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Research Article

A Phase IIIb, Multicentre, Interventional, Randomised, Placebo-Controlled Clinical Trial Investigating the Efficacy and Safety of Guselkumab for the Treatment of Nonpustular Palmoplantar Psoriasis (G-PLUS)

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Introduction. Despite the availability of effective biologic therapies for psoriasis, there is no gold-standard treatment for nonpustular palmoplantar psoriasis (ppPsO). *Methods*. G-PLUS, a phase IIIb, double-blind, placebo-controlled, multicentre clinical trial, randomised adults with moderate-to-severe nonpustular ppPsO and limited plaque psoriasis (Psoriasis Area and Severity Index (PASI) ≥3 but <10) to guselkumab (an interleukin-23p19 blocker) or placebo. Placebo participants were crossed over to receive guselkumab at week (Wk) 16. The primary efficacy endpoint was the proportion of participants achieving palmoplantar PASI (ppPASI) 75 response at Wk16; clinical, biomarker, and quality-of-life endpoints were assessed through Wk48 and safety through Wk56. *Results*. At Wk16, ppPASI75 response was achieved by 35.9% of the guselkumab participants compared with 28.2% in the placebo group, resulting in a 7.7% difference in response rates (95% confidence interval: −11.5 and 24.7), which was not statistically significant ($p = 0.533$). More pronounced numerical improvements favouring guselkumab were observed for more stringent efficacy endpoints, such as Wk16 palmoplantar Investigator's Global Assessment (ppIGA) 0/1 response (guselkumab 34.6% vs. placebo 15.4%). Through Wk48, further improvements were observed in ppPASI75 response (55.1% and 64.1%) and ppIGA 0/1 response (42.3% and 48.7%) for the guselkumab and placebo-crossover groups, respectively. Dermatology Life Quality Index responses showed comparable trends at both timepoints. Safety and pharmacodynamic findings were consistent with the established profile for guselkumab. Serum biomarker levels were significantly reduced with guselkumab and

correlated with the baseline PASI score but not the ppPASI score. *Conclusion*. Although the primary endpoint was not met, analysis of stringent secondary endpoints and post hoc analyses showed numerical improvements favouring guselkumab at Wk16. There were no new safety signals. Further studies are warranted to better understand the impact of guselkumab treatment in patients with ppPsO. This trial is registered with NCT03998683.

1. Introduction

Palmoplantar psoriasis (ppPsO) is characterised by erythematous, hyperkeratotic, and fissuring plaques of the palms and soles, leading to pain and itch [1]. Pustular, hyperkeratotic, and mixed forms have been described [1]. An estimated 11–39% of psoriasis cases may have palmoplantar involvement [2].

Furthermore, ppPsO may be underdiagnosed, undertreated, and challenging to manage [3]. ppPsO and chronic hand eczema can be exacerbated by seasonal changes, activities of daily living, and environmental exposures, leading to misdiagnosis [1, 4]. Physical insults can exacerbate ppPsO (Koebnerisation), making it particularly difficult to treat [5, 6]. Given the limitations in patient-reported measures of disease severity, the impact of ppPsO remains underestimated [7, 8]; however, the presence of ppPsO skin lesions and associated symptoms has been reported to considerably diminish patients' quality of life and work productivity [7, 8].

Despite the availability of broad and effective biologic treatment options for the management of moderate-to-severe plaque psoriasis, no gold-standard therapy is currently recognised for ppPsO. First-line treatment consists of topical therapy such as potent or very potent corticosteroids and photo (chemo) therapy; because of the thickness of stratum corneum on the palms and soles, responses are often unsatisfactory, and the majority of patients eventually require systemic therapy [2, 9, 10]. There is a lack of randomised controlled trials evaluating conventional and biologic systemic therapies for ppPsO [9, 10]. In particular, few clinical studies focussing on patients with nonpustular ppPsO have been conducted, and among these, outcomes have generally been disappointing [11]. Trials have been challenging because of the phenotypic and underlying pathophysiological heterogeneity of pustular and nonpustular forms of ppPsO and because many patients with ppPsO do not meet typical clinical trial inclusion criteria, owing to low overall body surface area (BSA) involvement of psoriasis (e.g., BSA often <10%) [9].

Guselkumab, a fully human immunoglobulin G1 lambda monoclonal antibody that binds the p19 subunit of human interleukin (IL)-23, is approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis [12, 13]. The VOYAGE 1 and 2 studies demonstrated high levels of clinical response coupled with a highly favourable safety profile for guselkumab in patients with moderate-to-severe plaque psoriasis [14, 15]. The efficacy profile observed in the guselkumab clinical trial programme has been further supported by subsequent real-world studies; recent retrospective studies have shown that guselkumab is effective in patients with moderate-to-severe plaque psoriasis, including in those who previously failed anti-IL-17 therapy [16] and over time through up to 3 years [17]. Hand and foot Physician's Global Assessment (hf-PGA) outcomes were assessed in the phase III VOYAGE 1 and 2 clinical trials in patients with moderate-to-severe plaque psoriasis. At week (Wk) 16, 75.5% of the patients receiving guselkumab with hand/foot involvement achieved a hf-PGA 0/1 score (clear or almost clear) compared with 14.2% of the patients receiving placebo, and at Wk24, 80.4% of the patients receiving guselkumab achieved a hf-PGA 0/1 score compared with 60.3% of the patients receiving adalimumab [18].

However, patients with hand and foot involvement as a part of the phenotypic spectrum of their moderate-to-severe plaque psoriasis may not reflect patients with ppPsO. To help address this gap, we conducted a phase IIIb clinical trial, G-PLUS, to investigate the efficacy and safety of guselkumab in participants with moderate-to-severe nonpustular ppPsO but limited overall plaque psoriasis burden (Psoriasis Area and Severity Index (PASI) ≥3 but <10 at the baseline).

2. Materials and Methods

2.1. Trial Design. G-PLUS (NCT03998683) was a phase IIIb, 56-week, randomised, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of guselkumab for the treatment of nonpustular ppPsO. The trial was conducted at 24 sites across five Western European countries between 3 September 2019 and 30 November 2021.

An interactive web response system based on randomly permutated blocks was used for central randomisation (2 : 1, guselkumab : placebo). An overview of the trial design is presented in Figure 1. Guidance for virtual study visits and home administration of study medication was added in June 2020 in light of the COVID-19 pandemic.

2.2. Participants. Participants (≥18 years of age) had moderate-to-severe nonpustular ppPsO (palmoplantar Investigator's Global Assessment (ppIGA) score ≥3) and limited overall skin involvement (PASI score ≥3 but <10) with at least one plaque at a body site other than the palms or soles present for ≥6 months. Participants must have been eligible to receive biological treatments; only participants who were naïve to biological treatments were included. Other inclusion criteria included reproductive status, tuberculosis (TB) status (no history of latent or active TB, no signs or symptoms of active TB, and no recent close contacts), laboratory screening parameters, and willingness to refrain from complementary therapies, including UV tanning, during the study. Participants were permitted to use topical emollients for psoriasis. Guidance on the study conducted during the COVID-19 pandemic was added to the

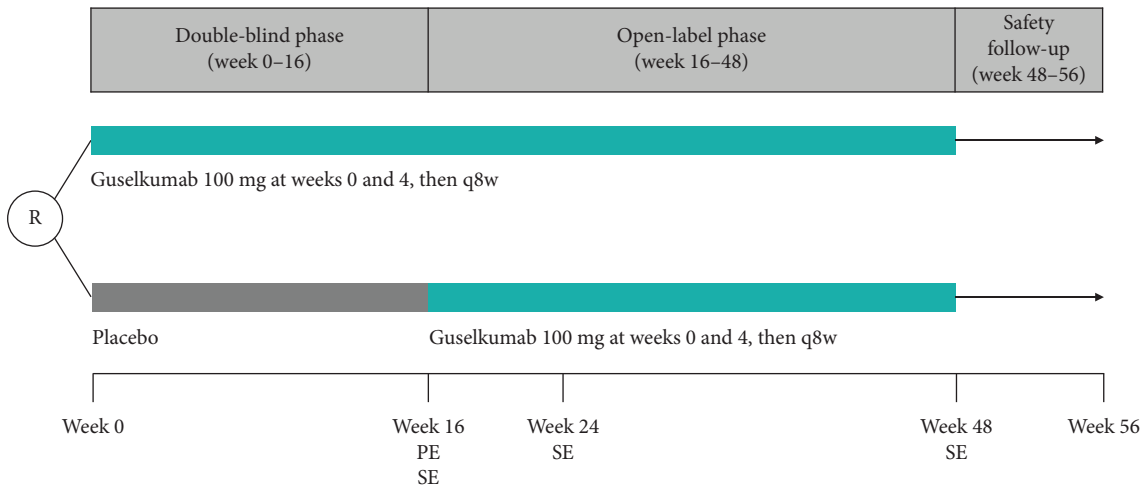

Figure 1: G-PLUS trial design. The trial comprised a placebo-controlled, double-blind period (weeks 0–16), an open-label active treatment phase (weeks 16–48), with participants initially receiving placebo crossing over to receive guselkumab starting at week 16 and through week 48 (last dose of trial intervention was administered at week 44) and an additional 12-week safety follow-up period from week 48 through week 56. An interactive web response system based on randomly permutated blocks was used for central randomisation (2 : 1 guselkumab : placebo). Participants received guselkumab 100 mg at weeks 0, 4, and 12, and q8w thereafter through week 44 or placebo at weeks 0, 4, and 12, followed by guselkumab at weeks 16 and 20, and q8w thereafter through week 44 (referred to as the placebo-crossover group). To maintain blinding, matching placebo was used. PE, primary endpoint; q8w, every 8 weeks; R, randomisation; SE, secondary endpoint.

protocol in April 2020, and a SARS-CoV-2 (COVID-19) exclusion criterion was added to the protocol in June 2020. Potential participants were excluded if they had any of the following: (a) confirmed SARS-CoV-2 infection (test positive), (b) suspected SARS-CoV-2 infection (clinical features without documented test results), or (c) close contact with a person with known or suspected SARS-CoV-2 infection during the 6 weeks prior to the baseline; depending on local guideline recommendations, an exception could be made if the participants had a documented negative SAR-CoV-2 test result at least 2 weeks after resolution of (a), (b), and (c), with no further symptoms between the negative test and the baseline. The full set of exclusion criteria is listed in Appendix A, Table S1.

2.3. Assessments and Endpoints. The primary efficacy endpoint was the proportion of participants achieving a palmoplantar PASI (ppPASI) 75 response (≥75% improvement from the baseline in the ppPASI score) at Wk16, comparing the guselkumab group vs. the placebo group. Major secondary efficacy endpoints included change from the baseline to Wk16 in the following scores: ppPASI, absolute PASI, ppIGA, fingernail Physician's Global Assessment, BSA, Dermatology Life Quality Index (DLQI), palmoplantar Quality-of-Life Instrument (ppQLI), and European Quality of Life, 5-Dimension, 5-Level measure.

Other efficacy endpoints included the proportions of participants achieving, over time, ppPASI90 and ppPASI100 responses, ppIGA response of 0 or 1 (0/1; defined as a ppIGA score of clear or minimal and a reduction of ≥2 points from the baseline), PASI75, PASI90, and PASI100 responses, and DLQI 0/1 score (among participants with the baseline DLQI score >1). Treatment-emergent adverse events (TEAEs) were assessed through Wk56.

2.3.1. Biomarker Analyses. Serum samples were collected at Wks 0, 16, 24, and 48. Serum IL-17A, IL-17F, and IL-22 levels were measured using MilliporeSigma's single molecule counting (SMC) technology performed by PBL Assay Science (Piscataway, New Jersey). Healthy control (HC) samples were matched for age, sex, and race/ethnicity. Comparisons of baseline cytokine levels were performed using Welch's *t*-test. Associations between baseline cytokine levels and disease severity (based on ppPASI and PASI scores) were evaluated using the Pearson correlation coefficient. Pharmacodynamic parameters over time were assessed using mixed effect linear regression models, with baseline cytokine levels and body mass index (BMI) as covariates. Serum protein levels were considered elevated if >1.5-fold above those for HCs (with $p < 0.05$).

2.4. Statistical Analyses. The sample size calculation assumed a guselkumab ppPASI75 response rate ≥45% vs. ≤12.5% for the placebo group. These assumptions were based on a secondary analysis of palm and/or sole data in patients treated with guselkumab in two phase III trials and on results from three phase III trials in participants with palmoplantar involvement in patients with plaque psoriasis treated with ixekizumab [19]. Based on these calculations, 64 guselkumab and 32 placebo participants were required to achieve ≥90% power based on Fisher's exact test at a two-sided significance level of 5% and a 2 : 1 randomisation ratio. In a June 2020 protocol amendment, the planned sample size was increased from 105 to 114 participants to allow for 15% of the participants being non-evaluable and, therefore, compensate for protocol deviations related to the COVID-19 pandemic that could impact the primary endpoint. This corresponded to planned randomisation of approximately 76 participants to the guselkumab

group and 38 participants to the placebo group. Ultimately, 78 participants were randomised to the guselkumab group and 39 to the placebo group.

Database locks (DBLs) occurred at Wk16 and the end of the trial (Wk56). Blinding was maintained until after the Wk56 DBL. The full analysis set included all randomised participants who received at least one dose of trial intervention, and data were analysed by the randomised treatment group. The primary efficacy endpoint and eight major secondary efficacy endpoints were analysed using a composite estimand strategy. Handling of participants meeting any treatment failure criteria is described in Appendix A, Table S2.

Statistical comparisons between the guselkumab and placebo groups were performed through Wk16, with no adjustment for multiplicity for major secondary efficacy endpoints. Treatment comparisons were performed using Fisher's exact test with 95% confidence intervals (CIs). For continuous endpoints, a mixed model for repeated measures was used, as appropriate. All Wk24 and Wk48 efficacy endpoints were descriptively summarised by the treatment group without formal treatment comparisons. Binary response and continuous endpoints were analysed using multiple imputation for missing data and nonresponse imputation in cases of premature discontinuation from trial intervention. Safety assessments were based on the safety analysis set, according to trial intervention actually received.

2.4.1. Post Hoc Analyses. Post hoc analyses were performed after the final DBL and included assessment of demographic and baseline disease characteristics for participants who met the primary efficacy endpoint (ppPASI75 responders at Wk16). In addition, selected efficacy endpoints (ppPASI75, ppIGA, and PASI75 responses) were evaluated by the baseline obesity status (obese vs. non-obese), and ppPASI scores were analysed separately for palms and soles to explore the differential impact of the components that contribute to the total score. These analyses were based on observed data, without imputation rules for missing data.

3. Results

3.1. Participant Disposition. Of 146 participants screened, 117 were randomised to receive either guselkumab ($n = 78$) or placebo ($n = 39$). All patients received at least one dose and were included in the full analysis set; 15.4% ($n = 12$) in the guselkumab group and 20.5% ($n = 8$) in the placebo-crossover group discontinued study intervention prior to Wk56 (Figure 2 and Appendix B, Table S1). Demographic and baseline disease characteristics were relatively well-balanced between treatment groups (Table 1); however, compared with the placebo group, the median age of guselkumab participants was higher (guselkumab vs. placebo: 55.0 vs. 52.0 years) and a higher proportion of guselkumab participants was female (53.8% vs. 38.5%). Characteristics associated with difficult-to-treat disease were more common among participants in the guselkumab group vs. the placebo group, with a higher rate of obesity (41.6% vs. 33.3%) and longer duration of palm and sole involvement (median 5.0 vs. 4.0 years for both components) in the former.

3.2. Efficacy. Outcomes for efficacy endpoints are shown in Table 2 (primary and major secondary efficacy endpoints at Wk16) and Table 3 (primary and other clinical and quality-of-life endpoints by visit through Wk48). For the primary endpoint, ppPASI75 response at Wk16 was achieved by 35.9% of the guselkumab participants compared with 28.2% in the placebo group, resulting in a 7.7% difference in response rates (95% CI: −11.5 and 24.7), which was not statistically significant ($p = 0.533$); therefore, the primary endpoint was not met (Table 2 and Figure 3).

More pronounced numerical improvements favouring guselkumab were seen for more stringent efficacy endpoints such as ppIGA 0/1 response at Wk16 (guselkumab 34.6% and placebo 15.4%; Figure 4) and ppPASI90 response at Wk16 (guselkumab 24.4% and placebo 15.4%; Table 3). Regarding broader skin outcomes, 14.1% vs. 5.1% of the participants in the guselkumab group vs. the placebo group, respectively, achieved a PASI90 response at Wk16 (Table 3 and Appendix C, Figure S1). Regarding the quality of life, a numerically greater proportion of participants in the guselkumab group reported a DLQI 0/1 score at Wk16 compared with the placebo group (19.2% vs. 7.7%, respectively; Table 3).

From Wk16 through Wk48, outcomes generally continued to improve for the guselkumab and placebo-crossover groups (Table 3). At Wk48, response rates for the guselkumab and placebo-crossover groups, respectively, were as follows: ppPASI75, 55.1% and 64.1%; ppIGA 0/1, 42.3% and 48.7%; and DLQI 0/1, 34.2% and 38.5%.

3.2.1. Post Hoc Analyses. Demographic and baseline characteristics of ppPASI75 responders at Wk16 were analysed to further characterise their potential impact on treatment. A higher proportion of guselkumab responders than placebo responders were obese (32.1% vs. 9.1%), and guselkumab responders had longer duration of plaque psoriasis (median 10.0 vs. 7.0 years) and palmoplantar involvement (palms: median 8.0 vs. 4.0 years; soles: median 7.5 vs. 2.0 years) and higher baseline ppQLI scores (median 45.5 vs. 42.0) (Appendix D, Table S1).

The improvements with guselkumab treatment appeared more pronounced in subgroup analyses limited to obese participants. At Wk16, 31.0% and 7.7% of the obese (BMI ≥30) participants randomised to guselkumab and placebo, respectively, achieved a ppPASI75 response. Similar observations were noted for ppIGA 0/1 and PASI90 responses (Appendix E, Figure S1).

ppPASI palm and sole scores over time were evaluated independently to determine whether they contributed any differential impact on the total score. Baseline median ppPASI scores were higher for the guselkumab group compared with the placebo group. Greater numerical improvements were observed for the guselkumab group compared with the placebo group at Wk16; similar scores were observed for the guselkumab and placebo-crossover groups at Wk48 (Appendix F, Table S1). Median palm scores

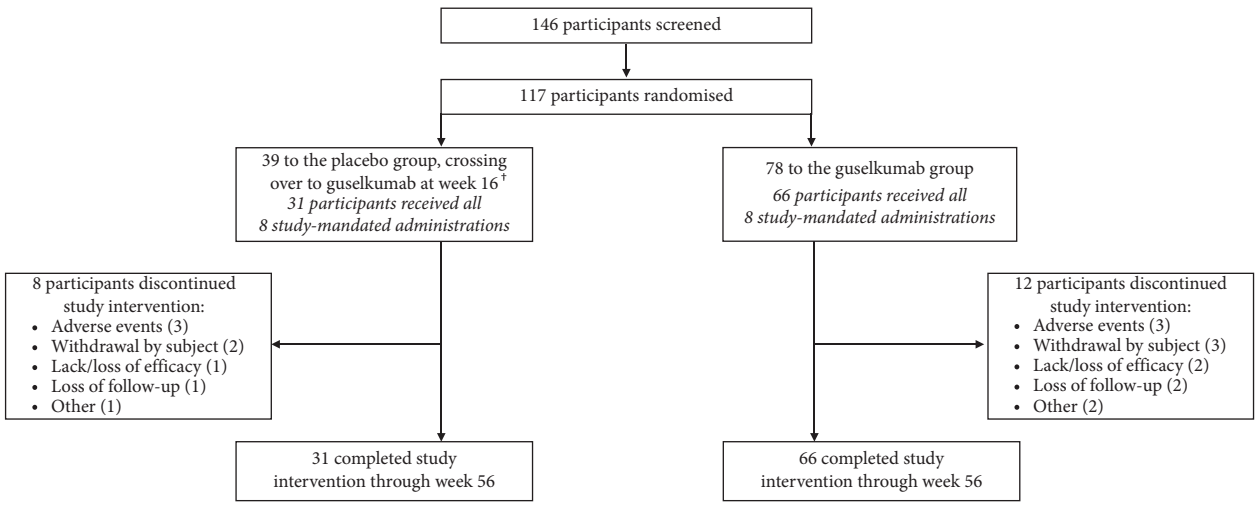

Figure 2: G-PLUS participant disposition. †Participants randomised to placebo at the baseline received placebo at weeks 0–16 and then crossed over to guselkumab from week 16 to trial end. All discontinuations occurred after the week 16 visit.

Table 1: Demographic and baseline disease characteristics (full analysis set).

Variable	Placebo	Guselkumab 100 mg q8w
Age, years	$n = 39$	$n = 78$
Mean (SD)	47.8 (13.14)	51.6 (13.27)
Median (IQR)	52 (37.0; 57.0)	55 (43.0; 61.0)
Male	$n = 39$	$n = 78$
n (%)	24 (61.5)	36 (46.2)
Weight, kg	$n = 39$	$n = 77$
Mean (SD)	894 (20.03)	84.8 (19.76)
Median (IQR)	85.0 (77.0; 97.0)	83.0 (72.1; 95.0)
BMI, kg/m^2	$n = 39$	$n = 77$
Mean (SD)	29.7 (6.66)	29.0 (6.29)
Median (IQR)	28.5 (26.2; 31.7)	28.3 (24.5; 32.4)
Normal, <25, n (%)	6 (15.4)	23 (29.9)
Overweight, ≥25 to <30, n (%)	20 (51.3)	22 (28.6)
Obese, ≥30, n (%)	13 (33.3)	32 (41.6)
Plaque psoriasis disease duration, years	$n = 39$	$n = 78$
Mean (SD)	11.1 (10.31)	13.3 (12.93)
Median (IQR)	8.0 (3.8; 15.0)	8.5 (3.0; 19.0)
Palm involvement disease duration, years	$n = 37$	$n = 74$
Mean (SD)	8.1 (9.15)	9.9 (12.07)
Median (IQR)	4.0 (2.0; 10.0)	5.0 (2.0; 11.0)
Sole involvement disease duration, years	$n = 31$	$n = 67$
Mean (SD)	7.9 (8.70)	10.6 (12.69)
Median (IQR)	4.0 (2.0; 14.0)	5.0 (2.0; 13.0)
ppPASI score (0–48)	$n = 39$	$n = 78$
Mean (SD)	12.7 (7.05)	14.8 (9.70)
Median (IQR)	12.0 (6.6; 19.5)	11.9 (7.2; 20.4)
ppIGA score	$n = 39$	$n = 78$
Moderate (3), n (%)	25 (64.1)	53 (67.9)
Severe (4), n (%)	14 (35.9)	25 (32.1)
BSA score (%)	$n = 39$	$n = 78$
Mean (SD)	6.9 (3.74)	7.0 (4.25)
Median (IQR)	6.0 (4.0; 8.0)	6.0 (4.0; 9.0)
PASI score (0–72)	$n = 39$	$n = 78$
Mean (SD)	6.0 (2.27)	6.2 (1.93)
Median (IQR)	5.7 (3.7; 8.0)	6.0 (4.8; 7.9)
ppQLI score	$n = 39$	$n = 78$
Palms		
Mean (SD)	41.0 (14.21)	43.4 (15.74)
Median (IQR)	41.0 (29.0; 52.0)	42.5 (31.0; 55.0)

Table 1: Continued.

Variable	Placebo	Guselkumab 100 mg q8w
Soles		
Mean (SD)	33.0 (13.78)	33.9 (14.54)
Median (IQR)	32.0 (19.0; 44.0)	32.5 (21.0; 49.0)
Total score		
Mean (SD)	43.4 (13.02)	45.9 (14.34)
Median (IQR)	42.0 (32.0; 54.0)	46.5 (33.0; 57.0)
DLQI score (0–30)	$n = 39$	$n = 77$
Mean (SD)	14.4 (5.87)	15.0 (7.49)
Median (IQR)	14.0 (10.0; 19.0)	15.0 (9.0; 21.0)
WPAI: PSO questionnaire	$n = 29$	$n = 50$
Absenteeism, mean (SD)	13.9 (31.65)	8.6 (24.10)
Total work productivity impairment, mean (SD)	38.5 (34.98)	41.3 (34.29)
	$n = 39$	$n = 78$
Psoriasis-related nonbiologic, *n* (%)	2 (5.1%)	2 (2.6%)
Other emollients and protectives, *n* (%)	0	2 (2.6%)

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; ppIGA, palmoplantar Investigator's Global Assessment; ppPASI, palmoplantar PASI; ppQLI, palmoplantar Quality-of-Life Instrument; q8w, every 8 weeks; SD, standard deviation; WPAI:PSO, Work Productivity and Activity Impairment: Psoriasis.

Table 2: Primary efficacy endpoint and major secondary efficacy endpoints during double-blind phase (week 16) based on the composite estimand strategy (full analysis set).

	Double-blind phase (week 16)	
	Placebo	Guselkumab 100 mg q8w
Full analysis set	$n = 39$	$n = 78$
Primary efficacy endpoint		
ppPASI75 response at week 16, *n* (%)	11 (28.2)	28 (35.9)
% Difference (95% CI)		7.7 (−11.5, 24.7)
p value		0.533
Major secondary efficacy endpoints: changes from the baseline to week 16		
ppPASI change from the baseline[†‡§]		
LS mean (95% CI)	−7.670 (−9.614, −5.727)	−6.713 (−8.083, −5.343)
LS mean difference (95% CI)		0.957 (−1.427, 3.341)
p value		0.428
aPASI change from the baseline[†‡§]		
LS mean (95% CI)	−1.361 (−2.439, −0.283)	−2.924 (−3.686, −2.162)
LS mean difference (95% CI)		−1.563 (−2.884, −0.241)
p value		0.021
ppIGA change from the baseline[†‡§]		
LS mean (95% CI)	−0.865 (−1.244, −0.486)	−1.094 (−1.362, −0.826)
LS mean difference (95% CI)		−0.229 (−0.693, 0.235)
p value		0.330
f-PGA change from the baseline[†‡§]		
LS mean (95% CI)	−0.300 (−0.629, 0.030)	−0.429 (−0.662, −0.197)
LS mean difference (95% CI)		−0.130 (−0.533, 0.274)
p value		0.526
BSA change from the baseline[†‡§]		
LS mean (95% CI)	−1.076 (−2.247, 0.095)	−3.645 (−4.473, −2.817)
LS mean difference (95% CI)		−2.570 (−4.004, −1.135)
p value		<0.001
DLQI change from the baseline[†‡§]		
LS mean (95% CI)	−3.892 (−6.034, −1.750)	−5.977 (−7.501, −4.453)
LS mean difference (95% CI)		−2.085 (−4.715, 0.545)
p value		0.119
ppQLI change from the baseline[†‡§]		
LS mean (95% CI)	−7.654 (−11.453, −3.855)	−9.417 (−12.099, −6.734)
LS mean difference (95% CI)		−1.763 (−6.421, 2.896)
p value		0.455

Table 2: Continued.

	Double-blind phase (week 16)	
	Placebo	Guselkumab 100 mg q8w
EQ-5D-5L change from the baseline[†‡§]		
LS mean (95% CI)	0.128 (0.052, 0.203)	0.111 (0.057, 0.164)
LS mean difference (95% CI)		−0.017 (−0.109, 0.076)
p value		0.718

[†]The change from the baseline using observed data or 0 (no improvement) if a participant met treatment failure criteria prior to week 16. Participants with missing week 16 score are included with a score of "no improvement." [‡]LS means and p values are based on a mixed model for repeated measures under the missing at random assumption for missing data except for missing week 16 data. [§]95% CIs were based on the Chan–Zhang method for binary response efficacy endpoints. *Note.* Under the composite estimand strategy, treatment effects are assessed not only based on the variable measurements but also on intercurrent events defined in treatment failure criteria. The participant is assigned a score of no improvement for continuous variables if the participant meets any treatment failure criteria. ppPASI75 response is defined as ≥75% improvement in the ppPASI score from the baseline. In the calculation of ppPASI, the pustules score is considered 0 and the index has a maximum score of 48. aPASI, absolute Psoriasis Area and Severity Index; BSA, body surface area; CI, confidence interval; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life, 5-Dimension, 5-Level; f-PGA, fingernail Physician's Global Assessment; LS, least squares; ppIGA, palmoplantar Investigator's Global Assessment; ppPASI, palmoplantar Psoriasis Area and Severity Index; ppQLI, palmoplantar Quality-of-Life Instrument; q8w, every 8 weeks.

for the guselkumab and placebo groups were 5.6 and 4.8 at the baseline and 0.8 and 1.6 at Wk16, and median sole scores were 7.2 and 6.0 at the baseline and 1.2 and 2.4 at Wk16, respectively. Median palm scores at Wk48 were 0.4 for both the guselkumab and placebo-crossover groups, while median sole scores were 0.15 and 0.3, respectively.

3.2.2. Biomarker Analysis. Baseline serum IL-17A and IL-22 levels for participants with ppPsO were significantly elevated compared with those for HCs (1.59-fold, $p = 0.01$; 1.88-fold, $p = 4 \times 10^{-4}$, respectively) and were significantly correlated with baseline PASI scores (Appendix G, Figure S1). Serum IL-17F levels were not significantly elevated at the baseline for ppPsO participants compared with those for HCs (1.1-fold, $p = 0.4$) but were correlated with the baseline PASI score ($r = 0.36$; $p < 1 \times 10^{-4}$). However, levels for none of the analytes correlated with the baseline ppPASI score (Appendix G, Figure S2). Baseline serum biomarker levels were comparable between ppPASI75 responders and nonresponders (Appendix G, Figure S3).

Further analyses showed that serum IL-17A, IL-17F, and IL-22 levels were significantly decreased at Wk16 from the baseline in the guselkumab group but not in the placebo group (Figure 5). The degree of reduction in IL-17F levels at Wk16 was significantly greater for the guselkumab group compared with that for the placebo group; however, reductions of serum IL-17A and IL-22 at Wk16 in the guselkumab group were larger than but not statistically different from the placebo group. From Wk16 through Wk48, IL-17A, IL-17F, and IL-22 levels in the guselkumab and placebo-crossover groups were significantly reduced compared with the baseline.

3.3. Safety. Safety findings were consistent with other guselkumab psoriasis trials, with no new safety signals or adverse events of special interest identified. An overall summary of TEAEs through Wk16 and Wk56 is presented in Table 4. Through Wk56, TEAEs were reported by 87.2% ($n = 68$) of the guselkumab participants and 56.4% ($n = 22$) of the placebo-crossover participants. There were no deaths or cases of anaphylactic reaction/serum sickness, malignancy, inflammatory bowel disease, or active TB.

4. Discussion

G-PLUS is the first clinical trial to evaluate biologic treatment in a cohort of participants with moderate-to-severe nonpustular ppPsO but limited psoriasis involving other body regions (PASI ≥3 and <10). Previous trials have either included pustular and nonpustular forms of ppPsO and/or patients with more extensive BSA involvement [20–22]. The strength of G-PLUS is that it focussed on individuals whose predominant disease feature was palm/sole involvement because such patients are typically under-represented in clinical trials, leading to limited available data [14, 15, 20–25]. Clearance of skin lesions is a goal for patients with psoriasis irrespective of disease location or severity [8]. G-PLUS was, therefore, designed to study the impact of guselkumab treatment in this patient population with high unmet need and difficult-to-treat disease.

Guselkumab improved signs and symptoms of nonpustular ppPsO based on ppPASI75 response at Wk16. Although a numerically higher ppPASI75 response at Wk16 was observed for the guselkumab group compared with the placebo group, the difference in response rates was not statistically significant; therefore, the primary efficacy endpoint was not met. However, when assessing more stringent clinical endpoints, such as ppIGA 0/1, ppPASI90, and ppPASI100 responses at Wk16, greater numerical improvements were observed with guselkumab vs. placebo treatment. Improvements for the guselkumab group vs. the placebo group appeared further accentuated in post hoc subgroup analyses limited to participants who were obese at the baseline, a characteristic typically associated with more difficult-to-treat disease.

The therapeutic profile of guselkumab as a highly effective treatment for moderate-to-severe psoriasis is well established [14–17, 26–29], and prespecified analyses of patients with moderate-to-severe plaque psoriasis (PASI ≥12) in the VOYAGE 1 and 2 trials showed that guselkumab treatment was associated with a significantly greater response rate in achieving clear/near-clear skin on the hands/feet (hf-PGA 0/1;

Table 3: Primary and other clinical and quality-of-life efficacy endpoints by visit through week 48 using multiple imputation and including nonresponse of discontinuations (full analysis set).

	Double-blind phase (week 16)		Open-label phase (week 24)		Open-label phase (week 48)	
	Placebo	Guselkumab 100 mg q8w	Placebo-crossover	Guselkumab 100 mg q8w	Placebo-crossover	Guselkumab 100 mg q8w
ppPASI response						
ppPASI75, *n*/*N* (%)	11/39 (28.2)	28/78 (35.9)	19/39 (48.7)	40/78 (51.3)	25/39 (64.1)	43/78 (55.1)
95% CI[†]	15.55, 45.10	25.57, 47.62	32.71, 64.97	39.78, 62.66	47.15, 78.32	43.49, 66.26
ppPASI90, *n*/*N* (%)	6/39 (15.4)	19/78 (24.4)	8/39 (20.5)	28/78 (35.9)	16/39 (41.0)	30/78 (38.5)
95% CI[†]	6.41, 31.21	15.65, 35.63	9.87, 36.94	25.57, 47.62	25.98, 57.81	27.87, 50.20
ppPASI100, *n*/*N* (%)	2/39 (5.1)	11/78 (14.1)	5/39 (12.8)	20/78 (25.6)	8/39 (20.5)	21/78 (26.9)
95% CI[†]	0.89, 18.63	7.59, 24.26	4.82, 28.23	16.72, 37.00	9.87, 36.94	17.79, 38.36
ppIGA 0/1 response and ≥2-point reduction from baseline in ppIGA score, *n*/*N* (%)	6/39 (15.4)	27/78 (34.6)	9/39 (23.1)	28/78 (35.9)	19/39 (48.7)	33/78 (42.3)
95% CI[†]	6.41, 31.21	24.44, 46.32	11.71, 39.72	25.57, 47.62	32.71, 64.97	31.37, 54.01
PASI response						
PASI75, *n*/*N* (%)	10/39 (25.6)	23/78 (29.5)	15/39 (38.5)	35/78 (44.9)	22/39 (56.4)	42/78 (53.8)
95% CI[†]	13.60, 42.43	19.97, 41.04	23.81, 55.35	33.74, 56.51	39.77, 71.81	42.24, 65.07
PASI90, *n*/*N* (%)	2/39 (5.1)	11/78 (14.1)	4/39 (10.3)	24/78 (30.8)	12/39 (30.8)	27/78 (34.6)
95% CI[†]	0.89, 18.63	7.59, 24.26	3.34, 25.16	21.08, 42.38	17.55, 47.73	24.44, 46.32
PASI100, *n*/*N* (%)	1/39 (2.6)	7/78 (9.0)	3/39 (7.7)	16/78 (20.5)	6/39 (15.4)	15/78 (19.2)
95% CI[†]	0.13, 15.08	3.99, 18.17	2.01, 21.97	12.53, 31.46	6.41, 31.21	11.51, 30.05
DLQI 0/1 score, *n*/*N* (%)	3/39 (7.7)	14/73 (19.2)	9/39 (23.1)	16/73 (21.9)	15/39 (38.5)	25/73 (34.2)
95% CI[†]	2.01, 21.97	11.25, 30.42	11.71, 39.72	13.41, 33.42	23.81, 55.35	23.79, 46.37

[†]95% CIs are based on Wilson with continuity correction. ppPASI75/90/100 response is defined as ≥75/90/100% improvement in the ppPASI score from the baseline. ppIGA response is defined as a ppIGA score of 0 (cleared) or 1 (almost clear/minimal) AND ≥ 2-grade reduction from the baseline in the IGA score. PASI75/90/100 response is defined as ≥75/90/100% improvement in PASI score from baseline. In the calculation of the ppPASI, the pustules score is considered 0 and the index has a maximum score of 48. CI, confidence interval; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; ppIGA, palmoplantar Investigator's Global Assessment; ppPASI, palmoplantar PASI; q8w, every 8 weeks.

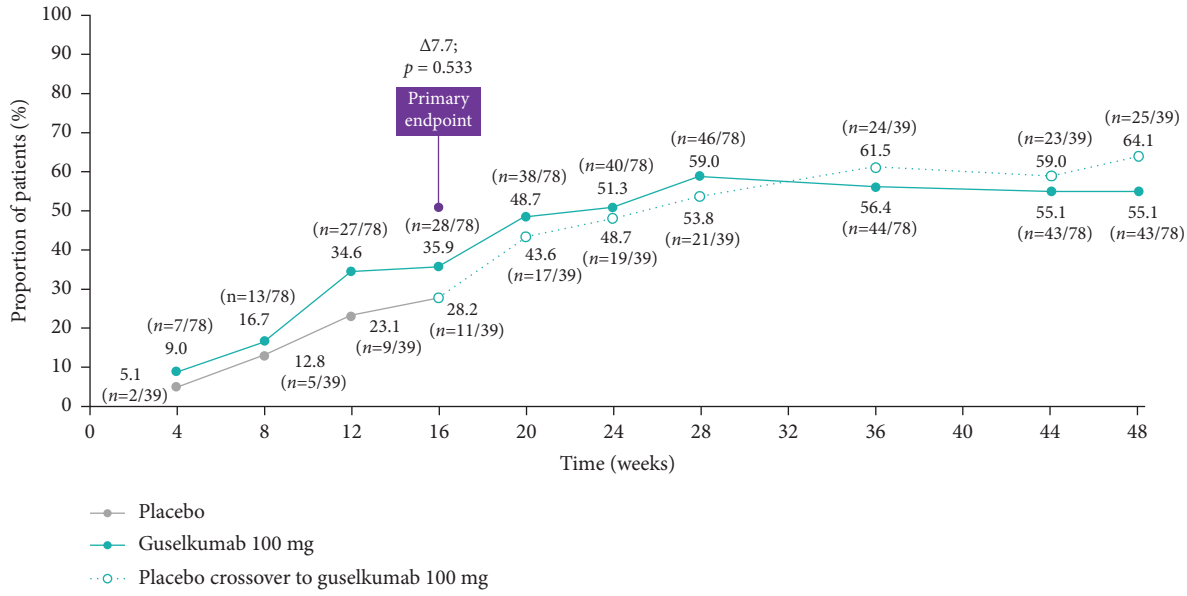

FIGURE 3: Proportion of participants achieving ppPASI75 response by visit through week 48 (full analysis set). Data missing due to discontinuation of treatment are imputed with nonresponse (0). Data missing due to reasons other than discontinuation of treatment are imputed using multiple imputation. The ppPASI evaluates erythema, pustules, and desquamation on a 5-point scale (where 0 = absent and 4 = very severe) along with the extent to which the palms and/or soles are affected on a 6-point scale (where 0 = absent and 6 = 90–100%). In line with the inclusion criteria, the score for pustules was set at 0; thus, the index had a maximum score of 48. ppPASI75 response is defined as ≥75% improvement in the ppPASI score from the baseline. ppPASI, palmoplantar Psoriasis Area and Severity Index.

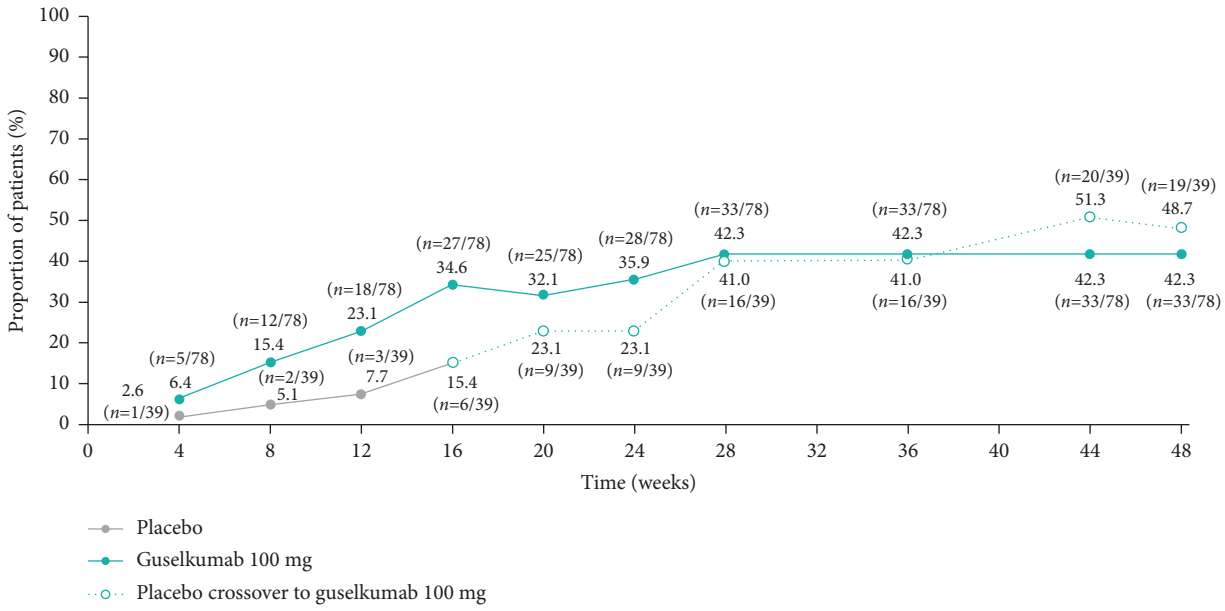

FIGURE 4: Proportion of participants achieving a ppIGA response by visit through week 48 (full analysis set). Data missing due to discontinuation of treatment are imputed with nonresponse (0). Data missing due to reasons other than discontinuation of treatment are imputed using multiple imputation. The ppIGA scale score is based on the version of the IGA modified in 2011. ppIGA response is defined as a ppIGA score of 0 (clear) or 1 (almost clear/minimal) and a ≥2-point reduction from the baseline in the ppIGA score. IGA, Investigator's Global Assessment; ppIGA, palmoplantar Investigator's Global Assessment.

an endpoint not reported in G-PLUS) vs. placebo at Wk16 and vs. adalimumab at Wk24 [18]. Moreover, guselkumab has demonstrated efficacy for the treatment of palmoplantar pustulosis, leading to regulatory approval for this indication in several countries [30]. Consequently, not meeting the primary endpoint in G-PLUS was unexpected.

A limitation of G-PLUS is that the trial was conducted during the COVID-19 pandemic. Most (≥80%) of the primary

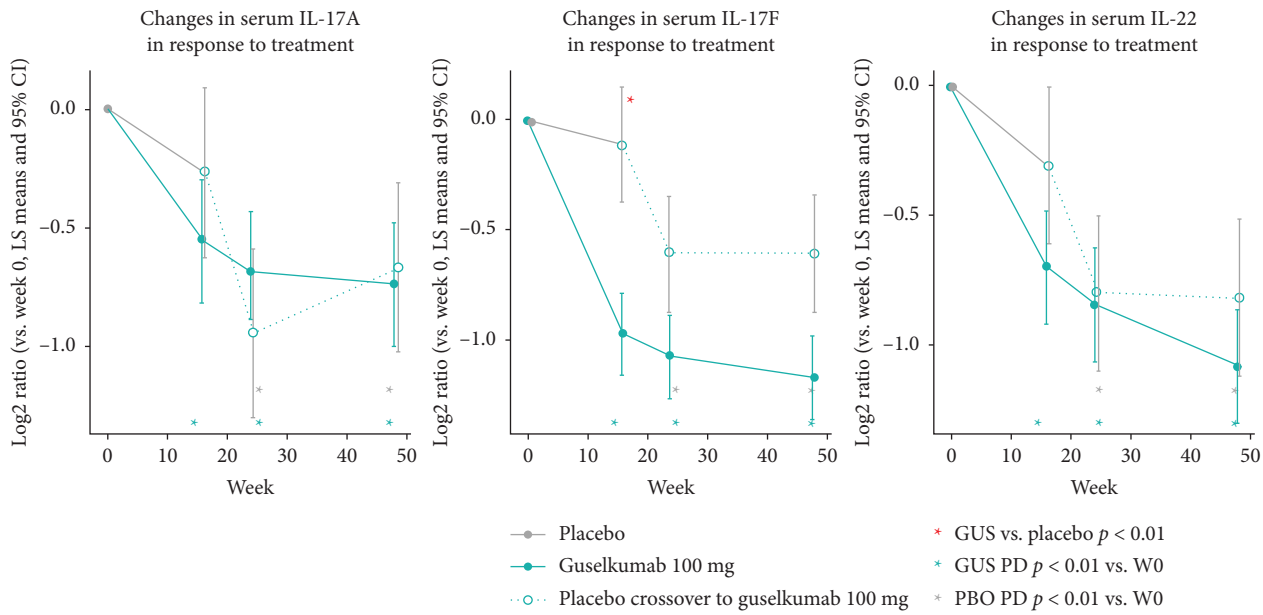

Figure 5: Pharmacodynamic effects on IL-17A, IL-17F, and IL-22 are different for guselkumab and placebo groups at week 16. CI, confidence interval; GUS, guselkumab; IL, interleukin; LS, least squares; PBO, placebo; PD, pharmacodynamic; W, week.

endpoint assessments were conducted between April 2020 and March 2021, and the results may have been impacted by national lockdowns that took place in France, Germany, Italy, Spain, and the United Kingdom during this time [31–35]. Restricted movement outside the home and reduced capacity to work may have limited exposure to triggering factors and physical insults that often lead to Koebnerisation and exacerbation of palmoplantar disease [36]. In addition, the use of topical emollients was permitted throughout the trial. These factors may have contributed [37] to the second key limitation, the higher-than-expected placebo response across all clinical endpoints, which was more than double the placebo response rates from earlier trials used for purposes of sample size calculation in G-PLUS. In the GESTURE trial for secukinumab in ppPsO, the Wk16 ppIGA 0/1 response rate for placebo was <5% [21], while in the VOYAGE 1 phase III trial for guselkumab in plaque psoriasis, the hf-PGA 0/1 placebo response rate at Wk16 was 14.2% [18]. In contrast, in G-PLUS, the ppPASI75 placebo response rate at Wk16 was almost 30%. There was no equivalent variation in study biologic treatment response rates; for example, ppIGA 0/1 response was achieved by 33.3% of the participants receiving secukinumab in GESTURE and 34.6% of the participants receiving guselkumab in G-PLUS.

It is also important to note that trials of other biologic agents for the treatment of ppPsO differ from G-PLUS in important ways. As mentioned above, other trials recruited a broader range of patients, including those with pustular or nonpustular palmoplantar disease and more generalised involvement of plaque psoriasis elsewhere on the body. In addition, different primary efficacy endpoints were used in other trials. The primary efficacy endpoint of the GESTURE trial was the proportion of patients achieving ppIGA 0/1 response at Wk16, while in an open-label trial of adalimumab, change in the Physician's Global Assessment score from the baseline to Wk12 was used [20, 21]. In contrast, the primary efficacy endpoint in the G-PLUS trial was the proportion of ppPASI75 responders at Wk16. Although PASI-based outcomes generally provide robust assessments of response to treatment, they can be insensitive to changes in the context of relatively limited extent of disease, as is the case with palmoplantar disease [38].

Disease- and patient-specific factors may have also limited the separation of response rates for the guselkumab and placebo groups. In the context of ppPsO, which is widely considered to be a difficult-to-treat variant of psoriatic disease, a Wk16 endpoint may be too short to fully assess treatment response [4]. Consistent with this, continued improvements were observed beyond Wk16 in the guselkumab group, with a potential response plateau not being reached until Wk28. Furthermore, in patients with ppPsO who have limited psoriasis elsewhere on the body, palmoplantar disease represents a disproportionately high proportion of overall BSA involvement that may be particularly recalcitrant to treatment [2]. These factors likely account for why overall PASI skin responses in G-PLUS were substantially lower than those observed in previous guselkumab trials in moderate-to-severe plaque psoriasis and were lower than the rate assumed in our sample size calculations. These factors should be taken into consideration in the design of future trials in this patient population.

In addition, participants in the guselkumab group had more features at the baseline associated with challenging-to-treat disease compared with those randomised to placebo. In particular, the guselkumab group had a higher proportion of obese participants, and participants randomised to guselkumab had longer disease duration and more severe palm and/or sole involvement. Despite this, numerically greater reductions of median ppPASI palm and sole scores were observed in the guselkumab group compared with the placebo group at Wk16;

Table 4: Treatment-emergent adverse events through week 16 and week 56.

	Treatment-emergent AEs through week 16 (double-blind)		Treatment-emergent AEs on guselkumab through week 56		
	Placebo	Guselkumab 100 mg q8w	Placebo-crossover[†]	Guselkumab 100 mg q8w	Guselkumab combined q8w
Analysis set: safety analysis set, *n*	39	78	39	78	117
Participants with one or more of the following, *n* (%):					
AEs	24 (61.5)	50 (64.1)	22 (56.4)	68 (87.2)	90 (76.9)
Nasopharyngitis	—	—	9 (23.1)	35 (44.9)	44 (37.6)
Arthralgia	—	—	0	7 (9.0)	7 (6.0)
Back pain	—	—	3 (7.7)	3 (3.8)	6 (5.1)
Headache	—	—	4 (10.3)	6 (7.7)	10 (8.5)
Diarrhoea	—	—	2 (5.1)	13 (16.7)	15 (12.8)
Injury, poisoning, and procedural complications	—	—	3 (7.7)	12 (15.4)	15 (12.8)
Psoriasis	—	—	0	4 (5.1)	4 (3.4)
Fatigue	—	—	0	5 (6.4)	5 (4.3)
C-reactive protein increased	—	—	2 (5.1)	0	2 (1.7)
Metabolism and nutrition disorder	—	—	1 (2.6)	6 (7.7)	7 (6.0)
Respiratory, thoracic, and mediastinal disorders	—	—	1 (2.6)	6 (7.7)	7 (6.0)
Hypertension	—	—	0	5 (6.4)	5 (4.3)
SAEs	2 (5.1)	4 (5.1)	2 (5.1)	5 (6.4)	7 (6.0)
AEs leading to discontinuation of trial intervention	0	2 (2.6)	0	3 (3.8)	3 (2.6)
AEs with severe intensity	1 (2.6)	1 (1.3)	1 (2.6)	3 (3.8)	4 (3.4)
Infections	8 (20.5)	27 (34.6)	9 (23.1)	35 (44.9)	44 (37.6)
Serious infections	1 (2.6)	1 (1.3)	1 (2.6)	1 (1.3)	2 (1.7)
Injection site reactions	1 (2.6)	0	2 (5.1)	0	2 (1.7)
Anaphylactic reactions or serum sickness	0	0	0	0	0
Events of psoriasis	0	0	0	4 (5.1)	4 (3.4)
Events leading to death	0	0	0	0	0
Events of malignancy	0	0	0	0	0
Events of active tuberculosis	0	0	0	0	0

Note. Subjects were counted once only for any given event, regardless of the number of times they experienced the event. AEs are coded using Medical Dictionary for Regulatory Activities Version 21.1 for AEs through week 16 and 24.1 for AEs through week 56. [†]For placebo-randomised subjects, only those AEs with start date at or after crossover to guselkumab (i.e., week 16) are included in this column. AE, adverse event; q8w, every 8 weeks; SAE, serious adverse event.

moreover, comparable levels of improvement were seen for the guselkumab and placebo-crossover groups at Wk48. Taken together, these observations suggest an overall positive impact of guselkumab treatment on nonpustular ppPsO.

Reductions in serum biomarker levels also trended with improvements in nonpustular ppPsO. Serum IL-17A and IL-22 levels were found to be elevated in participants with ppPsO compared with HCs, and consistent with findings from the VOYAGE 1 trial in patients with moderate-to-severe plaque psoriasis, treatment with guselkumab led to reductions in serum IL-17A, IL-17F, and IL-22 levels at Wk16 and Wk48 compared with the baseline [39]. Placebo-crossover participants also had significantly decreased levels of these cytokines at Wk48 compared with the baseline, consistent with the on-target pharmacodynamic effects of guselkumab. In addition to the intriguing and unexpected finding that baseline biomarker levels did not correlate with ppPsO severity based on ppPASI scores, it is notable that the magnitude of cytokine reductions was lower than in moderate-to-severe plaque psoriasis in VOYAGE 1 [39]. This may potentially reflect the overall lower burden of generalised plaque psoriasis in the G-PLUS trial population or the more recalcitrant nature of palmoplantar disease. The biomarker results of G-PLUS add to the findings of a recent study that identified distinct patterns of inflammatory activation in participants with pustular and nonpustular ppPsO [40]; in particular, in nonpustular ppPsO, IL-17A signalling may be less relevant and interferon-γ may be relatively more important, a profile that could have contributed to the lower-than-anticipated treatment benefit with guselkumab.

5. Conclusion

G-PLUS is the first clinical trial to evaluate biologic treatment of nonpustular ppPsO in individuals with limited involvement of plaque psoriasis elsewhere on the body. Although the primary efficacy endpoint was not met, given the unanticipated high placebo response, more stringent clinical endpoints showed greater numerical improvements favouring guselkumab at Wk16. Similar observations were noted for participants with characteristics associated with more challenging-to-treat disease, such as obesity. Further studies are warranted to better understand the impact of guselkumab treatment in patients with ppPsO.

Data Availability

The data used to support the findings of this study are available on request from the corresponding author.

Ethical Approval

An institutional review board or Ethics Committee approved the trial protocol at each participating site.

Consent

All participants provided written informed consent before trial initiation.

Conflicts of Interest

Thierry Passeron is an investigator for and/or receives honoraria for consultancy/advisory boards from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi Genzyme, Sun Pharma, and UCB. Jose Manuel Carrascosa received honoraria for participation in advisory boards, as a clinical trial investigator and/or as a speaker from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Mylan, Novartis, Pfizer, Sandoz, and UCB. Richard B. Warren receives research grants and/or consultancy/speaker honoraria from AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Janssen, LEO Pharma, Medac, Novartis, Pfizer, and UCB and received consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE Therapeutics, Eli Lilly, GSK, Janssen, LEO Pharma, Medac, Novartis, Pfizer, Sanofi, Sun Pharma, UCB, and UNION. Andreas Pinter received honoraria as an investigator, speaker honoraria, and/or grants from the following companies and/or has been an advisor for the following companies: AbbVie, Almirall Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GSK, Hexal, Janssen, LEO Pharma, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz Biopharmaceuticals, Schering-Plough, Tigercat Pharma, and UCB. Marco Romanelli receives research grants from AbbVie, Almirall, Eli Lilly, EmoLED, Janssen, LEO Pharma, and Novartis. Ahlem Azzabi, Michela Efficace, Patricia Gorecki, Maria Jazra, and Katya Lemos are employees of Janssen-Cilag and own stock or stock options in Johnson & Johnson. Steve Fakharzadeh and Ya-Wen Yang are employees of Janssen Global Services, LLC, and own stock or stock options in Johnson & Johnson. Yanqing Chen and Monica Leung are employees of Janssen Research and Development, LLC, and own stock or stock options in Johnson & Johnson. Diamant Thaçi is a lecturer and/or consultant for AbbVie, Almirall, Amgen, Asana Biosciences, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Novartis, Regeneron, Sandoz, Sanofi-Aventis, and UCB and has received grants from LEO Pharma and Novartis (paid to institution).

Authors' Contributions

All the authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Supplementary Materials

File: Appendices. File name: G-PLUS appendices_04Oct23.docx. File contents: Appendices A to G of additional content for our manuscript. The contents of each appendix are listed below. (i) Appendix A: exclusion criteria and treatment failure criteria. (a) Table S1: exclusion criteria. (b) Table S2: treatment failure criteria. (ii) Appendix B: trial intervention discontinuations prior to week 56. (a) Table S1: number of participants who discontinued trial intervention prior to week 56 by reason for discontinuation (full analysis set). (iii) Appendix C: proportion of participants achieving PASI90 through week 48. (a) Figure S1: proportion of participants achieving PASI90 response by visit through week 48 (full analysis set). (iv) Appendix D: demographic and baseline disease characteristics for participants achieving a ppPASI75 response at week 16. (a) Table S1: demographic and baseline disease characteristics for participants achieving a ppPASI75 response at week 16. (v) Appendix E: post hoc analyses: selected efficacy endpoints by the obesity status at the baseline. (a) Figure S1: proportion of participants achieving ppPASI75, ppIGA 0/1, and PASI90 responses at week 16 and week 48 for obese (BMI $\geq$30 kg/m^2) and nonobese (BMI <30 kg/m^2) participants. (vi) Appendix F: post hoc analyses of ppPASI palm and sole scores by visit. (a) Table S1: summary of ppPASI palm and sole scores by visit through week 48 observed data (full analysis set). (vii) Appendix G: biomarker data. (a) Figure S1: serum IL-17A, IL-17F, and IL-22 significantly correlate with PASI scores at the baseline. (b) Figure S2: serum IL-17A, IL-17F, and IL-22 do not correlate with ppPASI scores at the baseline. (c) Figure S3: no significant difference in baseline biomarkers between week 16 ppPASI75 responders and nonresponders. (*Supplementary Materials*)

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