. 4).

C-reactive protein At week 52, the mean (SD) change in CRP level from baseline among all PAO patients was −1.7 (8.2) for the guselkumab group (Table 7). The mean (SD) change in CRP level from baseline was −2.0 (12.3) among patients in the guselkumab group with an improved MRI score at week 52 and −0.9 (1.6) in patients with an unchanged MRI score at week 52 (Table 7). In all PPP patients, baseline CRP level and change from baseline in CRP level at week 52 were 3.1 (5.48) and −0.64 (5.34), respectively, which were slightly lower than that of PAO patients.

Discussion

To date, the literature for PAO is sparse, limited mostly to case reports or small case series, and there is a lack of well-documented clinical studies.[4,10,12,36,37] In a study including 10 patients with PAO treated weekly with granulocyte and monocyte adsorption apheresis over 5 weeks, improvement in joint symptoms in 5/10 patients was demonstrated.[38] Some working groups have considered PPP to be closely related to psoriasis rather than a separate disease; however, a recently published study suggests PPP to be a distinct entity.[39] In addition to skin manifestation, clinical features of PAO observed in this study suggest difference between PAO and PsA. In PsA, the involvement of small distal joints is higher than anterior chest, which is consistent with previously published study.[6] In this exploratory analysis, 41.5% of patients enrolled in a Japanese clinical trial for guselkumab in PPP were diagnosed with concomitant PAO. The efficacy of guselkumab for the treatment of PAO with the context of PPP was demonstrated based on improvement in MRI score at week 52. Specifically, improvements in inflammatory indicators including, bone marrow oedema/osteitis and soft tissue swelling/oedema were observed by MRI at week 52. Moreover, structural changes including, bone erosion and bone proliferation, when present did not show evidence of progression. Taken together, these findings indicate that guselkumab attenuates inflammation in affected joint in patients with PAO.

Improvements in another endpoint, the EQ-5D index were observed at week 52 compared to baseline, indicating improvement of quality of life among PAO patients receiving guselkumab treatment. Pain is one of the most characteristic clinical symptoms associated with PAO, and baseline EQ-5D pain/discomfort dimension scores suggested that patients with PAO suffered from greater pain than patients without PAO. Improvements in EQ-5D pain/discomfort dimension scores were observed at week 16 in all the treatment groups, and the magnitude of improvement was numerically greater in the guselkumab group compared with the placebo group. Also, slightly greater improvements in EQ-5D pain/discomfort scores were observed among patients with improved MRI scores compared to patients with unchanged MRI scores suggesting a correlation between symptoms characteristic of PAO and more objective MRI findings.

Table 5 EQ-5D pain/discomfort dimension score from baseline through week 52 in patients with pustulotic arthro-osteitis

	Placebo	Guselkumab
All PAO patients		
n	21	45
Baseline		
No pain/discomfort (1)	3 (14.3)	0
Slight pain/discomfort (2)	4 (19.0)	13 (28.9)
Moderate pain/discomfort (3)	8 (38.1)	12 (26.7)
Severe pain/discomfort (4)	5 (23.8)	16 (35.6)
Extreme pain/discomfort (5)	1 (4.8)	4 (8.9)
No or slight pain/discomfort (1, 2)	7 (33.3)	13 (28.9)
Moderate or above pain/discomfort (3, 4, 5)	14 (66.7)	32 (71.1)
Week 16		
n	19	45
No pain/discomfort (1)	3 (15.8)	10 (22.2)
Slight pain/discomfort (2)	6 (31.6)	23 (51.1)
Moderate pain/discomfort (3)	6 (31.6)	5 (11.1)
Severe pain/discomfort (4)	2 (10.5)	6 (13.3)
Extreme pain/discomfort (5)	2 (10.5)	1 (2.2)
No or slight pain/discomfort (1, 2)	9 (47.4)	33 (73.3)
Moderate or above pain/discomfort (3, 4, 5)	10 (52.6)	12 (26.7)
Week 52		
n	18*	40
No pain/discomfort (1)	8 (44.4)	13 (32.5)
Slight pain/discomfort (2)	9 (50.0)	22 (55.0)
Moderate pain/discomfort (3)	1 (5.6)	2 (5.0)
Severe pain/discomfort (4)	0	3 (7.5)
Extreme pain/discomfort (5)	0	0
No or slight pain/discomfort (1, 2)	17 (94.4)	35 (87.5)
Moderate or above pain/discomfort (3, 4, 5)	1 (5.6)	5 (12.5)
Patients with improved MRI score at week 52		
Baseline		
n	7	16
No pain/discomfort (1)	1 (14.3)	0
Slight pain/discomfort (2)	1 (14.3)	4 (25.0)
Moderate pain/discomfort (3)	3 (42.9)	5 (31.3)
Severe pain/discomfort (4)	2 (28.6)	5 (31.3)
Extreme pain/discomfort (5)	0	2 (12.5)
No or slight pain/discomfort (1, 2)	2 (28.6)	4 (25.0)
Moderate or above pain/discomfort (3, 4, 5)	5 (71.4)	12 (75.0)
Week 52		
n	7*	16
No pain/discomfort (1)	3 (42.9)	6 (37.5)
Slight pain/discomfort (2)	4 (57.1)	10 (62.5)
Moderate pain/discomfort (3)	0	0
Severe pain/discomfort (4)	0	0
Extreme pain/discomfort (5)	0	0
No or slight pain/discomfort (1, 2)	7 (100.0)	16 (100.0)
Moderate or above pain/discomfort (3, 4, 5)	0	0
Patients with unchanged MRI score at week 52		
Baseline		
n	9	20
No pain/discomfort (1)	1 (11.1)	0
Slight pain/discomfort (2)	3 (33.3)	8 (40.0)
Moderate pain/discomfort (3)	4 (44.4)	2 (10.0)
Severe pain/discomfort (4)	1 (11.1)	9 (45.0)
Extreme pain/discomfort (5)	0	1 (5.0)
No or slight pain/discomfort (1, 2)	4 (44.4)	8 (40.0)
Moderate or above pain/discomfort (3, 4, 5)	5 (55.6)	12 (60.0)
Week 52		
n	9*	20
No pain/discomfort (1)	4 (44.4)	7 (35.0)
Slight pain/discomfort (2)	5 (55.6)	9 (45.0)
Moderate pain/discomfort (3)	0	2 (10.0)
Severe pain/discomfort (4)	0	2 (10.0)
Extreme pain/discomfort (5)	0	0
No or slight pain/discomfort (1, 2)	9 (100.0)	16 (80.0)
Moderate or above pain/discomfort (3, 4, 5)	0	4 (20.0)

Values are presented as *n* (%).Data were analysed based on the observed data by randomized treatment group at week 0.
EQ-5D, EuroQOL-5 dimensions questionnaire; MRI, magnetic resonance imaging; *n*, number of patients; PAO, pustulotic arthro-osteitis.
*Patients in placebo group crossed over to receive guselkumab 100 mg or 200 mg starting at week 16.

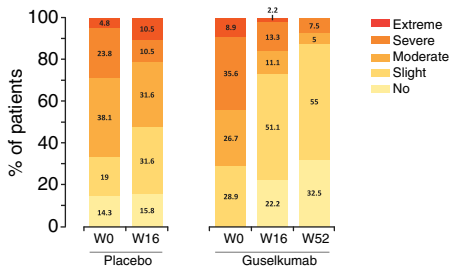

Figure 4 EQ-5D pain/discomfort dimension score from baseline through week 52 in pustulotic arthro-osteitis patients. Note: Patients in placebo group crossed over to receive guselkumab 100 mg or guselkumab 200 mg at week 16 and onwards. EQ-5D, EuroQOL-5 dimensions questionnaire; W0, baseline; W16, week 16; W52, week 52.

In a few case reports, elevated CRP levels were noted among patients with PAO[4,36,37] and lowering in CRP level was associated with alleviating symptoms of PAO. Findings from our study show no clear correlation between improvements in MRI scores and CRP levels. However, a slight decrease in CRP level was observed among PAO patients in the guselkumab group at week 52 compared to baseline, which may reflect changes in inflammatory indicators observed by MRI.

Whether PAO may be considered a seronegative spondyloarthropathy is still controversial. Increased expression of IL-23 mRNA has been reported in the peripheral blood of patients

Table 6 EQ-5D pain/discomfort dimension score from baseline through week 52 in non-pustulotic arthro-osteitis patients

	Placebo	Guselkumab
Baseline		
n	32	61
No pain/discomfort (1)	4 (12.5)	7 (11.5)
Slight pain/discomfort (2)	10 (31.3)	33 (54.1)
Moderate pain/discomfort (3)	8 (25.0)	8 (13.1)
Severe pain/discomfort (4)	8 (25.0)	11 (18.0)
Extreme pain/discomfort (5)	2 (6.3)	2 (3.3)
No or slight pain/discomfort (1, 2)	14 (43.8)	40 (65.6)
Moderate or above pain/discomfort (3, 4, 5)	18 (56.3)	21 (34.4)
Week 16		
n	32	58
No pain/discomfort (1)	6 (18.8)	24 (41.4)
Slight pain/discomfort (2)	16 (50.0)	23 (39.7)
Moderate pain/discomfort (3)	6 (18.8)	8 (13.8)
Severe pain/discomfort (4)	4 (12.5)	3 (5.2)
Extreme pain/discomfort (5)	0	0
No or slight pain/discomfort (1, 2)	22 (68.8)	47 (81.0)
Moderate or above pain/discomfort (3, 4, 5)	10 (31.3)	11 (19.0)
Week 52		
n	29*	51
No pain/discomfort (1)	11 (37.9)	27 (52.9)
Slight pain/discomfort (2)	14 (48.3)	23 (45.1)
Moderate pain/discomfort (3)	3 (10.3)	1 (2.0)
Severe pain/discomfort (4)	1 (3.4)	0
Extreme pain/discomfort (5)	0	0
No or slight pain/discomfort (1, 2)	25 (86.2)	50 (98.0)
Moderate or above pain/discomfort (3, 4, 5)	4 (13.8)	1 (2.0)

Values are presented as *n* (%). Data were analysed based on the observed data by randomized treatment group at week 0.
EQ-5D, EuroQOL-5 dimensions questionnaire; *n*, number of patients.
*Patients in placebo group at week 52 were administrated guselkumab either 100 or 200 mg starting at week 16.

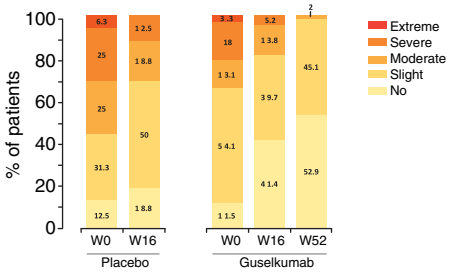

Figure 5 EQ-5D pain/discomfort dimension score from baseline through week 52 in non-pustulotic arthro-osteitis patients. Note: Patients in placebo group crossed over to receive guselkumab 100 mg or guselkumab 200 mg at week 16 and onwards. EQ-5D, EuroQOL-5 dimensions questionnaire; W0, baseline; W16, week 16; W52, week 52.

Table 7 Change from baseline in C-reactive protein (mg/L) at week 52 in patients with pustulotic arthro-osteitis

C-reactive protein (mg/L)	Placebo	Guselkumab
All PAO patients		
Baseline		
n	21	45
Mean (SD)	2.86 (4.92)	4.75 (7.20)
Week 52		
n	18*	40
Mean (SD)	1.80 (2.30)	3.00 (7.08)
Change from baseline at week 52		
n	18*	40
Mean (SD)	−1.45 (4.09)	−1.71 (8.16)
Patients with improved MRI score at week 52		
Baseline		
n	7	16
Mean (SD)	2.36 (2.78)	6.01 (8.25)
Week 52		
n	7*	16
Mean (SD)	1.99 (2.70)	4.00 (10.54)
Change from baseline at week 52		
n	7*	16
Mean (SD)	−0.37 (3.13)	−2.01 (12.30)
Patients with unchanged MRI score at week 52		
Baseline		
n	9	20
Mean (SD)	4.53 (6.93)	2.79 (3.41)
Week 52		
n	9*	20
Mean (SD)	1.96 (2.28)	1.86 (2.67)
Change from baseline at week 52		
n	9*	20
Mean (SD)	−2.58 (5.03)	−0.93 (1.62)

Values are presented as mean (SD).
MRI, magnetic resonance imaging; *n*, number of patients; PAO, pustulotic arthro-osteitis SD, standard deviation.
*Patients in placebo group crossed over to receive guselkumab 100 or 200 mg starting at week 16.

with ankylosing spondylitis (AS);[40] however, another study has reported no correlation between IL-23 expression and disease activity.[41] These studies suggest that the expression of IL-23 at the site of disease activity may be important. Further still, ustekinumab (an anti-IL-12/IL-23 p40 monoclonal antibody),[42] and guselkumab (an anti-IL-23 p19 monoclonal antibody)[29,31] have demonstrated efficacy in treating PsA, and secukinumab (a monoclonal antibody that targets IL-17A that may be produced in response to the stimulation of IL-23)[43] is effective in treating both PsA and AS. These observations corroborate the involvement of the Th17/IL-23 pathway in these conditions. Findings observed in this exploratory analysis support the role of the IL-23 pathway in PAO and that by targeting the IL-23 pathway,

guselkumab can be effective in reducing and preventing worsening of PAO signs and symptoms in patients with PPP.

Of note, this study is subject to 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. In particular, as MRI assessments were only performed at baseline and at week 52, no comparisons between guselkumab and placebo for improvement in MRI-based features of PAO were feasible. EQ-5D pain/discomfort dimension is not a bone/joint-specific measurement and may be influenced by skin-associated symptoms in the context of PPP. Furthermore, there are no established or validated efficacy endpoints specific for assessing severity or change in disease activity for PAO. Lastly, this was a secondary substudy and the overall number of patients included in the analysis was small.

Conclusion

In this exploratory analysis, guselkumab treatment resulted in improvement of PAO signs and symptoms in Japanese patients treated for concomitant PPP. These findings suggest that guselkumab has potential as a novel therapeutic option for treating PAO for both Japanese patients and patients worldwide with PAO.

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Author contributions

TY, AM, and TT were investigators, and KF was MRI central reader. TK and HM had primary roles in the study design, results assessment and data interpretation as clinical lead for the study. RZ was involved in data analysis. All authors contributed to the data interpretation for the results. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to publish these data and approved submission to this journal.

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