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Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study*

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Conflicts of interest
K.Y. serves as a consultant and speaker for Maruho Co. Ltd and is an investigator and speaker for Kyowa Hakko Kirin Co. Ltd, Janssen Pharmaceutical K.K. and Torii Pharmaceutical Co. Ltd, and is an investigator for MSD K.K. and a speaker for Mitsubishi-Tanabe Pharma, Galderma, Shionogi & Co. Ltd, POLA Pharma, GlaxoSmithKline K.K., AbbVie, Novartis Pharma K.K. and LEO Pharma. H.N. is a consultant and/or has received research grants and/or speaker honoraria from Kyowa Hakko Kirin Co. Ltd, AbbVie, Mitsubishi-Tanabe Pharma, Janssen Pharmaceutical K.K., Eli Lilly Japan K.K., LEO Pharma, Maruho Co. Ltd and MSD K.K. Y.K. has received research grants and speaker honoraria from Kyowa Hakko Kirin Co. Ltd. K.O. is an employee of Kyowa Hakko Kirin Co. Ltd.

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Summary

Background A T-helper (Th) cell subset Th17 preferentially produces interleukin (IL)-17 and plays a pivotal role in the pathogenesis of psoriasis. However, the pathological roles of IL-17 cascades in generalized pustular psoriasis (GPP) and psoriatic erythroderma (PsE) have not been well established.

Objectives To evaluate the efficacy and safety of brodalumab, a human immunoglobulin G2 monoclonal antibody against human IL-17-receptor A (IL-17RA), in Japanese patients with GPP and PsE.

Methods This was an open-label, multicentre, long-term phase III study in Japanese patients with rare and severe types of psoriasis. Patients received brodalumab 140 mg at day 1 and weeks 1 and 2, and then every 2 weeks until week 52. The primary endpoint was the Clinical Global Impression of Improvement (CGI). Safety evaluations included treatment-emergent adverse events (AEs) and changes in laboratory parameters.

Results A total of 12 patients with GPP and 18 with PsE were enrolled. Ten patients with GPP and 16 with PsE completed the study. At week 52 (last observation carried forward), CGI remission or improvement was achieved in 11 patients with GPP and 18 with PsE. The most commonly reported AE was nasopharyngitis (33·3%). Five serious AEs occurred during the study. However, none was considered treatment-related.

Conclusions Brodalumab significantly improved the symptoms of patients with GPP and PsE throughout the 52 weeks, and demonstrated favourable safety profiles without any new safety signals. Inhibition of IL-17RA-mediated signalling by brodalumab is expected to be a promising new treatment option for patients with GPP and PsE.

What's already known about this topic?

- The pathological roles of interleukin (IL)-17 cascades in severe types of psoriasis including generalized pustular psoriasis (GPP) and psoriatic erythroderma (PsE) have not been well established.

What does this study add?

- Brodalumab significantly improved the symptoms of patients with GPP and PsE throughout the 52 weeks and demonstrated favourable safety profiles without any new safety signals.

- Brodalumab is expected to be a promising new treatment option for patients with GPP and PsE by blocking IL-17-receptor A-mediated signalling.

Psoriasis is a chronic inflammatory skin disease characterized histologically by hyperproliferation and abnormal differentiation of keratinocytes and inflammatory cell infiltration. Generalized pustular psoriasis (GPP) is the most severe type, producing sterile pustules over a wide area of the body and occasionally causing fatal systemic symptoms. It is characterized by repeating recurrence or worsening.[1] Psoriatic erythroderma (PsE) is another severe form characterized by diffuse redness and scaling covering nearly the whole body, potentially leading to fatal symptoms.

T-helper (Th) 17 cells preferentially produce interleukin (IL)-17, and IL-17A, IL-17F, IL-17A/F heterodimer and IL-17E (IL-25) share a common receptor subunit, IL-17 receptor A (IL-17RA), for intracellular signalling. Excessive IL-17 signalling is thought to play an important role in the pathogenesis of psoriasis.[2] In patients with GPP and PsE, increased Th17 cells and elevated IL-17 levels are also reported.[3–7]

Brodalumab is a Chinese hamster ovary cell-derived human immunoglobulin G2 monoclonal antibody against human IL-17RA that blocks the biological activities of IL-17. Findings from phase II and III studies of brodalumab in the U.S.A., Europe and other countries showed significant improvements in plaque psoriasis and psoriatic arthritis.[8–13] However, the efficacy and safety of IL-17RA blockade in the severe forms of psoriasis (GPP and PsE) have not been established. The aim of this study is to validate the efficacy and safety of brodalumab in Japanese patients with GPP or PsE.

Methods

Study design

This study was a phase III, open-label multicentre study in patients with GPP or PsE. Patients received subcutaneous injections of brodalumab 140 mg at day 1, weeks 1 and 2, and thereafter every 2 weeks until week 52. Patients were allowed to increase the dose to 210 mg at week 4 and beyond if the Pustular Symptom Score (PSS) in patients with GPP was rated as moderate or severe (Table 1) and if patients with PsE did not achieve ≥ 50% reduction of the Psoriasis Area and Severity Index (PASI) scores. Patients who received an increased dose of 210 mg were not allowed to return to 140 mg. This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. The institutional review boards at each study site approved the study protocol. Each patient provided written informed consent before participating. The first patient provided written informed consent on 15 January 2013, and the last patient last visit was on 21 May 2014.

Patients

Patients at least 18 years of age were eligible for the study if they met the diagnostic criteria provided in the therapeutic guidelines for the treatment of GPP in Japan (Table 2)[1] or had a diagnosis of PsE with more than 80% body surface area (BSA) involvement at baseline.[14] Enrolment required negative test results for hepatitis B virus surface antigen, hepatitis C virus antibodies, human immunodeficiency virus antigen and antibodies, human T-cell lymphotropic virus type-1 antibodies, and tuberculosis. Patients were excluded if they had guttate psoriasis or drug-induced PsE, or if they had experienced serious infections in the 8 weeks prior to signing the informed consent form, congestive heart failure (New York Heart Association class II, III or IV), myocardial infarction or unstable angina pectoris within the preceding year, or if they had an active malignancy or a history of malignancy within 5 years prior to consent.

Patients were excluded if they had received treatment with ustekinumab within 12 weeks, infliximab within 8 weeks,

Table 1 Pustular symptom score evaluation

Severity classification	Mild	Moderate		Severe
A + B (combined scores)	0–6	7–10		11–17
A. Skin symptoms (total scores; 0–9)				
Scores	3	2	1	0
Erythematous area (BSA %)	≥ 75	≥ 25, < 75	< 25	0
Erythematous area with pustule (BSA %)	≥ 50	≥ 10, < 50	< 10	0
Oedematous area (BSA %)	≥ 50	≥ 10, < 50	< 10	0
B. Systemic symptoms and laboratory findings (total scores; 0–8)				
Scores	2	1		0
Fever (°C)	≥ 38·5	≥ 37·0 to < 38·5		< 37·0
White blood cell count (μL^{-1})	≥ 15 000	≥ 10 000 to < 15 000		< 10 000
CRP (mg dL^{-1})	≥ 7·0	≥ 0·3 to < 7·0		< 0·3
Serum albumin (g dL^{-1})	< 3·0	≥ 3·0 to < 3·8		≥ 3·8

BSA, body surface area (0–100); CRP, C-reactive protein.

Table 2 Diagnostic and exclusion criteria in Japan for generalized pustular psoriasis (GPP)

Criteria
Diagnostic criteria
1. Systemic symptoms such as fever and general malaise are present
2. Multiple, aseptic pustules are present in flushed skin over the whole body or over a wide area. Occasionally, several small pustules fuse together, forming a larger confluent pustule
3. Neutrophilic subcorneal pustular dermatosis, which is characterized by the Kogoj's spongiform pustules, is confirmed histopathologically
4. Recurrence of the above-listed clinical and histological findings
The diagnosis of absolute GPP is made if all the above criteria are met; the diagnosis of suspected GPP is made if criteria 2 and 3 are met. In the case of new-onset GPP, the following diseases can be excluded by the clinical course:
Exclusion criteria
1. As a general rule, the diagnosis of GPP should not be made in patients who have an apparent history of previous psoriasis vulgaris that has become transiently pustular due to adrenocorticosteroid hormones or other drugs or due to withdrawal of these drugs. However, its diagnosis may be made at the discretion of a dermatologist if he or she closely monitors the patient for a designated period of time and finds that pustulation takes place repeatedly and readily in the patient
2. The type classified as 'circinate annular form' is excluded as it is generally associated with minimal systemic symptoms. The diagnosis of GPP should be made only in patients in whom the condition has clearly progressed to GPP
3. The diagnosis of GPP should not be made if the diagnosis of subcorneal pustular dermatosis or pustular-type drug eruption (including acute generalized exanthematous pustulosis) is confirmed as a result of close monitoring for a designated period of time

psoralen plus ultraviolet (UV) A light therapy within 4 weeks, adalimumab or UVB phototherapy within 2 weeks, etanercept or granulocytapheresis within 1 week, or if they had received another anti-IL-17 antibody before starting the study. The use of ciclosporin was not allowed during the study. The use of methotrexate, vitamin A preparations, and/or oral steroids was allowed provided the patient had been using such medication(s) since before starting the study. Dose reduction of these drugs was allowed as well; however, dose increase after dose reduction was limited to the level at the start of the study.

Efficacy assessments

The primary endpoint of this trial was the Clinical Global Impression of Improvement (CGI). CGI was evaluated by the investigators on a four-point scale (remission, improved, no change, worsened) based on changes from the baseline findings of psoriasis.

Secondary endpoints included the percentage improvement in PASI scores from baseline. In the patients with PsE, the proportion of patients with a static Physician's Global Assessment (sPGA) of 0 or 1 and a change in BSA involvement were also evaluated. The severity of patients with GPP was evaluated according to the PSS provided in the 2010 therapeutic guidelines for GPP treatment by the Japanese Research Team on Intractable Skin Diseases, based on skin symptoms (erythematous area, erythematous area with pustule, oedematous area) and systemic symptoms/laboratory findings (fever, white blood cell count, C-reactive protein, serum albumin) (Table 1).[1] Severity was evaluated at each visit, with the total score (0–17) determined [0–6 (mild), 7–10 (moderate), 11–17 (severe)].

Explanatory endpoints included the Nail Psoriasis Severity Index (NAPSI), the Psoriasis Scalp Severity Index (PSSI) and patient-reported outcomes. NAPSI and PSSI evaluations were performed only in patients who had symptoms at baseline. Patient-reported outcomes included the Dermatology Life Quality Index (DLQI),[15] the Psoriasis Disability Index (PDI),[16] and the 36-item Short Form Health Survey (SF-36).[17] Photographic records of lesions were taken from patients who gave informed consent.

Safety assessments

Safety evaluations included adverse events (AEs), serious AEs (SAEs), and changes in laboratory parameters. The Common Terminology Criteria for Adverse Events version 4.0 was used to grade AE severity. Frequencies of all AEs that occurred or worsened after the start of the study were analysed by both preferred term and system organ class as described in the Japanese version of the International Conference on Harmonisation medical dictionary for regulatory activities, version 17.0.

Pharmacokinetics and antidrug antibody assays

Serum concentrations of brodalumab were measured at baseline, and at weeks 2, 4, 8, 12, 24 and 48. Pharmacokinetic parameters, including the time to peak concentration (t_{max}), peak concentration (C_{max}) and the area under the concentration–time curve over the dosing interval ($AUC_{0-\tau}$) for weeks 8–10 were calculated with additional pharmacokinetic sampling data from patients who had given consent. Serum anti-brodalumab-binding antibody levels were measured at baseline, and at weeks 4, 12, 24, 36 and 52 or discontinuation. If the binding antibody was detected, neutralizing activity was also measured.

Data and statistical analysis

The CGI was summarized by the number and percentage of patients for each scale. The number and percentage of patients classified as 'improved' or 'remission' were also determined. On secondary and explanatory endpoints, categorical data were expressed in terms of frequency and percentage of

patients, while continuous variables were summarized in terms of summary statistics (number of patients, mean, standard deviation, minimum, median and maximum). Missing values were not imputed and were analysed as observed. In addition to observed case analysis, last observation carried forward (LOCF) analysis was utilized for week 52. Given the very small number of patients with GPP or PsE in Japan, the target number of patients was set to be at least eight, with at least four patients with each disease.

Results

Patient disposition and baseline characteristics

Thirty-two patients gave written informed consent. Twelve patients with GPP and 18 patients with PsE were enrolled (Fig. 1); two were excluded by the exclusion criteria. Twenty-six patients completed the evaluation at week 52. Four patients were discontinued: two patients with GPP because of AE and investigators' discretion owing to worsening symptoms, and two patients with PsE because of AE and pregnancy. Dosages for three patients with GPP and five patients with PsE were increased to 210 mg according to the investigators' decision. Patient demographics and other baseline clinical characteristics are shown in Table 3.

Efficacy

Efficacy results at week 12 and week 52 (LOCF) are shown in Table 4. In patients with GPP, nine of 12 (75·0%) and 10 of 12 (83·3%) achieved a CGI classified as 'improved' or 'remission' at week 2 and at week 12, respectively. At week 52 (LOCF), 11 of 12 (91·7%) achieved 'improved' or 'remission' (Fig. 2a). In patients with PsE, 17 of 18 (94·4%) and 18 of 18 (100%) achieved a CGI classified as 'improved' or 'remission' at week 2 and at week 12, respectively. At week 52 (LOCF), 18 of 18 (100%) were classified as 'improved' or 'remission' (Fig. 2b). Representative photographs of a patient with GPP and one with PsE are shown in Figures 2c,d.

In patients with GPP, the PSS (0–17) was 'mild' (0–6) in 10 of 12 (83·3%) and 'moderate' (7–10) in two of 12 (16·7%) at baseline. After brodalumab treatment, four of 12 (33·3%) had a score of 1 at week 2. At week 12, three of 12 (25·0%) had a score of 0 and five of 12 (41·7%) had a score of 1. At week 52 (LOCF), six of 12 (50·0%) had a score of 0, five of 12 (41·7%) had a score of 1, and one of 12 (8·3%) had a score of 5. Changes in PSS are shown in Figure 3a.

Changes in PASI scores over time are shown in Figure 3b. Among the patients with PsE, the mean PASI score improvement was 48·03% at week 2 and 85·06% at week 12. At week 52 (LOCF), the average PASI score improvement including two discontinued cases was 93·41%. Both PASI 75 and PASI 90 achievement rates at week 52 (LOCF) were 88·9% (Table 4). PASI 100 response was 61·1% at week 52 (LOCF). PASI 75, PASI 90 and PASI 100 achievement rates for patients with GPP are shown in Figure 4a. The percentage of patients with PsE with sPGA of 0 or 1 increased over time after brodalumab treatment, with five of 18 (27·8%) at week 2, 12 of 18 (66·7%) at week 12 and 16 of 18 (88·9%) at week 52 (LOCF).

Other efficacy assessment results are shown in Table 4. Mean BSA improvement was 72·70% at week 12 and 84·61% at week 52 (LOCF) in PsE. At week 52 (LOCF), the change in DLQI score was −5·5 and −6·1 in GPP and PsE, respectively. At week 52 (LOCF), 66·7% of patients with GPP and 88·9% of patients with PsE reported a DLQI total score of '0 or 1'.

Two patients with GPP and five with PsE had been using vitamin A preparations since before starting the study. Of these patients, one patient with GPP and four with PsE discontinued the treatment with vitamin A preparations after brodalumab administration.

Safety and adverse events

Incidences of AEs are summarized in Table 5. Of the 30 patients, AEs occurred in 11 of 12 (91·7%) patients with GPP and in 17 of 18 (94·4%) of patients with PsE. Among patients with GPP and PsE, the most common AE was nasopharyngitis in four of 12 (33·3%) and six of 18 (33·3%) of patients with GPP and PsE, respectively. There were no AEs leading to death.

Serious adverse events occurred in five patients: three of 12 patients with GPP (lumbar vertebral fracture, exacerbation of pustular psoriasis and hepatocellular carcinoma) and two of

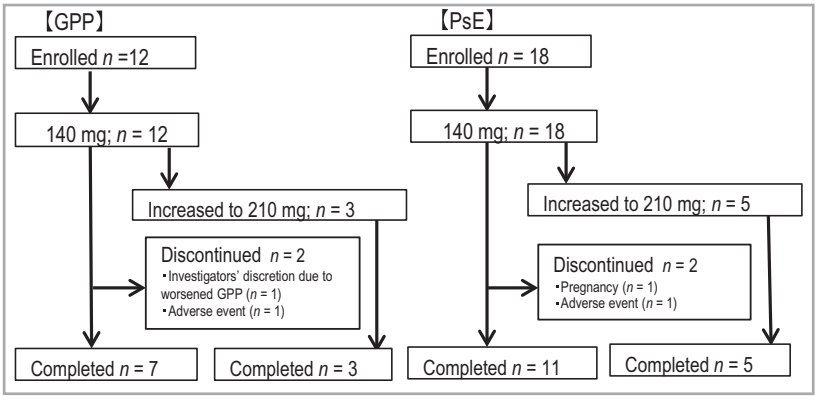

Fig 1. Patient disposition chart. GPP, generalized pustular psoriasis; PsE, psoriatic erythroderma

Table 3 Baseline demographics and clinical characteristics

	GPP (N = 12)	PsE (N = 18)	All (N = 30)
Age (years), mean (± SD)	43·1 (± 16·8)	50·8 (± 12·2)	47·7 (± 14·5)
Sex (male), n (%)	3 (25·0)	14 (77·8)	17 (56·7)
Body weight (kg), mean (± SD)	58·57 (± 16·69)	65·75 (± 12·16)	62·88 (± 14·33)
BMI (kg m^{-2}), mean (± SD)	22·54 (± 5·46)	24·33 (± 4·89)	23·62 (± 5·11)
Duration of disease (years), mean (± SD)	6·56 (± 7·20)	6·37 (± 10·12)	NA
Prior systemic therapy – nonbiologics, n (%)	10 (83·3)	14 (77·8)	24 (80·0)
Ciclosporin, n (%)	10 (83·3)	10 (55·6)	20 (66·7)
Retinoid, n (%)	8 (66·7)	9 (50·0)	17 (56·7)
Steroid, n (%)	6 (50·0)	3 (16·7)	9 (30·0)
Methotrexate, n (%)	1 (8·3)	4 (22·2)	5 (16·7)
Other, n (%)	0	2 (11·1)	2 (6·7)
Phototherapy, n (%)	8 (66·7)	17 (94·4)	25 (83·3)
UVB treatment, n (%)	6 (50·0)	12 (66·7)	18 (60·0)
PUVA treatment, n (%)	4 (33·3)	10 (55·6)	14 (46·7)
Prior biologics, n (%)	6 (50·0)	2 (11·1)	8 (26·7)
Adalimumab, n (%)	2 (16·7)	2 (11·1)	4 (13·3)
Infliximab, n (%)	6 (50·0)	1 (5·6)	7 (23·3)
Ustekinumab, n (%)	2 (16·7)	0	2 (6·7)
Plaque psoriasis in the past or complication, n (%)	7 (58·3)	NA	NA
PASI score, mean (± SD)	15·01 (± 12·08)	36·10 (± 13·11)	27·66 (± 16·32)
PSS, mean (± SD)	4·4 (± 2·4)	NA	NA
sPGA			
0 (clear), n (%)	NA	0	NA
1 (minimal), n (%)	NA	1 (5·6)	NA
2 (mild), n (%)	NA	5 (27·8)	NA
3 (moderate), n (%)	NA	3 (16·7)	NA
4 (severe), n (%)	NA	3 (16·7)	NA
5 (very severe), n (%)	NA	6 (33·3)	NA
BSA involvement (%), mean (± SD)	NA	87·94 (± 4·60)	NA
NAPSI, mean score (± SD), n	10·8 (± 7·9), 4	6·2 (± 3·3), 13	7·2 (± 4·9), 17
PSSI, mean score (± SD), n	16·7 (± 13·0), 9	35·4 (± 18·2), 18	29·1 (± 18·7), 27
DLQI, mean score (± SD)	7·9 (± 5·5)	7·1 (± 6·8)	7·4 (± 6·2)
PDI, mean score (± SD)	11·2 (± 8·8)	14·2 (± 8·4)	13·0 (± 8·5)
SF-36			
Physical component, mean score (± SD)	45·16 (± 14·62)	48·99 (± 12·03)	47·46 (± 13·02)
Mental component, mean score (± SD)	48·60 (± 9·96)	47·94 (± 11·19)	48·20 (± 10·54)

BSA, Body surface area (0–100); BMI, body mass index; DLQI, Dermatology Life Quality Index (0–30); GPP, generalized pustular psoriasis; NA, not assessed; NAPSI, Nail Psoriasis Severity Index (0–32); PASI, Psoriasis Area and Severity Index (0–72); PDI, Psoriasis Disability Index (0–45); PSS, Pustular Symptom Score (0–17); PsE, psoriatic erythroderma; PSSI, Psoriasis Scalp Severity Index (0–72); PUVA, psoralen plus ultraviolet A light therapy; SF-36, 36-item Short Form Health Survey from the Medical Outcomes Study (0–100); sPGA, static Physician's Global Assessment (0–5); UVB, narrowband ultraviolet B therapy.

18 patients with PsE (ectopic pregnancy and prostate cancer), but only hepatocellular carcinoma and prostate cancer led to study discontinuation. The 'prostate cancer' was noted on day 148 in a 75-year-old male patient with PsE. The investigator judged that the event was 'not related' to brodalumab and was likely developed naturally given the patient's age and dietary style. The 'hepatocellular carcinoma' was noted on day 261 in a 70-year-old female patient with GPP. The investigator judged that the event was 'not related' to brodalumab given the history of hepatitis B, long-term treatment with concomitant drugs and the patient's age. The 'lumbar vertebral fracture' occurred on day 23 in a 39-year-old male patient with GPP who used topical/oral steroids for the treatment of psoriasis and had osteoporosis as a concomitant disease. The 'exacerbation of pustular psoriasis' event of a 36-year-old male patient on day 225 stabilized after the brodalumab dose was increased to 210 mg on day 225 and resolved on day 242. The 'ectopic pregnancy' was noted on day 132 in a

Table 4 Efficacy result at week 12 and week 52 (LOCF)

	GPP (N = 12)		PsE (N = 18)		All (N = 30)	
Efficacy endpoints	Week 12	Week 52 (LOCF)[a]	Week 12	Week 52 (LOCF)[a]	Week 12	Week 52 (LOCF)[a]
CGI						
Remission, n (%)	3 (25·0)	7 (58·3)	3 (16·7)	12 (66·7)	6 (20·0)	19 (63·3)
Remission or improved, n (%)	10 (83·3)	11 (91·7)	18 (100·0)	18 (100·0)	28 (93·3)	29 (96·7)
PASI score, mean (± SD)	5·24 (± 8·55)	1·83 (± 4·86)	4·34 (± 5·00)	2·02 (± 5·19)	4·70 (± 6·53)	1·94 (± 4·97)
PASI 75, n (%)	7 (58·3)	10 (83·3)	14 (77·8)	16 (88·9)	21 (70·0)	26 (86·7)
PASI 90, n (%)	4 (33·3)	10 (83·3)	9 (50·0)	16 (88·9)	13 (43·3)	26 (86·7)
PASI 100, n (%)	3 (25·0)	7 (58·3)	3 (16·7)	11 (61·1)	6 (20·0)	18 (60·0)
PSS (0 or 1), n (%)	8 (66·7)	11 (91·7)	NA	NA	NA	NA
sPGA clear (0), n (%)	NA	NA	4 (22·2)	12 (66·7)	NA	NA
sPGA clear or almost clear (0 or 1), n (%)	NA	NA	12 (66·7)	16 (88·9)	NA	NA
Improvement in BSA involvement, mean % (± SD)	NA	NA	72·70 ± 18·44	84·61 ± 11·65	NA	NA
NAPSI change from baseline, % (± SD), n	−47·6 (± 36·2), 4	−67·5 (± 39·5), 4	−45·5 (± 30·4), 13	−84·7 (± 26·7), 13	−46·0 (± 30·6), 17	−80·7 (± 29·7), 17
PSSI change from baseline, % (± SD), n	−77·7 (± 25·5), 9	−82·1 (± 43·7), 9	−82·5 (1 ± 37·4), 18	−95·3 (± 15·2), 18	−80·9 (± 33·5), 27	−90·9 (± 27·9), 27
DLQI change from baseline, mean (± SD)	−3·8 (± 6·3)	−5·5 (± 6·6)	−5·1 (± 6·9)	−6·1 (± 6·3)	−4·6 (± 6·6)	−5·8 (± 6·3)
DLQI score (0 or 1), n (%)	4 (33·3)	8 (66·7)	10 (55·6)	16 (88·9)	14 (46·7)	24 (80·0)
PDI change from baseline, mean (± SD)	−5·4 (± 8·0)	−7·8 (± 9·9)	−11·1 (± 7·3)	−11·8 (± 5·9)	−8·8 (± 8·0)	−10·2 (± 7·8)
SF-36 change from baseline						
Physical component, mean (± SD)	2·55 (± 9·60)	0·93 (± 14·29)	2·53 (± 11·31)	3·26 (± 12·60)	2·54 (± 10·49)	2·33 (± 13·11)
Mental component, mean (± SD)	1·50 (± 8·42)	3·13 (± 6·15)	5·03 (± 6·90)	6·23 (± 7·11)	3·62 (± 7·61)	4·99 (± 6·81)

BSA, body surface area (0–100); CGI, Clinical Global Impression of Improvement (1, remission; 2, improved; 3, no change; 4, worsened); DLQI, Dermatology Life Quality Index (0–30); LOCF, Last observation carried forward; NA, not assessed; NAPSI, Nail Psoriasis Severity Index (0–32); PASI, Psoriasis Area and Severity Index (0–72); PDI, Psoriasis Disability Index (0–45); PSS, Pustular Symptom Score (0–17); PSSI, Psoriasis Scalp Severity Index (0–72); SF-36, 36-item Short Form Health Survey from the Medical Outcomes Study (0–100); sPGA, static Physician's Global Assessment (0–5). [a]LOCF analysis was used to impute missing data for week 52.

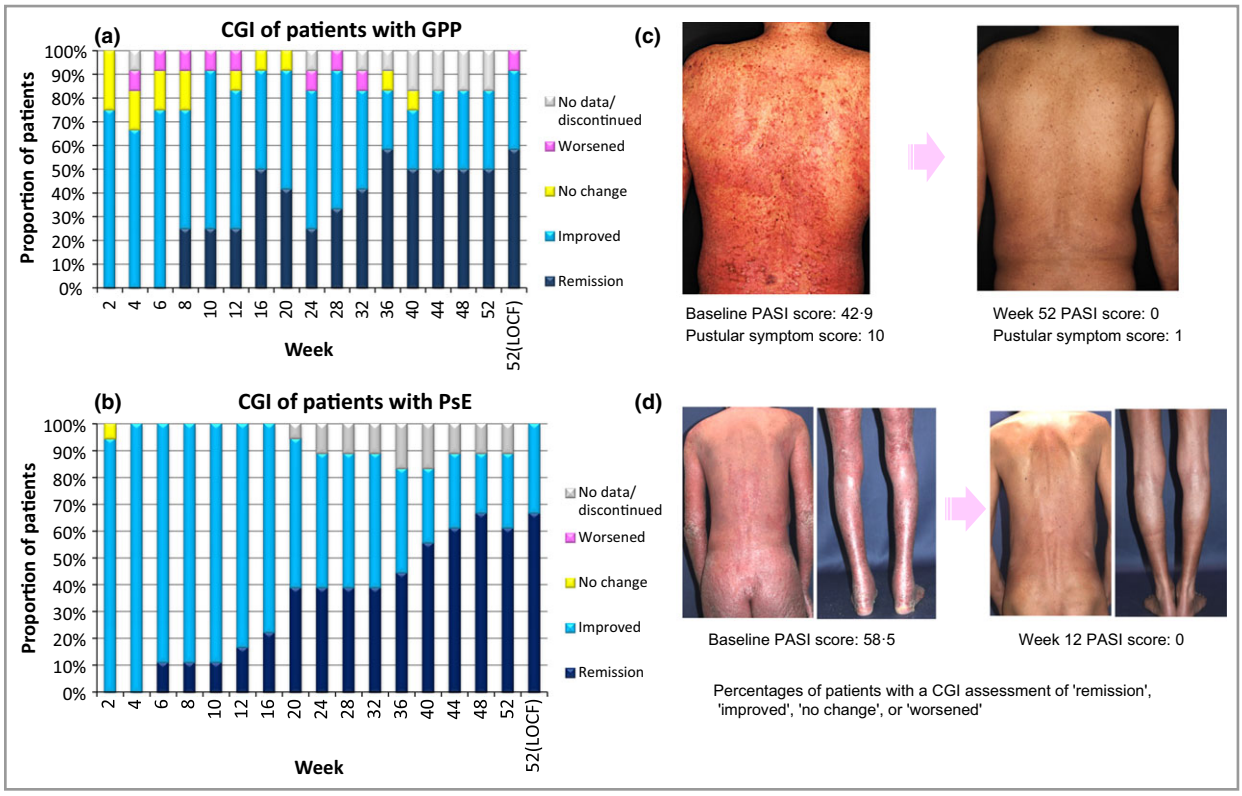

Fig 2. Percentages of patients with a CGI assessment of 'remission', 'improved', 'no change' or 'worsened' at each evaluation time point (symptom change from baseline) for patients with GPP (a) and patients with PsE (b). LOCF analysis was used to impute missing data for week 52. (c) Clinical response to brodalumab 210 mg after 140 mg in a patient with GPP (at baseline and after 52 weeks). (d) Clinical response to brodalumab 140 mg in a patient with PsE (at baseline and after 12 weeks). CGI, Clinical Global Impression of Improvement; GPP, generalized pustular psoriasis; LOCF, last observation carried forward; PsE, psoriatic erythroderma.

35-year-old female patient with PsE. This event was judged initially to be pregnancy and led to study discontinuation. After that, the diagnosis was changed to 'ectopic pregnancy'. None of the SAEs was considered treatment- or protocol-related.

All AEs related to infection were grade 1 or 2 in severity. Grade 3 'neutrophil count decreased' occurred in one of 12 (8·3%) patients with GPP, of which a causal relationship to brodalumab was judged 'not related' by the investigator because the event was accompanied by upper respiratory inflammation. The neutrophil count was 4913 μL^{-1} before the treatment (day 1) and decreased to 818 μL^{-1} on week 12. With the level decreased to < 1000 μL^{-1}, brodalumab was not administered on week 12 as per protocol requirement. Thereafter, the level returned to 7112 μL^{-1} on week 14. Brodalumab was resumed on week 14 and continued up to week 52. Grade 2 'oesophageal candidiasis' occurred in one of 18 (5·6%) patients with PsE and grade 2 'oral candidiasis' occurred in one of 12 (8·3%) patients with GPP. These patients used the concomitant anti-candida medication and completed the study. 'Injection site irritation', 'injection site swelling' and 'injection site macule', were each observed in one of 12 patients with GPP (8·3%). All of these events were grade 1. No suicide-related events occurred. Of the 30 patients, one (3·3%) tested positive for anti-brodalumab-binding antibodies; however, no anti-brodalumab neutralizing antibodies were detected.

Pharmacokinetics

Trough serum concentrations of brodalumab reached a steady state by week 8 and remained nearly constant. The serum concentration–time profiles for weeks 8–10 after multiple 140 mg subcutaneous administrations showed no marked difference between patients with GPP and those with PsE: C_{max} (mean ± SD) was 10·1 ± 9·1 and 11·8 ± 8·6 μg mL^{-1}, $AUC_{0-\tau}$ (mean ± SD) was 92·0 ± 89·9 and 125 ± 108 μg d mL^{-1}, and t_{max} (median) after a dose of 140 mg at week 8 was 2·97 and 1·99 days in GPP (n = 4) and PsE (n = 4), respectively.

Discussion

Generalized pustular psoriasis affects approximately 2000 patients in Japan.[18] Because GPP occasionally causes extensive sterile pustules and fatal systemic symptoms, GPP has been designated as a target disease by the Practical Research Project for Rare/Intractable Diseases (Research Team on Rare and Intractable Skin Diseases), and all patients with GPP in Japan

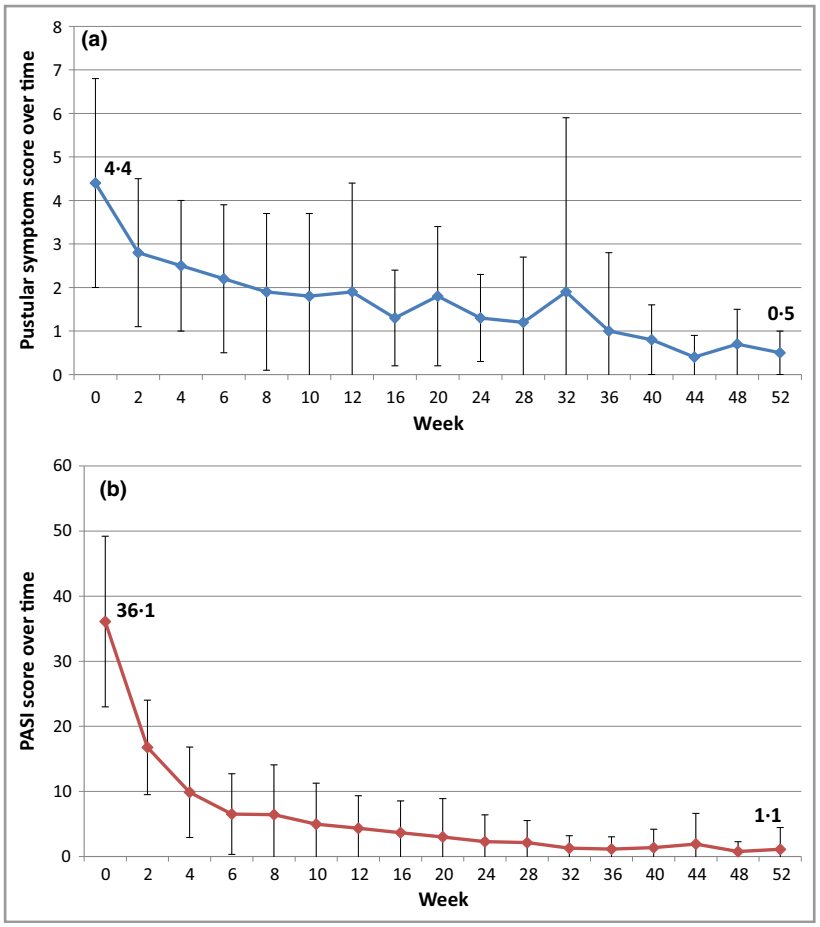

Fig 3. (a) Pustular symptom score over time in patients with generalized pustular psoriasis (mean ± SD). (b) Psoriasis Area and Severity Index (PASI) score over time in patients with psoriatic erythroderma (mean ± SD).

are registered.[19] PsE causes erythema and scaling over a large area of the body, leading to fatal systemic symptoms including depletion of serum proteins. GPP and PsE are rare diseases with each estimated to affect 1% of all patients with psoriasis. Patients with GPP are currently treated with oral medications such as retinoids and ciclosporin or systemic therapies such as anti-tumour necrosis factor (TNF)-α agents, according to the Japanese Guidelines for GPP.[1] Furthermore, only infliximab has been approved for GPP and PsE in Japan so far. Therefore, there is an increasing need for a new treatment option for patients with these two types of severe and treatment-refractory psoriasis.

The IL-17RA-mediated IL-17A signal transduction plays a significant role in plaque psoriasis. Patients with GPP have increased levels of IL-17 and an increased number of IL-17-producing cells in both blood and lesional skin.[3–6] In addition, the skin lesions of PsE show Th17 cell accumulations similar to those of plaque psoriasis.[7] Because brodalumab binds selectively to human IL-17RA and inhibits IL-17RA-mediated signalling, the investigators expected that brodalumab would improve clinical symptoms in GPP and PsE.

In patients with PsE, brodalumab significantly improved the symptoms from early visits, as shown in Figures 3 and 4. As observed in other clinical trials for plaque psoriasis,[8–10,12,13] brodalumab demonstrated robust efficacy against PsE and sustained symptom improvement up to week 52. We set the dose increase criteria in patients with PsE based on the PASI score, not on the primary endpoint CGI, in order to assess disease exacerbation objectively. Five patients with PsE met the dose increase criteria; in these patients, the dose was increased to 210 mg, and these patients improved rapidly at this higher dose.

We primarily evaluated efficacy for patients with GPP by CGI and used PASI as reference information because the percentage improvement in PASI scores from baseline was defined as secondary endpoints in other clinical trials for patients with GPP in Japan.[14,20] Although patients with GPP often experience repeated cycles of systemic and pustular symptoms over the course of a year, brodalumab prevented these symptoms from worsening throughout the study period. The PSS, but not the CGI and PASI scores, was set for the dose increase criteria in patients with GPP because the PSS evaluates general symptoms as well as skin symptoms objectively and because the PASI score is not an optimal instrument for GPP, which often has general symptoms. One patient with GPP with CGI classified as 'worsened' withdrew from the study on day 201. The patient was a 45-year-old female with type 2 diabetes, hyperlipidaemia, and 95·5 kg body weight at baseline. The patient did not meet the dose increase criteria because her PSS was 5 on day 201 and she was switched to another biologic therapy after week 28 without increasing to 210 mg. The other three patients with GPP who met the dose increase criteria experienced symptom improvement at the 210-mg dose.

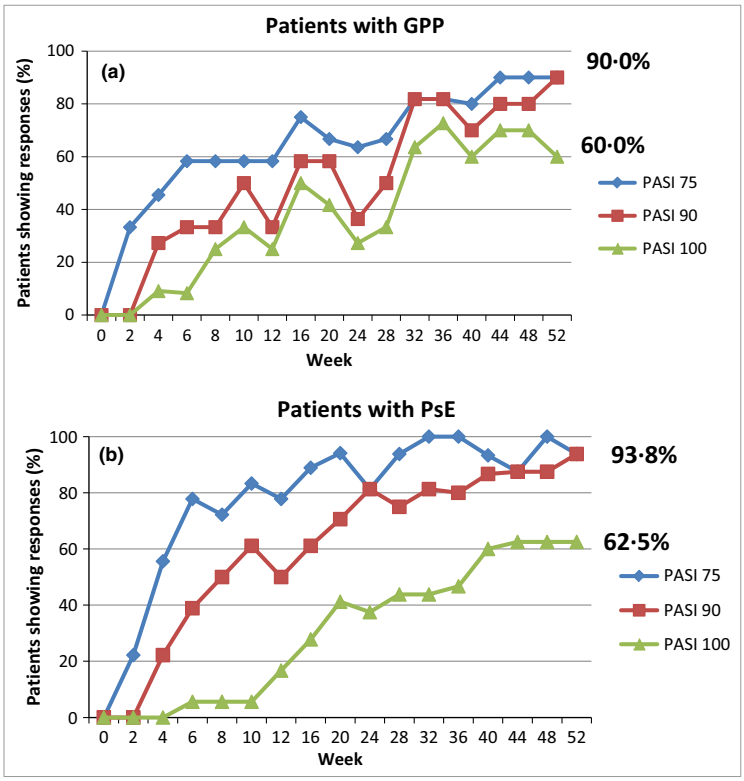

Fig 4. (a) PASI 75, PASI 90 and PASI 100 responses over time for patients with generalized pustular psoriasis (GPP). (b) PASI 75, PASI 90 and PASI 100 responses over time for patients with psoriatic erythroderma (PsE). PASI, Psoriasis Area and Severity Index

Table 5 Incidences of adverse events

	GPP (N = 12)	PsE (N = 18)	All (N = 30)
Adverse events, n (%)			
All	11 (91·7)	17 (94·4)	28 (93·3)
Death	0	0	0
Serious	3 (25·0)	2 (11·1)	5 (16·7)
Common adverse events[a]			
Nasopharyngitis	4 (33·3)	6 (33·3)	10 (33·3)
Diarrhoea	2 (16·7)	1 (5·6)	3 (10·0)
Folliculitis	2 (16·7)	1 (5·6)	3 (10·0)
Skin papilloma	2 (16·7)	1 (5·6)	3 (10·0)
Dry skin	2 (16·7)	1 (5·6)	3 (10·0)
Periarthritis	1 (8·3)	2 (11·1)	3 (10·0)
Dental caries	0	2 (11·1)	2 (6·7)
Tooth fracture	0	2 (11·1)	2 (6·7)
Event of interest			
Neutrophil count decreased	1 (8·3)	0	1 (3·3)
Candidiasis[b]	1 (8·3)	1 (5·6)	2 (6·7)
Injection site reactions[c]	3 (25·0)	0	3 (10·0)

GPP, generalized pustular psoriasis; PsE, psoriatic erythroderma; N, number of patients in the safety analysis set; n, number of patients reporting at least one occurrence of an adverse event. [a]Common adverse events were observed in at least two patients in either the GPP or PsE patient group. [b]Candidiasis includes 'oesophageal candidiasis' and 'oral candidiasis'. [c]Injection site reactions include 'injection site irritation', 'injection site swelling' and 'injection site macule'.

Given the data observed so far, an initial dose of 140 mg might be insufficient for some patients with either of these diseases.

Rapid symptom improvements were observed across all endpoints, with sustained efficacy throughout the study. A DLQI total score of '0 or 1' is important to augment a patient's satisfaction with treatment.[21,22] In this study, 66·7% of patients with GPP and 88·9% of patients with PsE achieved the DLQI total score of '0 or 1' at week 52 (LOCF), which demonstrates that brodalumab improved the quality of life of these patients.

The severity of most AEs was either grade 1 or 2. No particular events raised any concerns of delayed-type AEs, confirming brodalumab's safety and tolerability up to week 52. As reported in other clinical trials,[8–13] the incidence rate of anti-brodalumab antibody development in our trial was very low, and the efficacy was maintained even over long-term administration. Consequently, patient discontinuation due to insufficient efficacy was low. Therefore, brodalumab appears suitable for long-term use in patients with GPP and PsE.

Six patients with GPP and two patients with PsE reported prior treatment with a biologic. In this subgroup, the CGI was assessed as 'improved' or 'remission' in five (83·3%) patients with GPP and two (100%) patients with PsE at week 52 (LOCF). With a pharmacological action different from that of anti-TNF-α agents, brodalumab may be effective for patients with GPP and those with PsE with a prior history of biologics.

Among patients with GPP, four had new-onset GPP, seven had GPP preceded by plaque psoriasis and for one patient this information was not provided. Recent evidence has suggested

that new-onset GPP not preceding plaque psoriasis is attributable to the functional loss or genetic mutation of IL-36 receptor antagonists.[23,24] However, because of higher IL-17 levels in patients with GPP,[3–6] brodalumab showed efficacy for both types of GPP.

Results from this study confirm that brodalumab can improve patient symptoms not long after treatment is initiated. Despite this trial's open-label status and small sample size, these data on rapid onset of action producing an excellent clinical efficacy revealed that Th17 and IL-17 play important and central roles in the pathogenesis of GPP and PsE. Consequently, IL-17RA blocking will be a promising therapeutic target in patients with GPP and PsE. The safety profile and low expression of anti-brodalumab antibody led us to conclude that brodalumab is suitable for long-term use. Although the follow-up period is limited to 52 weeks and longer observation is required for these chronic diseases, the clinical efficacy and safety of brodalumab represent significant values as a new first-line therapeutic option for patients with GPP and PsE.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Video S1. Author video.