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Imsidolimab, an anti-interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis: results from the phase II GALLOP trial

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Abstract

Background Generalized pustular psoriasis (GPP) is a systemic inflammatory disease that can be severe, debilitating and life threatening. Uncontrolled activation of interleukin (IL)-36 proinflammatory activity may underlie the pathogenesis of GPP. Currently, GPP-specific treatment options are limited.

Objectives To evaluate the efficacy and safety of the anti-IL-36 receptor antibody imsidolimab in patients with GPP.

Methods In an open-label, single-arm, multiple-dose study, patients with GPP were treated with imsidolimab to assess clinical efficacy, tolerability and safety. Patients received an intravenous dose of imsidolimab 750 mg on day 1, followed by three subcutaneous doses of imsidolimab 100 mg administered on days 29, 57 and 85. The primary efficacy endpoint was the proportion of patients who achieved a clinical response at weeks 4 and 16 following treatment with imsidolimab, as measured by the Clinical Global Impression scale.

Results Eight patients were enrolled and six completed the study. Responses were observed as early as day 3, most rapidly for pustulation relative to other manifestations of GPP, with continued and consistent improvement across multiple efficacy assessments at day 8, day 29 and through day 113. Most treatment-emergent adverse events (TEAEs) were mild to moderate in severity. No patient discontinued the study owing to a nonserious TEAE. Two patients experienced serious adverse events (SAEs); no deaths were reported.

Conclusions Imsidolimab demonstrated a rapid and sustained resolution of symptoms and pustular eruptions in patients with GPP. It was generally well tolerated, with an acceptable safety profile, and is advancing to phase III trials. These data support the targeting of IL-36 signalling with a specific antibody – imsidolimab – as a therapeutic option for this severely debilitating condition.

What is already known about this topic?

- Generalized pustular psoriasis (GPP) is a systemic inflammatory disease. Uncontrolled activation of interleukin-36 proinflammatory activity may underlie the pathogenesis of GPP. Treatment options for GPP are currently limited.

What does this study add?

- Imsidolimab is being developed as a targeted therapy for GPP. Results from this phase II study demonstrated a rapid resolution of symptoms and pustular eruptions in patients with a GPP flare after treatment with imsidolimab.

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Generalized pustular psoriasis (GPP) is a rare, severe and debilitating disease characterized by widespread sterile pustules on erythematous skin;[1–4] it is often accompanied by systemic signs and symptoms such as fever, nausea, pain, anorexia and general malaise.[1,4–6] Life-threatening complications of GPP can include sepsis, acute renal failure, high-output congestive cardiac failure and acute respiratory distress syndrome.[6,7]

Factors that may trigger the onset of GPP include viral or bacterial infections, corticosteroid use, hypocalcaemia, psychological stress and pregnancy.[7–9] Recurrent flares are common, even years after initial diagnosis.[10,11] While it is possible for GPP to manifest in the presence of psoriasis vulgaris (PV), studies suggest that the underlying pathophysiological mechanisms of GPP and PV may differ and that the innate immune system plays a greater role in the pathogenesis of GPP.[11–14] Dysregulated interleukin (IL)-36 signalling was implicated in the pathogenesis of GPP following the identification of loss-of-function mutations in *IL36RN*, the gene encoding IL-36 receptor antagonist (IL-36RA),[15–18] in a subset of patients with GPP. IL-36 cytokines (IL-36α, IL-36β and IL-36γ) engage with the IL-36 receptor (IL-36R) to initiate signalling events leading to proinflammatory responses.[19–21] IL-36RA normally opposes IL-36-mediated signalling.[22–24] Approximately 46–82% of patients with GPP without PV have mutations in *IL36RN*,[25,26] while the proportion of *IL36RN* mutant carriage is much lower (10–17%) in patients with GPP associated with PV.[27] It was subsequently determined that IL-36 is a dominant cytokine in GPP,[28] suggesting that excessive IL-36-mediated proinflammatory activity may broadly underlie the pathogenesis of GPP. Therefore, targeting IL-36R represents a rational therapeutic strategy to control the pathological inflammatory cascade in GPP.[14,29]

This phase II clinical trial was designed to evaluate the efficacy and safety of imsidolimab in patients with a GPP flare. Imsidolimab is a high-affinity humanized IgG4 monoclonal antibody (mAb) that specifically binds IL-36R, antagonizing IL-36 signalling. Targeting IL-36R represents an elegant therapeutic strategy to control pathogenic proinflammatory IL-36 pathway activation in GPP. The results of a placebo-controlled clinical trial of spesolimab – another mAb against IL-36R – showed significant efficacy in patients with a GPP flare.[30] Currently, chronic GPP can be difficult to manage,[30] and there is no standard guidance for GPP therapy in most countries.[5,31] While acitretin is indicated for extensive and severe refractory forms of psoriasis in the European Union, and the biological agents secukinumab, ixekizumab, brodalumab and guselkumab have been approved in Japan to treat GPP,[31,32] rigorous and well-controlled efficacy data in GPP are lacking. Therefore, there is a need for additional safe and more effective treatments to manage GPP.

Patients and methods

Study design and participants

GALLOP was an open-label, single-arm, multiple-dose study to assess the clinical efficacy, tolerability and safety of multiple doses of imsidolimab in patients with active GPP. The study was registered in EudraCT (2017-004021-33) and on ClinicalTrials.gov (NCT 03619902).

Eligible patients had to be 18–75 years old with a clinically confirmed diagnosis of active GPP, a Japanese Dermatology Association severity index (JDA-SI) total score of >6 with active pustules and erythema accounting for at least 10% of body surface area (BSA), or a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) score of at least moderate severity, and they must have been a candidate for systemic therapy or phototherapy. Patients were excluded if they had any other forms of psoriasis except concomitant PV. Any concurrent therapies likely to have efficacy in GPP or psoriasis were washed out and their use prohibited during participation in the study.

The study had a screening period of up to 42 days (6 weeks), a treatment period of 12 weeks and a follow-up period of 12 weeks for a total duration of 30 weeks (Figure 1). Written informed consent was obtained from each patient prior to initiating any study-related procedures. Ethics committee approval was obtained at all participating centres; the study complied with the International Council for Harmonisation on Good Clinical Practice and local

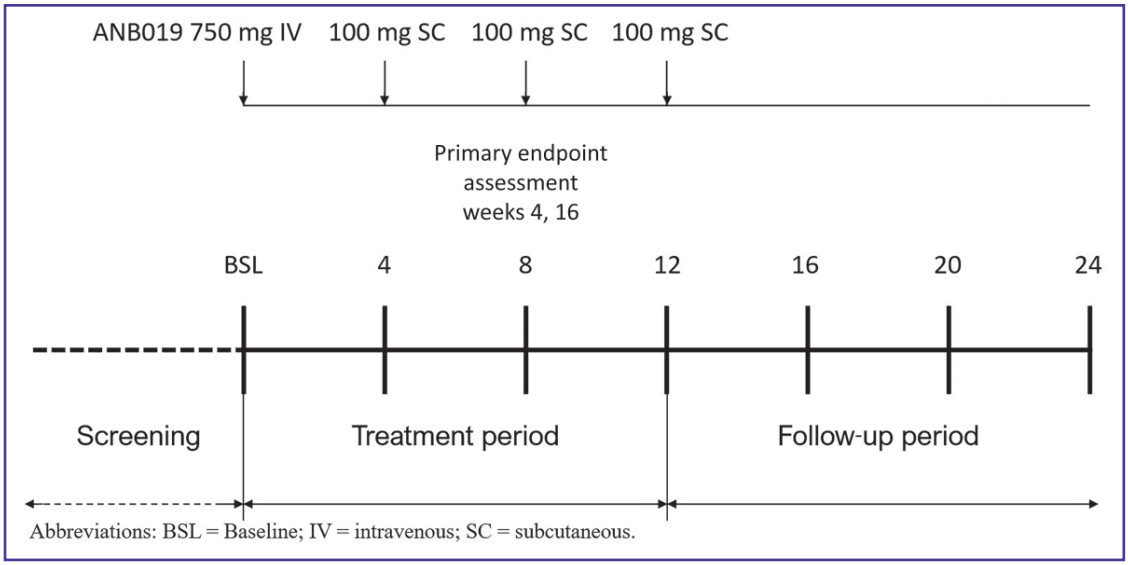

Figure 1 Phase II GALLOP trial design. Reproduced from AnaptysBio's study design. BSL, baseline; IV, intravenous; SC, subcutaneous.

regulations, and was conducted according to the principles of the Declaration of Helsinki.

Study treatments and assessments

Patients were to receive an intravenous (IV) dose of imsidolimab 750 mg on day 1, followed by three subcutaneous (SC) doses of imsidolimab 100 mg administered on days 29, 57 and 85. The doses selected for this study demonstrated a favourable safety profile and prolonged pharmacodynamic activity in a phase I study (ANB019-001). A loading dose of 750 mg IV was administered on day 1 to enable a steady-state concentration to be reached faster at initiation of the SC imsidolimab 100 mg dose.

At study visits, changes in disease activity (response to study treatment), safety and tolerability were monitored. Disease activity was evaluated using the Clinical Global Impression (CGI) scale according to the modified JDA-SI (mJDA-SI).[33] The mJDA-SI is a composite GPP instrument comprised of assessments of skin lesions [area of erythema with pustules, area of erythema (total), and area of oedema] and systemic manifestations and laboratory findings (fever, white blood cell count, C-reactive protein and serum albumin). The CGI is an instrument that categorizes overall GPP status as either 'very much improved', 'much improved', 'minimally improved', 'no change' or 'worsened' based on the change in mJDA-SI total score from baseline and/or descriptors of clinical severity. In addition, change in total BSA affected by GPP (as measured by the mJDA-SI, systemic manifestations and laboratory findings as per the mJDA-SI and GPPPGA scale)[29] and quality of life (QoL), using the Dermatology Life Quality Index (DLQI),[34] were assessed. The GPPPGA scale is scored from 0 (clear) to 4 (severe), with morphological descriptors of each level of disease severity that encompass major signs of the disease (erythema, pustulation, scaling/crusting). For inflammatory skin conditions, a change in DLQI of at least 4 points is generally considered a minimally clinically important difference.

Safety assessments, including adverse event (AE)/serious AE (SAE) monitoring, vital signs measurement, physical examination, electrocardiography, laboratory measurements and urine assessments, were performed during the study.

Endpoints

The primary efficacy endpoint was the proportion of patients in the full analysis set ($n=8$) that achieved a clinical response at weeks 4 and 16 following treatment with imsidolimab, as measured by the CGI scale. Clinical response was defined as achieving 'very much improved', 'much improved' or 'minimally improved' on the CGI scale according to the mJDA-SI total score.

The secondary efficacy endpoints were the change in affected BSA of erythema with pustules, erythema and oedema as measured by the mJDA-SI by study visit; the change from baseline in GPPPGA score by study visit; and the change in DLQI by study visit.

Efficacy was also evaluated using the GPPPGA scale; however, the GPPPGA scale was added to the study after the first three patients had already enrolled in response to a request from the US Food and Drug Administration. Therefore, data on GPPPGA at baseline were only available for five of eight patients. Additionally, one of the five patients with a baseline GPPPGA score discontinued from the study at day 29; thus, only four of five patients had GPPPGA scores from week 4 onward.

Statistical analysis

Statistical analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA). The default summary statistics for continuous variables include the number of contributing observations (n), mean (SD) and median (range). Unless otherwise specified, 'baseline' was defined as the last nonmissing measurement taken prior to the reference start date and time (including unscheduled visits). For numerical variables, change from baseline was calculated as the difference between the value of interest and the corresponding baseline value. Point estimates were accompanied with two-sided 95% confidence intervals (CIs), where applicable.

Results

Demographic and other baseline characteristics

Study participants ($n=8$) were enrolled at five sites across the UK and Poland and were 50% female, with a mean (SD) age of 51.3 (14.91) years, mean (SD) body mass index of 28.86 (3.417) kg m^{-2} and mean (SD) time since GPP diagnosis of 3.99 (6.48) years (Table 1). All but one patient was White. The mean (SD) baseline total mJDA-SI score was 9.1 (2.75), consistent with at least moderate disease severity (mild, $n=1$; moderate, $n=5$; severe, $n=2$). The mean (SD) area of erythema with pustules was 23.5% (18.1), and of the five patients administered the GPPPGA scale, the baseline score was 3.8 (moderate, $n=1$; severe, $n=4$). Genotypic testing, using Sanger sequencing, indicated homozygous wild-type *IL36RN*, *CARD14* and *AP1S3* alleles for all eight patients treated.

The full analysis set included all patients, regardless of whether treatment was received or not. All patients received the initial imsidolimab IV infusion and six (75%) received all three follow-up SC doses. The two patients who did not receive the follow-up SC doses of imsidolimab had discontinued from the study early. One patient discontinued due to use of a prohibited medication (infliximab), and the other discontinued due to lack of improvement.

Primary efficacy endpoint: proportion of patients achieving clinical response at week 4 and separately at week 16 following treatment with imsidolimab as measured by the Clinical Global Impression scale

At weeks 4 and 16, 75% of patients were CGI responders (Figure 2). Of the responders, 50% were 'very much improved'.

Secondary efficacy endpoints

Change in the body surface area affected by erythema with pustules, erythema and oedema as measured by modified Japanese Dermatology Association severity index by study visit

Concurrent and substantial improvement was observed in the three skin components of GPP: pustules, erythema and

Table 1 Demographics and baseline characteristics of patients included in the phase II GALLOP trial (safety analysis set)

Demographics	Safety analysis set ($n=8$)
Age (years)	
Mean (SD)	51.3 (14.9)
Median (range)	53 (29–69)
Sex	
Male	4 (50)
Female	4 (50)
Ethnicity	
Hispanic or Latino	0
Not Hispanic or Latino	8 (100)
Race	
American Indian or Alaska Native	0 (0)
Asian	1 (12)
Black or African American	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)
White	7 (87)
Other	0 (0)
Missing	0 (0)
Weight at baseline (kg)	
Mean (SD)	78.8 (13.3)
Median (range)	75.0 (60.0–98.0)
BMI at baseline (kg m^{-2})	
Mean (SD)	28.9 (3.4)
Median (range)	29.2 (24.5–33.9)
mJDA-SI total score at baseline[a]	
Mean (SD)	9.1 (2.8)
Median (range)	8.5 (6–14)
mJDA-SI at baseline	
Mild	1 (12)
Moderate	5 (62)
Severe	2 (25)
Skin lesions score at baseline (%)	
Area of erythema with pustules	
Mean (SD)	23.5 (18.2)
Median (range)	13.5 (8.0–55.1)
Area of erythema (total)	
Mean (SD)	50.9 (30.1)
Median (range)	45.6 (15.0–91.0)
Area of oedema	
Mean (SD)	33.8 (18.8)
Median (range)	27.5 (11.0–60.0)
GPPPGA score at baseline	
Clear	0 (0.0)
Almost clear	0 (0.0)
Mild	0 (0.0)
Moderate	1 (12)
Severe	4 (50)
Number of years since GPP diagnosis	
Mean (SD)	4.0 (6.5)
Median (range)	1.1 (0.0–19.0)
Mean (SD) PASI score at baseline ($n=5$)[b]	21.18 (16.77)

Data are presented as *n* (%) unless otherwise stated. Age is relative to informed consent. If the date of birth was partial, age was calculated using the available parts of the date. If the medical history start date of generalized pustular psoriasis (GPP) was partial, the number of years since GPP diagnosis was calculated using the available parts of the date. 'Baseline' was defined as the last observed value of the parameter of interest prior to the first intake of study drug. BMI, body mass index; mJDA-SI, modified Japanese Dermatological Association severity index; GPPPGA, Generalized Pustular Psoriasis Physician Global Assessment; PASI, Psoriasis Area and Severity Index. [a]The study population ($n=8$) included one patient who did not meet the inclusion criteria of a JDA-SI total score > 6 or presenting with active pustules and erythema accounting for at least 10% of the body surface area. This was considered to be an unimportant protocol deviation. [b]Change in PASI score from baseline was used to assess response to imsidolimab treatment in patients with concomitant plaque psoriasis.

oedema. Improvement was sustained throughout the duration of imsidolimab treatment. Following imsidolimab administration, BSA covered by erythema with pustules improved most rapidly based on the mJDA-SI skin component assessment. Mean BSA covered by erythema with pustules was 23.5% at baseline (Figure 3a). The percentage change from baseline was –60% by day 8 and –94% by week 4 (day 29; Figure 3b). Mean BSA affected by erythema was 50.9% at baseline (Figure 3c). The percentage change from baseline was –30% on day 29 and –60% on day 113 (Figure 3d). Mean BSA with oedema was 33.8% at baseline (Figure 3e). The percentage change from baseline was –77% on day 29 and –78% on day 113 (Figure 3f). Percentage changes from baseline were sustained throughout the duration of treatment.

Change from baseline in Generalized Pustular Psoriasis Physician Global Assessment scores by study visit

GPP severity was assessed with the GPPPGA scale, which captures the investigator's assessment of the overall disease severity at the time of evaluation. GPPPGA was added after the study started; therefore, a baseline assessment was only available for five patients and one discontinued before day 29. Therefore, week 4 and 16 GPPPGA assessments were only possible for four patients.

Following imsidolimab treatment, by week 4 the mean (SD) change from baseline GPPPGA score improved (decreased) by –2.5 (0.58) and the mean (SD) percentage change from baseline was –62.5% (14.4%) on the GPPPGA scale (Table 2). At week 16, the mean (SD) change from baseline was –3.0 (0.82) and the mean (SD) percentage change from baseline was –75.0% (20.4%).

Change in Dermatology Life Quality Index total score by study visit

Consistent with the improvements observed in the other clinical measures of GPP severity, the patient-reported DLQI measure also improved over time following imsidolimab treatment (Figure 4). Patients had a mean DLQI of 15.8 at baseline, indicating a very large effect on the patients' health-related QoL. Following administration of imsidolimab, DLQI continued to improve through week 20 (day 141). By day 29, the DLQI total score improved (decreased) from baseline to 11.7 and to 9.7 by day 141.

Photographic documentation of disease improvement

While photographs were not taken for all patients, observations from photographic images were consistent with improvements assessed in other clinical measures of GPP (Figure 5). The photographs documented a rapid and sustained improvement in disease severity following imsidolimab treatment in two patients.

Safety evaluation

No deaths occurred during the study and no patients withdrew due to a treatment-emergent AE (TEAE). Overall, six patients (75%) experienced at least one TEAE during the treatment period (Table 3). The most commonly reported TEAEs by system organ classes (25% each) were blood and lymphatic system disorders; gastrointestinal disorders; infections and infestations; investigations; respiratory, thoracic and mediastinal disorders; and skin

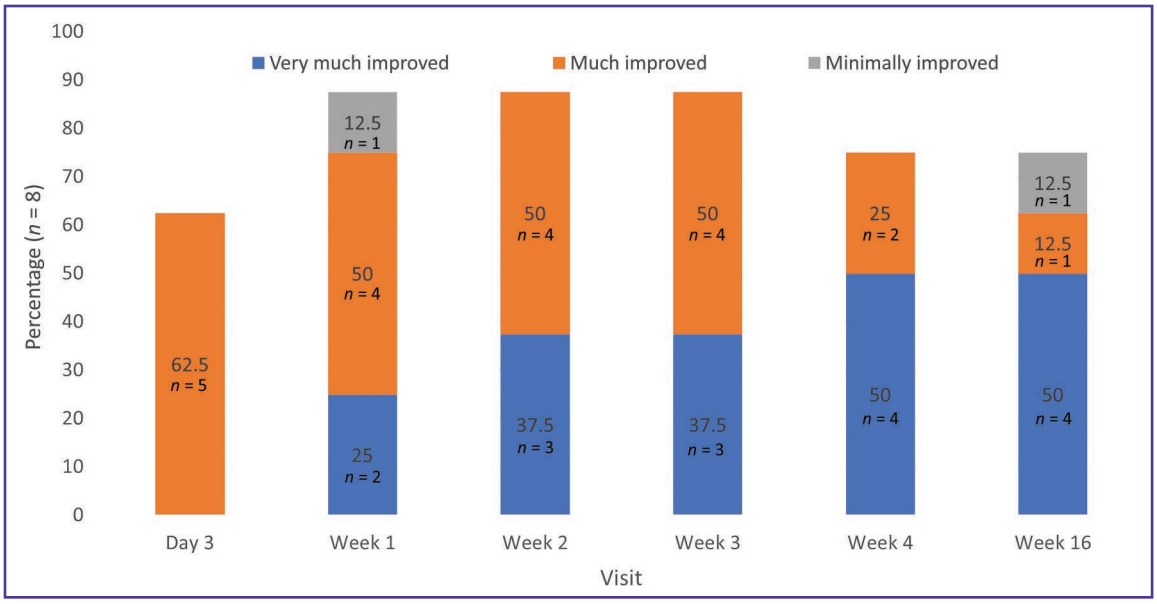

Figure 2 Primary efficacy endpoint: proportion and number of patients who achieved a clinical response, according to the Clinical Global Impression scale, by study visit (full analysis set).

and subcutaneous tissue disorders. Two patients reported TEAEs that were deemed to be moderate in severity and possibly related to study drug treatment: one patient experienced a moderate flare of plaque psoriasis, and the second experienced a moderately sore throat. No patient reported TEAEs associated with infusion or injection site reactions.

Two SAEs were reported. One subject developed a SAE of SARS-CoV-2 infection that was deemed to be unrelated to study drug treatment. The patient fully recovered and resumed the study treatment. Another patient developed sepsis, following a nonserious AE of *Staphylococcus aureus* bacteraemia, while in hospital, that was assessed to be possibly related to study drug treatment. The patient fully recovered with appropriate antibiotic therapy and subsequently discontinued from the study upon use of a prohibited medication (infliximab) for the treatment of GPP.

Discussion

Imsidolimab appeared to be generally well tolerated and demonstrated a rapid and sustained improvement of symptoms and pustular eruptions in patients with GPP flares, which was consistent across the clinical measures assessed. Taken together, these results indicate that imsidolimab may represent a useful approach to GPP treatment. In addition, an initial IV infusion of imsidolimab followed by monthly SC dosing, as applied in this study, is an attractive approach for GPP treatment as rapid control of the flare and convenient maintenance of the underlying disease is desirable.

The onset of action of imsidolimab was rapid following the initial infusion, with responses observed as early as day 3 (Figure 2). Continued and consistent improvement through week 16 was observed with subsequent monthly SC maintenance dosing. A rapid onset of action and response is particularly desirable in GPP as patients often experience uncomfortable and potentially life-threatening systemic signs and symptoms during a pustular flare. The two patients who discontinued the study before week 4 both had a 'much improved' score on the CGI scale at their last observation before study discontinuation. Reductions in pustules, oedema and erythema were observed over the course of the study. The mJDA-SI skin component assessment of BSA covered with erythema with pustules was the most rapidly improved skin component of GPP following imsidolimab administration (Figure 3). Following imsidolimab treatment, by week 4 the mean change from baseline GPPPGA score also improved (decreased; Table 2). The impact on patients' QoL was assessed by quantifying responses to the patient-reported outcome measure (DLQI). Consistent with the improvements seen in the objective clinical measures of GPP severity, the patient-reported DLQI measure also improved over time following imsidolimab treatment (Figure 4). Photographs documented rapid and sustained clinical improvement in disease severity following imsidolimab treatment in two patients (Figure 5). It is also notable that genotypic testing indicated homozygous wild-type *IL36RN*, *CARD14* and *AP1S3* alleles for eight patients treated in this study, which provides additional evidence that the pathogenic role of IL-36 activation in GPP extends beyond individuals with known *IL36RN* mutations.

The doses applied in this study (imsidolimab 750 mg IV dose on day 1, followed by three SC doses of imsidolimab 100 mg administered on days 29, 57 and 85) were generally well tolerated. The majority of TEAEs were mild to moderate in severity and no deaths were reported. No patient discontinued the study because of a TEAE. Three patients experienced TEAEs that were assessed as possibly related to study drug treatment.

Studies have shown the importance of IL-36 signalling in GPP, which represents a rational strategy to control the pathological inflammatory cascade in this condition. This

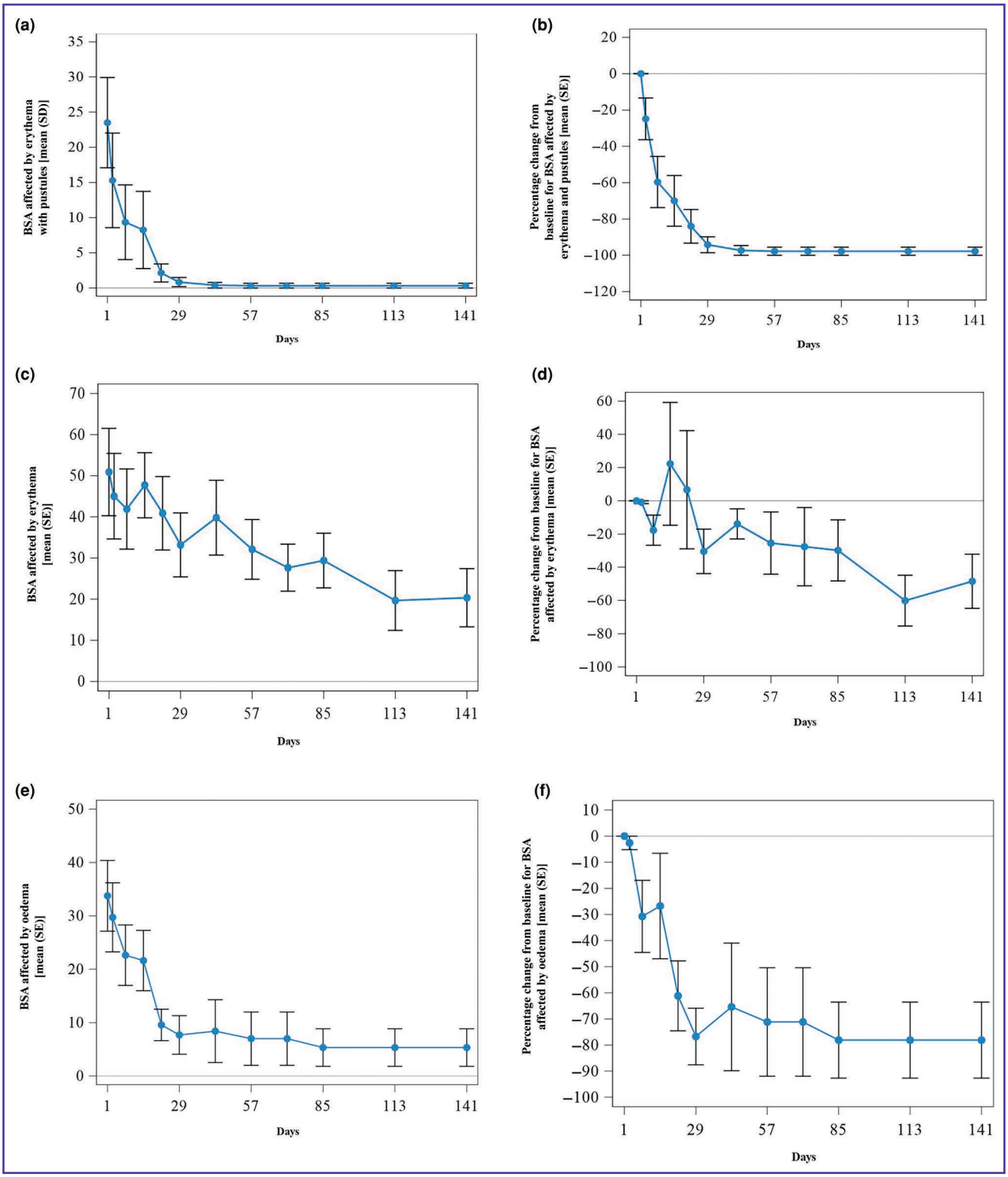

Figure 3 Secondary efficacy endpoint: descriptive statistics of actual and change from baseline for the percentage area affected by erythema with pustules, erythema and oedema (full analysis set). (a) Body surface area (BSA) affected by erythema with pustules and (b) percentage change in erythema with pustules from baseline; (c) BSA affected by erythema and (d) percentage change in erythema from baseline; and (e) BSA affected by oedema and (f) percentage change in oedema from baseline.

therapeutic approach was further validated by a recently reported placebo-controlled clinical trial of spesolimab.[15,16,28,30] While the GALLOP results provide useful and promising information about the emerging benefit–risk profile of imsidolimab in GPP, the small size and open-label design of this study were limitations. Double-blind, placebo-controlled, global multicentre phase III trials of imsidolimab in GPP, designed to provide a more robust

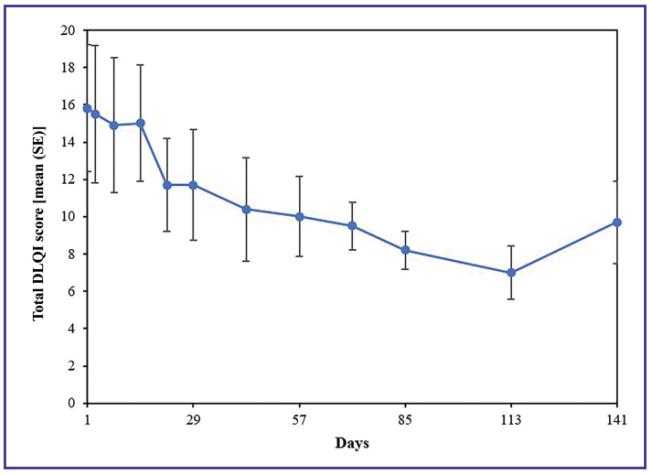

Figure 4 Secondary efficacy endpoint: total Dermatology Life Quality Index (DLQI) score by study visit (full analysis set).

evaluation of this promising approach to GPP treatment, are currently ongoing (NCT05352893 and NCT05366855).

In conclusion, the results of this phase II study demonstrated that treatment with imsidolimab produced a rapid resolution of symptoms and pustular eruptions in patients with GPP flares. These results suggest that specifically targeting IL-36 pathway activation, which is increasingly implicated as central to the pathophysiology of GPP, with a mAb to IL-36R could provide reliable, rapid and sustained efficacy in patients experiencing a GPP flare. This could potentially revolutionize GPP treatment in a manner similar to that produced by anticytokine therapies for PV.

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Conflicts of interest

R.B.W. has received honoraria and/or research funding from AbbVie, Almirall, Amgen, AnaptysBio, Inc., DiCE, Boehringer Ingelheim, Eli Lilly, LEO, Janssen, Novartis, UCB and UNION. C.E.M.G. has received honoraria and/or research funding from AbbVie, Almirall, Amgen, AnaptysBio, Inc., Boehringer Ingelheim, Janssen, Novartis and UCB. A.K. has consulted for and participated in advisory boards for Eli Lilly, Janssen and Novartis. J.E.G. has received honoraria and/or

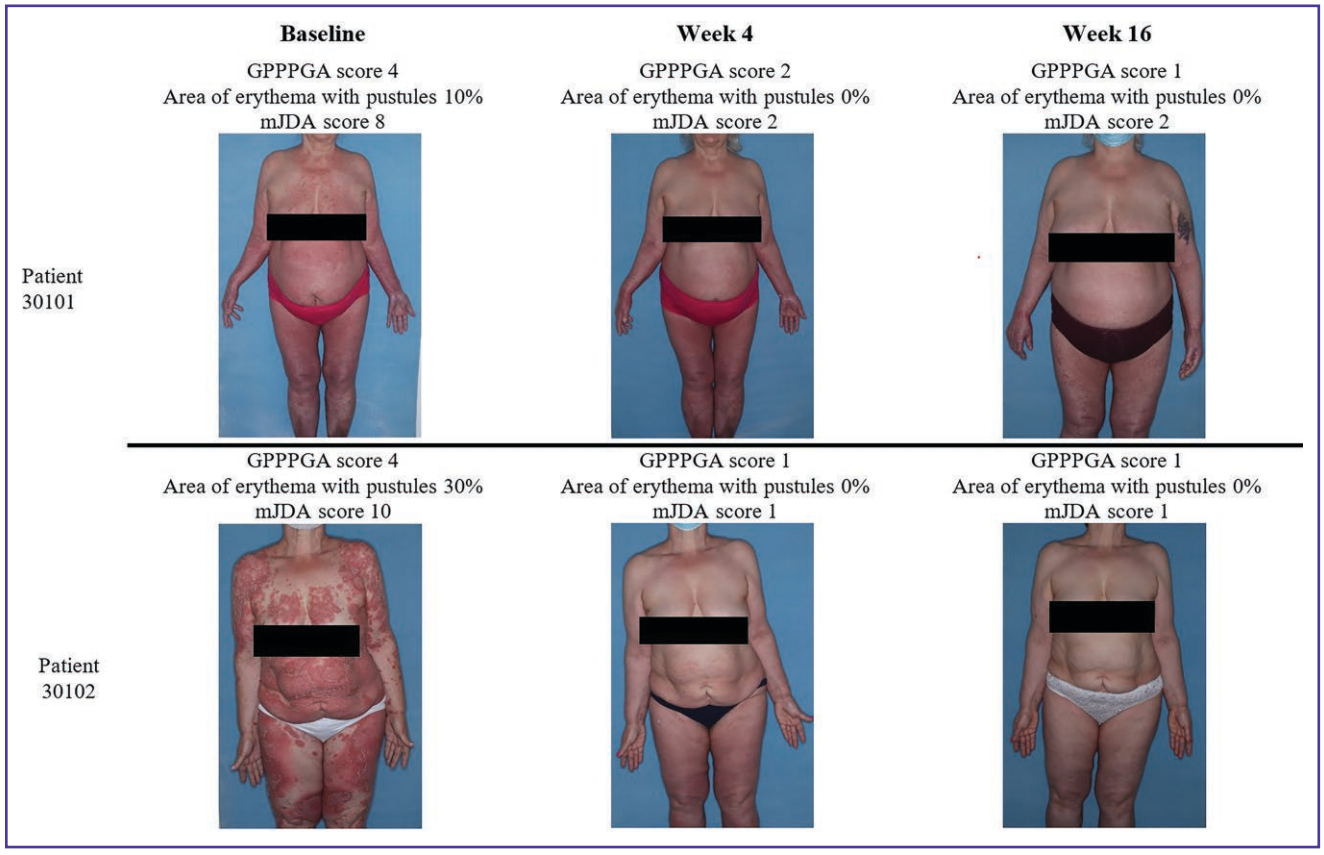

Figure 5 Longitudinal photographs of two patients with generalized pustular psoriasis treated with imsidolimab. GPPPGA, Generalized Pustular Psoriasis Physician Global Assessment; mJDA, modified Japanese Dermatology Association severity index.

Table 2 Secondary efficacy endpoint in the phase II GALLOP trial: descriptive statistics of actual and change from baseline for Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) scores of patients with GPPPGA recorded at baseline (full analysis set for patients with GPPPGA at baseline)

	Total ($n=5$)		
Visit statistic	**Result**	**Change from baseline**	**Change from baseline (%)**
Baseline			
n	5	NA	NA
Mean (SD) GPPPGA	3.8 (0.45)	NA	NA
95% CI	3.24–4.36	NA	NA
Median (range)	4 (3–4)	NA	NA
Week 4			
n	4	4	4
Mean (SD) GPPPGA	1.5 (0.58)	–2.5 (0.58)	–62.5 (14.4)
95% CI	0.58–2.42	–3.42 to –1.58)	–85.5 to –39.5
Median (range)	1.5 (1–2)	–2.5 (–3 to –2)	–62.5 (–75.0 to –50.0)
Week 16			
n	4	4	4
Mean (SD) GPPPGA	1.0 (0.82)	–3.0 (0.82)	–75.0 (20.4)
95% CI	–0.30 to 2.30	–4.30 to –1.70	–107.5 to –42.5
Median (range)	1 (0–2)	–3 (–4 to –2)	–75 (–100 to –50)

GPPPGA scores: 0 = clear (normal skin or postinflammatory hyperpigmentation, no visible pustules, no scaling or crusting); 1 = almost clear [faint, diffuse pink or slightly red erythema, low-density occasional small discrete pustules (noncoalescent), superficial focal scaling or crusting restricted to the periphery of lesions]; 2 = mild [light-red erythema, moderate-density grouped discrete small pustules (noncoalescent), predominantly fine scaling or crusting]; 3 = moderate (bright-red erythema, high-density pustules with some coalescence, moderate scaling or crusting covering most or all lesions); 4 = severe (deep fiery-red erythema, very-high-density pustules with pustular lakes, severe scaling or crusting covering most or all lesions). Baseline refers to the last nonmissing measurement taken prior to the reference start date (including unscheduled assessments). NA, not applicable; CI, confidence interval.

Table 3 Overview of treatment-emergent adverse events (TEAEs) in the phase II GALLOP trial (safety analysis set)

Characteristic	**Total ($n=8$)**
Patients with at least one:	
TEAE	6 (75)
Related or possibly related TEAE	3 (37)
Severe TEAE	1 (12)
Serious TEAE	2 (25)
TEAE leading to discontinuation of study drug	1 (12)
TEAE leading to study discontinuation	0 (0)
Infusion-related TEAE or injection site reaction	0 (0)
MedDRA system organ class preferred term	
Blood and lymphatic system disorders	2 (25)
Anaemia	1 (12)
Lymphadenopathy	1 (12)
Gastrointestinal disorders	2 (25)
Nausea	1 (12)
Toothache	1 (12)
Vomiting	1 (12)
Infections and infestations	2 (25)
COVID-19	1 (12)
Nosocomial infection	1 (12)
Investigations	2 (25)
Blood folate decreased	1 (12)
Blood glucose increased	1 (12)
C-reactive protein increased	1 (12)
White blood cell count increased	1 (12)
Respiratory, thoracic and mediastinal disorders	2 (25)
Oropharyngeal pain	2 (25)
Skin and subcutaneous tissue disorders	2 (25)
Psoriasis	1 (12)
Skin haemorrhage	1 (12)

MedDRA, Medical Dictionary for Regulatory Activities.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

Ethics committee approval was obtained from all participating centres.

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