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ORIGINAL ARTICLE

Early disease intervention with guselkumab in psoriasis leads to a higher rate of stable complete skin clearance ('clinical super response'): Week 28 results from the ongoing phase IIIb randomized, double-blind, parallel-group, GUIDE study

K. Schäkel¹  | K. Reich²  | K. Asadullah^{3,4} | A. Pinter⁵  | D. Jullien⁶  | P. Weisenseel⁷ | C. Paul⁸ | M. Gomez⁹ | S. Wegner⁹ | Y. Personke⁹  | F. Kreimendahl⁹ | Y. Chen¹⁰  | J. Angsana¹⁰ | M. W. L. Leung¹⁰ | K. Eyerich¹¹

¹Department of Dermatology, and Interdisciplinary Center for Inflammatory Diseases, Heidelberg University Hospital, Heidelberg, Germany

²Translational Research in Inflammatory Skin Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

³Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany

⁴Prof. Dr. med. Asadullah, Dermatological Practice, Potsdam, Germany

⁵University Hospital Frankfurt am Main, Frankfurt, Germany

⁶Department of Dermatology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

⁷Dermatologikum Hamburg, Hamburg, Germany

⁸Toulouse University, Toulouse, France

⁹Janssen-Cilag GmbH, Neuss, Germany

¹⁰Janssen R&D, LLC, San Diego, USA

¹¹Department of Dermatology and Venereology, Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

Correspondence

K. Schäkel, Department of Dermatology, and Interdisciplinary Center for Inflammatory Diseases, Heidelberg University Hospital, Heidelberg, Germany.
Email: knut.schaekel@med.uni-heidelberg.de

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Abstract

Background: Guselkumab is an interleukin (IL)-23 inhibitor with demonstrated efficacy in patients with psoriasis.

Objectives: Evaluate the impact of early disease intervention on clinical responses following 28 weeks of guselkumab treatment in patients with moderate-to-severe plaque psoriasis. Correlate clinical response and disease duration data with serum biomarker data.

Methods: GUIDE is a phase IIIb randomized, double-blind, parallel-group, multi-centre study of adults with moderate-to-severe plaque psoriasis. In study part 1, patients with a short disease duration (SDD [≤ 2 years]) or a long disease duration (LDD [> 2 years]) received guselkumab 100 mg at Week (W) 0, 4, 12, and 20. Those achieving complete skin clearance at W20 and W28 were defined as a super responder (SRe). A multivariable logistic regression analysed the association between baseline factors and the likelihood of becoming an SRe. The relationship between clinical response, disease duration and serum biomarker data was assessed at W0 and 4.

Results: In total, 880 patients were enrolled (SDD/LDD = 40.6%/59.4% of patients). More SDD than LDD patients achieved absolute Psoriasis Area and Severity Index (PASI) = 0 at W28 (51.8% vs. 39.4%) and were SRes (43.7% vs. 28.1% [overall 34.4%]). SDD patients also achieved PASI = 0 quicker than LDD patients (median 141 vs. 200 days). Disease duration and prior biologic use had the greatest impact on becoming an SRe, with no strong association among these independent variables. At baseline, there were no significant differences in the serum biomarker levels of IL-17A, IL-17F, IL-22 and β -defensin 2 between SDD and LDD patients, or between SRe and non-SRe patients. Guselkumab rapidly decreased these markers of systemic inflammation across all patient groups analysed at W4. Guselkumab was well tolerated.

Conclusions: Guselkumab efficacy was consistent across subpopulations, on the skin and systemically. The proportion of SRes was higher in SDD than LDD patients, indicating early treatment intervention may improve clinical outcomes.

Study code: NCT03818035 (ClinicalTrials.gov identifier)

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INTRODUCTION

Patients with moderate-to-severe plaque psoriasis have a substantial disease burden and impaired health-related quality of life (HRQoL), and usually require lifelong treatment.¹⁻⁴ Initially, patients are typically treated with a combination of ultraviolet light, topical and conventional systemic therapies.⁵⁻⁷ Thus, biologic therapy is often not provided until after other treatments have failed—registries have determined the mean disease duration is 17.1–21.8 years prior to receiving biologic therapy.⁸⁻¹⁰

Interleukin (IL)-23 has emerged as a key regulator of inflammatory pathways in psoriasis owing to its upstream role in the IL-23/IL-17A/IL-17F immune axis,^{1,4} and its role in maintaining the presence of tissue-resident memory T (T_{RM}) cells,¹¹ which are associated with recurrence of psoriatic lesions in previously affected skin sites.^{12,13} The expression of IL-23, IL-17A, IL-17F, as well as IL-22 and β -defensin 2 (BD-2), is increased within lesional versus non-lesional skin,¹⁴⁻¹⁷ and respective serum levels can correlate with clinical response.¹⁸⁻²² Preclinical research has indicated a role for these cytokines in the proliferation of keratinocytes and skin inflammation.^{23,24} IL-23 also impairs the function of regulatory T cells (T_{regs}), which normally suppress inflammation and effector T cells, and instead promotes differentiation of T_{regs} into pro-inflammatory T helper 17 (Th17)-like cells.²⁵⁻²⁸ Blockade of IL-23 reduces the level of lesional T_{RM} cells¹¹ and IL-17A.^{29,30}

Early intervention with biologic therapies increases remission rates and improves symptoms in rheumatoid arthritis,^{31,32} and similar findings may apply to patients with moderate-to-severe psoriasis.^{19,33} A multivariate prediction model from data of the VOYAGE 2 study demonstrated that disease duration, Investigator's Global Assessment 0 response and guselkumab concentration at Week (W) 28 resulted in a high predictive power for long-term maintenance of a relative Psoriasis Area and Severity Index (PASI) 90 response after guselkumab withdrawal.³⁴ These results may suggest that patients with a shorter disease duration may more readily achieve long-term, drug-free disease control than patients with a longer disease duration.

This interim analysis of the GUIDE study evaluates the impact of psoriasis duration on clinical response following 28 weeks of guselkumab treatment, including the proportion of patients who became a super responder (SRe), defined as complete skin clearance at W20 and W28.^{35,36} In addition, clinical response and disease duration data are correlated with blood serum biomarker data at W0 and W4. This analysis is distinct from the primary objective of the study, which is to demonstrate that SRes maintain disease control at W68 with prolonged treatment intervals. The study will also assess whether early intervention results in better clinical responses and a more durable maintenance of response following drug withdrawal. Primary endpoint data will be reported in a subsequent publication.

MATERIALS AND METHODS

Study design

GUIDE (NCT03818035) is an ongoing phase IIIb, randomized, double-blind, parallel-group, multicentre study in adults (≥ 18 years old) with moderate-to-severe plaque psoriasis.³⁶ The study has three parts (Figure 1): in part 1 (the focus of this publication), patients are not randomized, and receive guselkumab 100 mg at W0, 4, 12 and 20. Part 1 ends following clinical assessments at W28, and patients maintaining complete skin clearance (PASI=0) at W20 and W28 are termed SRes. In part 2 (W28–68), SRes are randomized to receive guselkumab every 8 weeks (q8w; group 2a) or every 16 weeks (q16w; group 2b), and patients with a short disease duration (SDD [first psoriasis symptoms ≤ 2 years before screening]) are equally stratified across both regimens. Participants with a PASI score of >0 at W20 and/or W28 continue to receive guselkumab injections q8w until W60 (group 2c). In part 3, SRes in groups 2a and 2b who achieve an absolute PASI score of <3 at W68 will be withdrawn from guselkumab and be followed up to W220 (groups 3a or 3b, respectively), while SRes with a PASI score of ≥ 3 at W68 or a PASI score of >5 at any visit during part 2 or 3 will enter the re-treatment arms (groups 2d or 3c) and receive guselkumab at that visit, and then 8 and 16 weeks later.

GUIDE was designed and will be conducted in accordance with the Harmonised Tripartite Guidelines for Good Clinical Practice from the International Conference on Harmonisation, with applicable local regulations, and in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Patients

A ratio of 40:60 for SDD:long disease duration (>2 years; LDD) patients was planned based on pivotal trial analysis.^{37,38} Key inclusion criteria (detailed in the Appendix S1) included moderate-to-severe plaque type psoriasis defined by a PASI score >10 or affected body surface area (BSA) $>10\%$, and a Dermatology Life Quality Index (DLQI) score >10 at baseline. All patients were eligible for biologic therapy.

Endpoints and assessments

The primary endpoint is the percentage of patients achieving absolute PASI <3 at W68. Secondary endpoints are presented in this publication and include time to PASI75/90 and PASI=0 response from baseline for SDD and LDD patients (and for SRes vs. non-SRes for PASI=0), and PASI response (relative PASI75/90 and absolute PASI <3 , ≤ 1 and 0) rates over time (including W20 and W28) per patient group. The proportion of patients achieving a DLQI score of 0/1 at W28 was also assessed. Safety was assessed by evaluating adverse events (AEs) using MedDRA-defined terms in the intention-to-treat population.

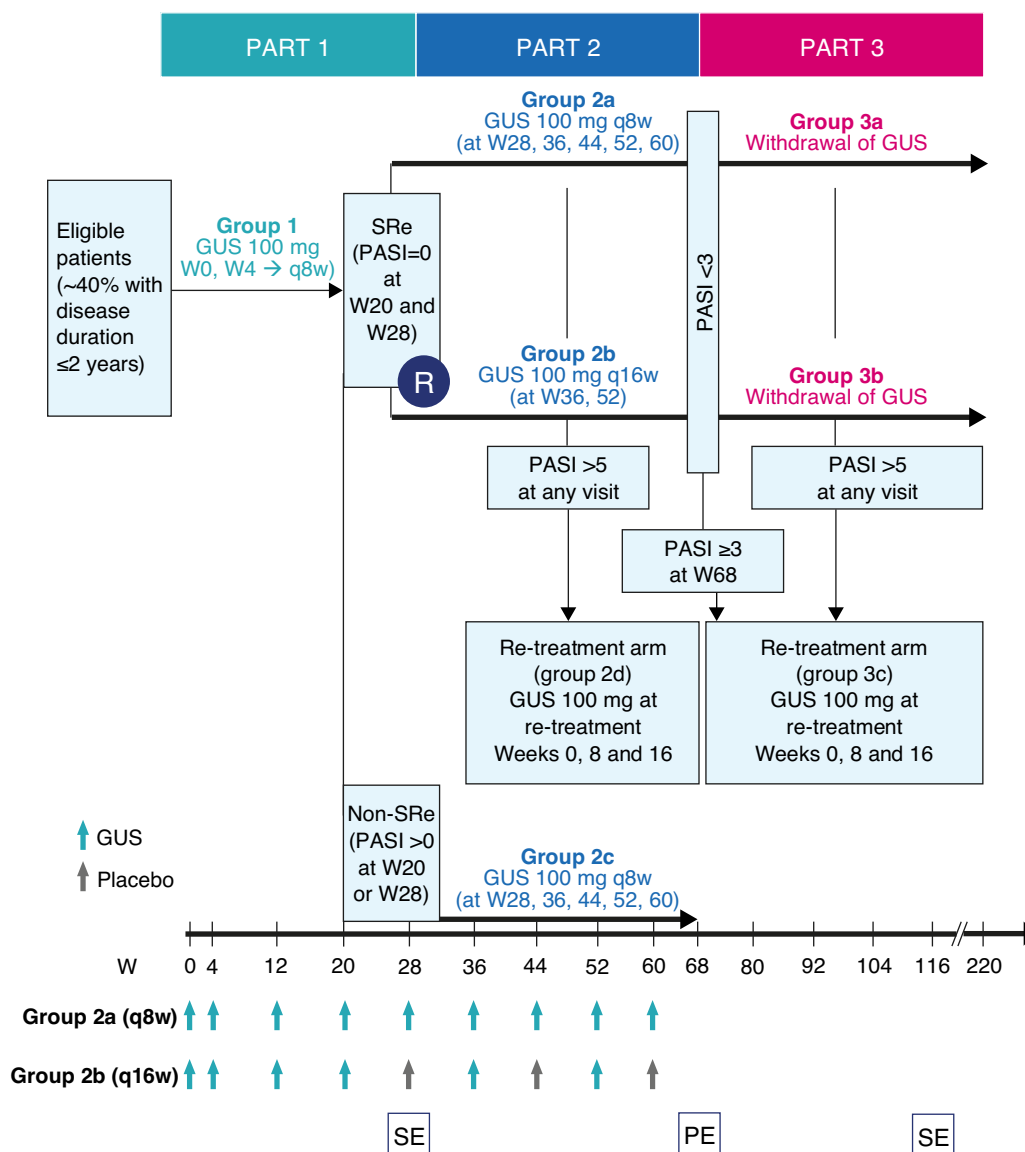


FIGURE 1 GUIDE study design. GUS, guselkumab; PASI, Psoriasis Area and Severity Index; PE, primary endpoint; q8w, every 8 weeks; q16w, every 16 weeks; R, randomization; SE, secondary endpoint; SRe, super responder; W, Week.

Statistical analysis and data handling

Statistical analyses in GUIDE have been described previously.³⁶ The study was designed to demonstrate that guselkumab 100 mg q16w (group 2b) is non-inferior to 100 mg q8w (group 2a) in SRes, through assessment of the proportions achieving absolute PASI <3 at W68 (primary endpoint). Only the primary endpoint was powered for statistical significance (detailed in the Appendix S1); all *p*-values reported in this interim analysis are considered nominal, and no adjustments for multiplicity were performed. A multivariable logistic regression analysis assessed the association between baseline age, sex, body mass index [BMI], PASI, psoriasis duration, prior biologics and the likelihood of becoming an SRe. If not otherwise specified, the intention-to-treat analysis set was used for all tabulations of efficacy data from study

part 1. Non-responder imputation (for binary endpoints) or last observation carried forward imputation (for continuous endpoints) was applied for patients with missing data. Time-to-event analyses of binary endpoints were as observed. Chi-square tests were used to test the difference of proportions between patients with an SDD and LDD. A 95% confidence interval (CI) for the difference was calculated based on Wald statistic.

Mechanistic biomarker substudies

Four mechanistic substudies of GUIDE are being conducted to evaluate the pharmacological effects of guselkumab, and assessments include the underlying genetic, cellular, serum and molecular changes associated with clinical response,

prolonged treatment intervals and disease recurrence.³⁶ In substudy 3, serum samples are collected at W0, W4, W28, W68 and W80. Serum concentrations of IL-17A, IL-17F, IL-22 (Millipore Sigma, Burlington, MA, USA) and BD-2 (Meso Scale Diagnostics, Rockville, MD, USA) were measured using immunoassays. Data at W0 and W4 from 60 SRes and 60 non-SRes (50% of patients in each group have an SDD) are reported in this publication.

RESULTS

Patients

Overall, 880 patients were enrolled into GUIDE; 357 (40.6%) had an SDD and 523 (59.4%) had an LDD. There were 58 (6.6%) patient withdrawals before W28. The main reasons for discontinuation were AEs ($n=17$), protocol violations ($n=11$) and loss to follow-up ($n=10$; [Figure S1](#)). Baseline demographics, disease characteristics and treatment history are reported in [Table 1](#). Patients with an SDD versus an LDD were on average younger (40.3 vs. 44.1 mean years; $p<0.001$) and had a notably shorter disease duration (1.2 vs. 20.2 mean years; $p<0.001$), while mean PASI (18.7 vs. 19.4; $p=0.199$) and affected BSA (25.8% vs. 26.8%; $p=0.336$) values were similar. SDD patients were less likely than LDD patients to have a BMI $>25\text{ kg/m}^2$ (61.3% vs. 73.0%; $p<0.001$), have nail involvement (38.4% vs. 60.6%; $p<0.001$) or have received prior biologic therapy (1.4% vs. 22.6%; $p<0.001$). Overall, 50.6% of patients had received a previous systemic treatment, including biologic therapy (24.6% SDD vs. 68.3% LDD; $p<0.001$; [Table 1](#); [Table S1](#)).

Clinical response to W28

Proportion of patients becoming an SRe

Overall, 34.4% of patients were SRes ([Figure 2](#)). A notably higher proportion of SDD patients were SRes compared with those with an LDD (43.7% vs. 28.1%, $p<0.001$). A post hoc analysis of the subpopulation with a baseline PASI score of ≥ 12 and a BSA $\geq 10\%$ demonstrated that a similar proportion to the overall study population were SRes ([Figure S2](#)). SRes had a shorter disease duration (mean 9.9 vs. 13.8 years), were younger (mean age 39.4 vs. 44.2 years), less likely to have a BMI $>25\text{ kg/m}^2$ (60.4% vs. 72.4%), less likely to have nail involvement (43.6% vs. 55.8%) and less likely to have received biologic therapies (6.9% vs. 17.7%) than non-SRes at baseline ([Table 2](#); [Table S2](#)).

A logistic regression analysis demonstrated that, of all the variables included in the model, the baseline factors that had the greatest impact on becoming an SRe were disease duration and prior biologic use ([Figure 3](#); [Table S3](#)). A psoriasis duration ≤ 2 years was associated with a higher likelihood of being an SRe (odds ratio [OR] = 1.58; 95% CI: 1.16–2.14;

$p=0.003$), while prior biologic use was associated with a lower likelihood (OR = 0.47; 95% CI: 0.28–0.78; $p=0.004$). Each year of increasing age (OR = 0.98; 95% CI: 0.97–0.99; $p<0.001$) and each kg/m^2 increase in BMI (OR = 0.95; 95% CI: 0.93–0.98; $p<0.001$) also decreased the odds of being an SRe. These associations were statistically significant in a nominal manner, and a test for multicollinearity revealed no significant correlations among the independent variables (indicating no multicollinearity [likelihood ratio, $p<0.001$]). Baseline PASI and sex had no influence on the likelihood of being an SRe.

PASI assessments

Differences in the proportions of patients with an SDD and LDD achieving a PASI90 response or absolute PASI = 0 were observed as early as W12 ([Figure 4a,b](#)). At W20, 73.6% of patients overall achieved a PASI90 response (SDD, 78.4%; LDD, 70.4% [$p=0.008$]) and this increased to 76.0% at W28 (SDD, 80.1%; LDD, 73.2% [$p=0.019$]; [Figure 4a](#)). At W20, 39.4% of the overall population achieved PASI = 0 (SDD, 49.3%; LDD, 32.7% [$p<0.001$]) and by W28, 44.4% of patients achieved PASI = 0 (SDD, 51.8%; LDD, 39.4% [$p<0.001$]; [Figure 4b](#)). The median number of days was markedly lower for SDD than LDD patients for the achievement of a PASI90 (89 vs. 106 days, $p=0.03$) and PASI = 0 response (141 vs. 200 days, $p<0.001$), but not for PASI75 response (84 vs. 84 days; [Figure 5](#)). The median number of days to PASI = 0 was substantially lower for SRes versus non-SRes, despite similar baseline mean PASI values ([Table 2](#); median 112 vs. 208 days, $p<0.001$ [[Figure S3](#)]). The proportion of patients achieving a PASI75 response and absolute PASI scores of <3 or ≤ 1 over time is shown in [Figure S4](#).

HRQoL

At W28, the proportion of patients with a DLQI score of 0/1 was similar between SDD (59.4%) and LDD (62.0%) patients ([Figure S5a](#)). More SRes than non-SRes achieved a DLQI score of 0/1 at W28 (81.8% vs. 49.9%; $p<0.001$; [Figure S5b](#)).

Biomarker analyses

At baseline, there were no significant differences in the serum levels of IL-17A, IL-17F, IL-22 and BD2 between SDD and LDD patients ([Figure 6](#)), or between SRe and non-SRe patients ([Figure S6](#)). However, serum IL-17A levels were significantly higher in LDD non-SRe patients than in all other groups (combinations of patients with an SDD vs. LDD and SRes vs. non-SRes) at baseline ([Figure 7](#)). As early as W4, the concentration of all four biomarkers significantly decreased compared with baseline, irrespective of disease duration, following guselkumab treatment ([Figure 6](#)). Regardless of super response and disease duration, a

TABLE 1 Baseline patient demographics, disease characteristics and treatment history.

	PSO duration ≤2 years (SDD; n = 357)	PSO duration >2 years (LDD; n = 523)	Overall (N = 880)	SDD versus LDD
Sex, n (%)				p = 0.202*
Female	114 (31.9)	146 (27.9)	260 (29.5)	
Male	243 (68.1)	377 (72.1)	620 (70.5)	
Age at baseline, years; mean ± SD	40.3 ± 16.0	44.1 ± 13.5	42.5 ± 14.7	p < 0.001†
<45, n (%)	223 (62.5)	264 (50.5)	487 (55.3)	p = 0.001‡
45–65, n (%)	110 (30.8)	223 (42.6)	333 (37.8)	
>65, n (%)	24 (6.7)	36 (6.9)	60 (6.8)	
Age at first diagnosis, years; mean ± SD	39.4 ± 16.1	25.2 ± 13.9	31.0 ± 16.4	p < 0.001†
Disease duration, years, mean ± SD	1.2 ± 0.6	20.2 ± 13.1	12.5 ± 13.8	p < 0.001†
BMI, kg/m ² ; mean ± SD	27.8 ± 6.0	28.7 ± 6.0 ^a	28.3 ± 6.0	p < 0.05†
Normal; ≤25, n (%)	138 (38.7)	140 (26.8)	278 (31.6)	p < 0.001‡
Overweight; >25–30, n (%)	110 (30.8)	200 (38.2)	310 (35.2)	
Obese; >30, n (%)	109 (30.5)	182 (34.8)	291 (33.1)	
PASI; mean ± SD	18.7 ± 8.1	19.4 ± 7.8	19.1 ± 7.9	p = 0.199†
BSA affected, %; mean ± SD	25.8 ± 15.3	26.8 ± 15.0	26.4 ± 15.1	p = 0.336†
DLQI; mean ± SD	19.1 ± 5.4	18.9 ± 5.2	19.0 ± 5.3	p = 0.581†
PSSD symptom; mean ± SD	67.4 ± 22.1	67.2 ± 22.3	67.2 ± 22.2	p = 0.896†
PSSD sign; mean ± SD	74.1 ± 16.6	74.0 ± 17.2	74.0 ± 16.9	p = 0.932†
PsA; active or inactive, n (%)	12 (3.4)	33 (6.3)	45 (5.1)	p = 0.061*
NAPPA; nail involvement, n (%)	137 (38.4)	317 (60.6)	454 (51.6)	p < 0.001*
Any prior PSO therapy, n (%)	341 (95.5)	523 (100)	864 (98.2)	p < 0.001*
Patients who never received any systemic and/or biologic therapy, n (%)	269 (75.4)	166 (31.7)	435 (49.4)	p < 0.001*
Patients with prior systemic and/or biologic therapy, n (%)	88 (24.6)	357 (68.3)	445 (50.6)	p < 0.001*
Patients receiving ≥1 biologic therapy, n (%)	5 (1.4)	118 (22.6)	123 (14.0)	p < 0.001*

Abbreviations: BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; LDD, long disease duration; NAPPA, Nail Assessment in Psoriasis and Psoriatic Arthritis; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSO, psoriasis; PSSD, Psoriasis Symptoms and Signs Diary; SD, standard deviation; SDD, short disease duration.

*Fisher's exact test.

†Unpaired *t*-test.

‡ χ^2 -test.

^aBMI at baseline was not recorded for one patient.

significant decrease in serum IL-17A, IL-17F and BD2 was observed across all patient groups (Figures 6 and 7) by W4. The significantly higher level of IL-17A at baseline in LDD non-SRes was maintained at W4 (Figure 7). IL-22 expression also significantly decreased by W4 across all groups except LDD non-SRes, in which the reduction did not reach significance ($p = 0.07$; Figure 7). At W4, levels of BD2 were similar between SDD and LDD patients, but significantly lower in SRes versus non-SRes (Figure 6; Figure S6).

Safety

Overall, 634 patients (72.0%) experienced 1602 treatment-emergent AEs (TEAEs; Table 3). The most common TEAEs were nasopharyngitis (24.3%), headache (9.0%) and

hypertension (5.5%). TEAEs that led to treatment discontinuation were reported for 17 patients (1.9%). Treatment-emergent serious AEs occurred in 38 patients (4.3%; Table 3; Table S4), and one patient died during the study, because of accidental asphyxiation. The overall infection rate was comparable between SDD and LDD groups, and the incidence rate of candida infection was low (0.1%). One SDD patient experienced a major adverse cardiovascular event, and 11 patients experienced a cardiac disorder, with a slightly higher incidence in LDD (1.5%) than SDD (0.8%) patients. There were no cases of inflammatory bowel disease, lymphoma or active tuberculosis, and the rate of malignancies and non-melanoma skin cancer was low (Table 3). Rates of abnormal laboratory results were low, and no between-group differences were noted. Injection-site reactions were reported in two patients (0.2%).

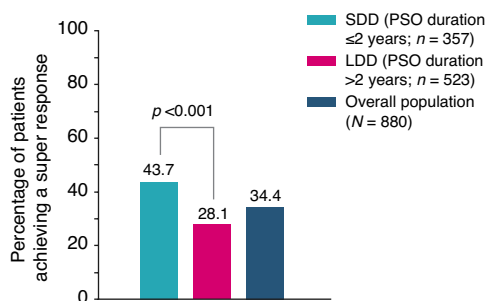


FIGURE 2 Proportion of patients achieving a super response (PASI score of 0 at W20 and W28), by disease duration (NRI). All nominal p -values <0.05 are displayed. LDD, long disease duration; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; SDD, short disease duration; W, Week.

DISCUSSION

We assessed whether starting guselkumab treatment early in the course of psoriasis impacts on efficacy and safety outcomes during the first 28 weeks of treatment, by evaluating both LDD and SDD patients. Using a logistic regression to analyse the baseline characteristics considered to be the most clinically relevant, we showed that patients with a psoriasis disease duration ≤ 2 years had a higher likelihood of becoming an SRe. Although use of prior biologic therapies was lower in SDD than LDD patients, the finding that SDD was associated with a higher likelihood of becoming an SRe was independent of prior biologics (and the other variables assessed). Analyses also determined that each year of age and each kg/m^2 increase in BMI negatively affected the likelihood of being an SRe,

TABLE 2 Baseline patient demographics, disease characteristics and treatment history by disease duration and SRe status.

	PSO duration ≤ 2 years (SDD; $n = 357$)		PSO duration > 2 years (LDD; $n = 523$)		Overall population ($N = 880$)	
	SRe ($n = 156$)	Non-SRe ($n = 201$)	SRe ($n = 147$)	Non-SRe ($n = 376$)	SRe ($n = 303$)	Non-SRe ($n = 577$)
Sex, n (%)						
Female	50 (32.1)	64 (31.8)	47 (32.0)	99 (26.3)	97 (32.0)	163 (28.2)
Male	106 (67.9)	137 (68.2)	100 (68.0)	277 (73.7)	206 (68.0)	414 (71.8)
Age at baseline, years; mean \pm SD	35.9 \pm 14.0	43.6 \pm 16.7	43.1 \pm 13.3	44.5 \pm 13.6	39.4 \pm 14.1	44.2 \pm 14.7
<45, n (%)	117 (75.0)	106 (52.7)	82 (55.8)	182 (48.4)	199 (65.7)	288 (49.9)
45–65, n (%)	35 (22.4)	75 (37.3)	58 (39.5)	165 (43.9)	93 (30.7)	240 (41.6)
>65, n (%)	4 (2.6)	20 (10.0)	7 (4.8)	29 (7.7)	11 (3.6)	49 (8.5)
Age at first diagnosis, years; mean \pm SD	34.9 \pm 14.1	42.8 \pm 16.8	25.1 \pm 14.2	25.3 \pm 13.8	30.1 \pm 14.9	31.4 \pm 17.1
Mean disease duration, years; mean \pm SD	1.2 \pm 0.6	1.2 \pm 0.6	19.2 \pm 12.3	20.6 \pm 13.5	9.9 \pm 12.4	13.8 \pm 14.3
BMI, kg/m^2 ; mean \pm SD	26.4 \pm 4.7	28.8 \pm 6.7	27.7 \pm 5.7	29.1 \pm 6.1 ^a	27.0 \pm 5.2	29.0 \pm 6.3
Normal; ≤ 25 , n (%)	68 (43.6)	70 (34.8)	52 (35.4)	88 (23.4)	120 (39.6)	158 (27.4)
Overweight; > 25 – 30 , n (%)	56 (35.9)	54 (26.9)	54 (36.7)	146 (38.8)	110 (36.3)	200 (34.7)
Obese; > 30 , n (%)	32 (20.5)	77 (38.3)	41 (27.9)	141 (37.5)	73 (24.1)	218 (37.8)
PASI; mean \pm SD	18.1 \pm 6.9	19.1 \pm 8.9	19.4 \pm 8.1	19.5 \pm 7.7	18.7 \pm 7.5	19.3 \pm 8.1
BSA affected, %; mean \pm SD	23.5 \pm 14.1	27.6 \pm 15.9	26.6 \pm 16.1	26.9 \pm 14.5	25.0 \pm 15.2	27.1 \pm 15.0
DLQI; mean \pm SD	18.9 \pm 5.1	19.3 \pm 5.6	18.9 \pm 4.9	18.9 \pm 5.3	18.9 \pm 5.0	19.0 \pm 5.4
PSSD symptom; mean \pm SD	65.7 \pm 21.3	68.6 \pm 22.7	68.1 \pm 20.4	66.8 \pm 23.0	66.9 \pm 20.9	67.4 \pm 22.9
PSSD sign; mean \pm SD	73.4 \pm 16.3	74.6 \pm 16.9	74.3 \pm 16.2	73.8 \pm 17.6	73.8 \pm 16.2	74.1 \pm 17.3
PsA; active or inactive, n (%)	4 (2.6)	8 (4.0)	8 (5.4)	25 (6.6)	12 (4.0)	33 (5.7)
NAPPA; nail involvement, n (%)	54 (34.6)	83 (41.3)	78 (53.1)	239 (63.6)	132 (43.6)	322 (55.8)
Any prior biologic therapy, n (%)	1 (0.6)	4 (2.0)	20 (13.6)	98 (26.1)	21 (6.9)	102 (17.7)

Abbreviations: BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; LDD, long disease duration; NAPPA, Nail Assessment in Psoriasis and Psoriatic Arthritis; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSO, psoriasis; PSSD, Psoriasis Symptoms and Signs Diary; SD, standard deviation; SDD, short disease duration; SRe, super responder.

^aBMI at baseline was not recorded for one patient.

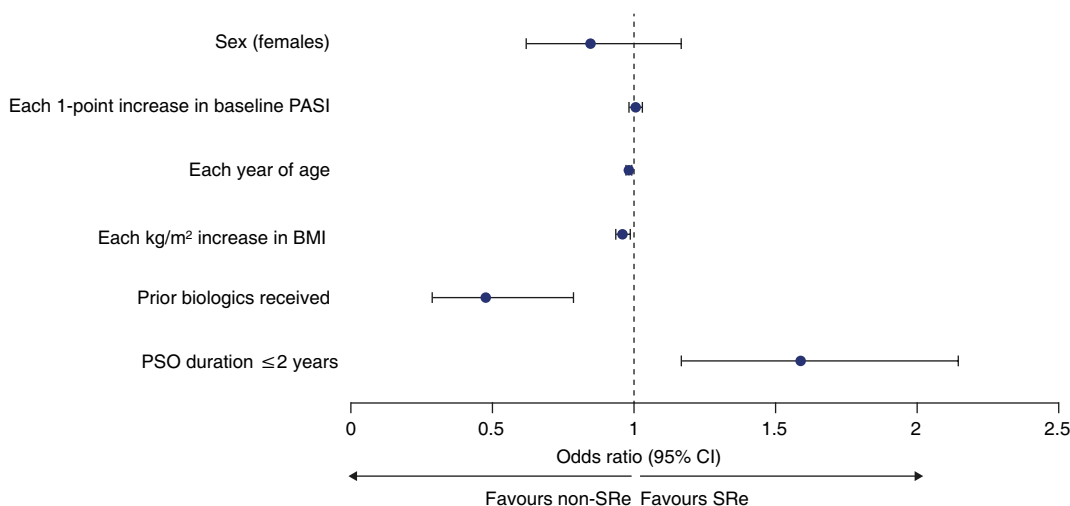


FIGURE 3 Baseline factors impacting on likelihood of becoming an SRe. BMI, body mass index; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; SRe, super responder.

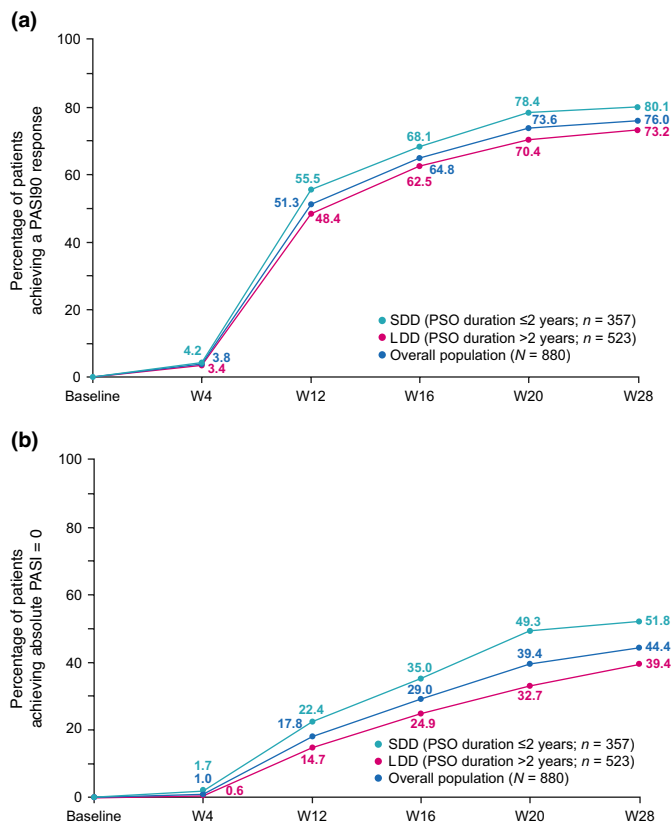


FIGURE 4 Proportion of patients achieving a PASI90 response (a) and an absolute PASI score of 0 (b) over time, by disease duration (NRI). LDD, long disease duration; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; SDD, short disease duration.

although to a lesser extent. In line with this, SRes were younger and less likely to have a BMI >25 kg/m² than non-SRes at baseline. Further analyses will be conducted at later time points to determine other factors impacting on super response.

Our data demonstrate that guselkumab is effective for all patients, regardless of disease duration. A PASI90 response

was observed in 76.0% of patients at W28, while complete skin clearance (PASI = 0) was observed in 44.4%. These findings are very similar to the pivotal VOYAGE 1 and 2 studies, in which PASI = 0 was achieved by 44.2% and 44.4% of patients at W24, respectively.^{37,38} Of note, an earlier disease intervention with guselkumab appears to provide a greater

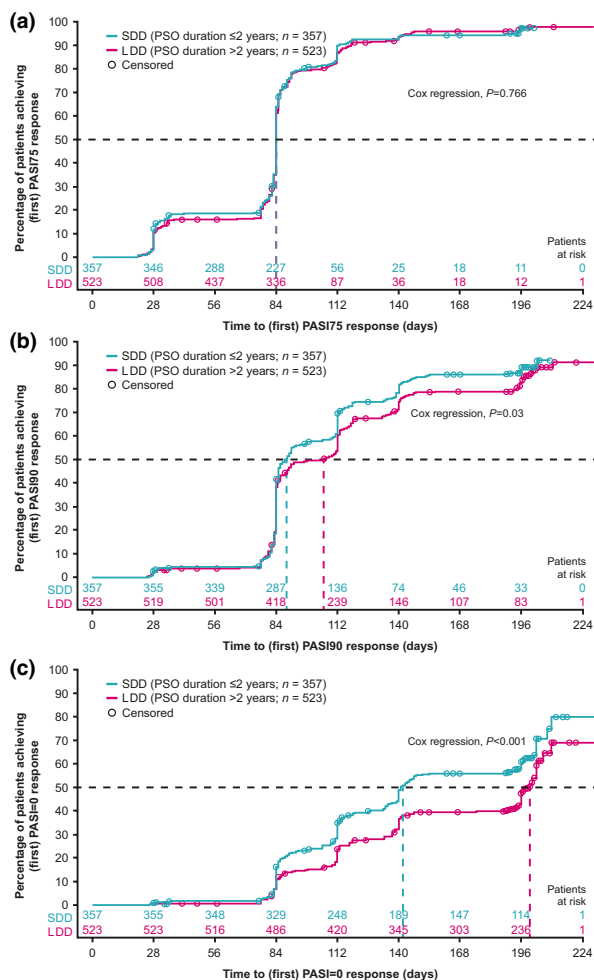


FIGURE 5 Time to PASI75 (a), PASI90 (b) and absolute PASI=0 (c) response by disease duration. LDD, long disease duration; PASI, Psoriasis Area and Severity Index; PSO, psoriasis; SDD, short disease duration.

benefit to patients. PASI90 and PASI=0 response rates were higher and achieved substantially faster in SDD than LDD patients. This benefit to SDD patients occurred despite a similar level of skin involvement at baseline between the patient groups. The difference in response between SDD and LDD patients could be because LDD patients were older than SDD patients and were diagnosed at an earlier age. As such and per definition, there was a substantial difference in mean disease duration between the two groups (1.2 [SDD] vs. 20.2 [LDD] years). Patients with a longer disease duration may be more difficult to treat than those with a shorter disease duration, and are also likely to have developed comorbidities, such as obesity and systemic inflammation, which impair response to treatment. LDD patients were more likely than SDD patients to have a BMI >25 kg/m², and nail involvement, potentially reflecting a link to disease progression and the greater burden of disease experienced by LDD patients. Future analyses will assess how age of onset/genetic predisposition to psoriasis impacts on treatment response.

The faster rate of skin clearance in SDD patients could have important clinical implications. In VOYAGE 2, patients who

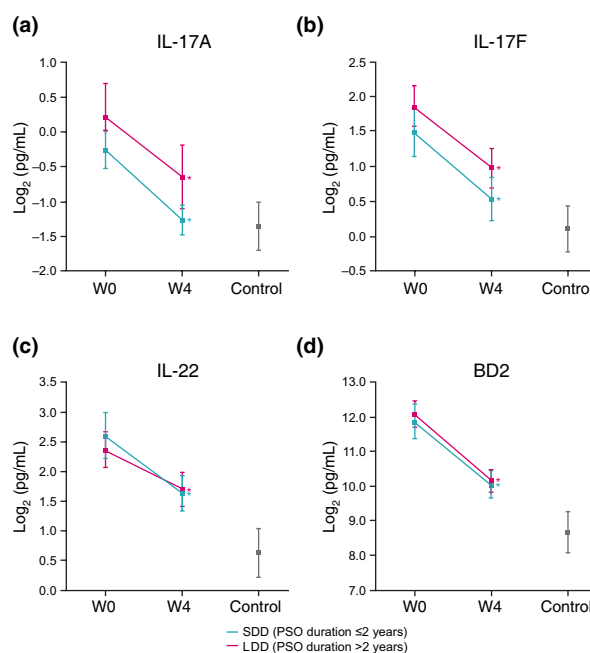


FIGURE 6 Change in serum IL-17A (a), IL-17F (b), IL-22 (c) and BD2 (d) levels from baseline to W4 by disease duration. Plotted are averaged log₂ concentration ± standard error of the mean for each group and time point. *p < 0.05 versus W0. BD2, β-defensin 2; IL, interleukin; LDD, long disease duration; PSO, psoriasis; SDD, short disease duration; W, Week.

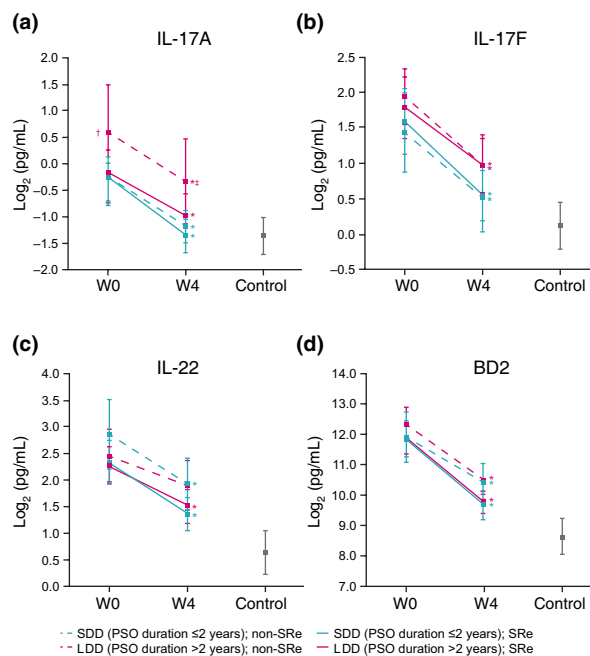


FIGURE 7 Change in serum IL-17A (a), IL-17F (b), IL-22 (c) and BD2 (d) levels from baseline to W4 by disease duration and SRe status. Plotted are averaged log₂ concentration ± standard error of the mean for each group and time point. *p < 0.05 versus W0; †p < 0.05 >2 years, non-SRe versus others, W0; ‡p < 0.05 >2 years, non-SRe versus others, W4. BD2, β-defensin 2; IL, interleukin; LDD, long disease duration; PSO, psoriasis; SDD, short disease duration; SRe, super responder; W, Week.

TABLE 3 Safety events by disease duration.

	PSO duration ≤2 years (SDD; n = 357)	PSO duration >2 years (LDD; n = 523)	Overall (N = 880)
	n (%)	n (%)	n (%)
Patients treated	357 (100)	523 (100)	880 (100)
Patients with ≥1 AE	266 (74.5)	392 (75.0)	658 (74.8)
Patients with TEAEs	253 (70.9)	381 (72.8)	634 (72.0)
Common TEAEs ^a			
Nasopharyngitis	82 (23.0)	132 (25.2)	214 (24.3)
Headache	31 (8.7)	48 (9.2)	79 (9.0)
Hypertension	17 (4.8)	31 (5.9)	48 (5.5)
Arthralgia	14 (3.9)	27 (5.2)	41 (4.7)
Patients with TEAEs leading to permanent discontinuation of guselkumab	9 (2.5)	8 (1.5)	17 (1.9)
Patients with ≥1 SAE	19 (5.3)	20 (3.8)	39 (4.4)
Patients with ≥1 TESAE	19 (5.3)	19 (3.6)	38 (4.3)
TEAE infections	145 (40.6)	221 (42.3)	366 (41.6)
Severe	4 (1.1)	5 (1.0)	9 (1.0)
Other TEAEs of interest			
Candida infection ^b	3 (0.8)	3 (0.6)	6 (0.7)
COVID-19	4 (1.1)	6 (1.1)	10 (1.1)
Malignant and benign neoplasms	8 (2.2)	15 (2.9)	23 (2.6)
NMSC	3 (0.8) ^c	–	3 (0.3)
Lymphoma	–	–	–
Gastrointestinal disorders other than IBD	28 (7.8)	64 (12.2)	92 (10.5)
IBD	–	–	–
Active TB ^d during study	–	–	–
Cardiac disorders (primary SOC)	3 (0.8)	8 (1.5)	11 (1.3)
MACE ^e	1 (0.3)	–	1 (0.1)
Deaths ^f	–	1 (0.2)	1 (0.1)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; LDD, long disease duration; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PSO, psoriasis; SAE, serious adverse event; SDD, short disease duration; SOC, system organ class; TB, tuberculosis; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

^a>5% in any group.

^bIncludes skin candida, oral candidiasis and candida infection.

^cTwo patients had basal cell carcinomas, and one patient had squamous cell carcinoma.

^dAt screening, latent TB was documented in 2 (0.6%) SDD, and 4 (0.8%) LDD patients (total of 6 [0.7%] patients) – there were no cases of active TB.

^eMACE was a cerebral infarction.

^fReason for death was 'accidental asphyxiation' and was not drug related.

had a faster skin response to guselkumab achieved longer-term control of their psoriasis; those who achieved PASI=0 at W28 were more likely than those who did not to have long-term maintenance of PASI90 response (45.7% vs. 24.0%; OR: 2.66; $p < 0.005$).³⁴ Together, data suggest that higher treatment targets (e.g. PASI90 response and PASI=0) may be more readily achieved in certain populations, that is SDD patients. In support of this, there was a notable difference between SDD and LDD groups for PASI score ≤1 at W20 and W28, but not for PASI score <3 or PASI75 response (Figure S4).

As the proportion of patients achieving a defined PASI response was lower in the LDD group, it might be expected that the proportion achieving DLQI 0/1 would also be lower.

However, the proportion of patients with a DLQI score of 0/1 at W28 was similar for SDD and LDD patients. Patient-reported outcomes such as the DLQI rely on patient perception of disease, and so the extent of change in HRQoL may be perceived differently in a patient who has endured the burden of disease for many years compared with those recently diagnosed with psoriasis. Notably, a greater proportion of SRes than non-SRes achieved a DLQI score of 0/1 at W28, indicating that, although guselkumab improves HRQoL regardless of disease duration, it is even more effective in certain populations.

In addition to the positive impact that guselkumab had on clinical responses in GUIDE, guselkumab rapidly

decreased pharmacodynamic markers of systemic inflammation across all groups analysed. A reduction of the serum biomarkers IL-17A, IL-17F, IL-22 and BD2 was observed as early as W4 in all groups, including combinations of patients with an SDD versus LDD and SRes versus non-SRes. However, assessment of baseline biomarker levels of IL-17A, IL-17F, IL-22 or BD2 alone did not predict a super response. Of note, in VOYAGE 2, sustained suppression of IL-17A, IL-17F and IL-22 was associated with maintenance of PASI90 response in patients who had been withdrawn from guselkumab treatment.^{19,33,34} Although only preliminary findings from our mechanistic analyses are presented in this publication, the association between changes in various exploratory biomarker endpoints and (1) efficacy of guselkumab, (2) psoriasis duration, (3) maintenance of response after stopping guselkumab and (4) likelihood of becoming an SRe will be explored in future analyses.

Several studies have suggested that T_{RM} cells producing IL-17A and IL-22 are responsible for the recurrence of psoriasis skin lesions in previously affected areas,^{39–41} and patients with a greater number of T_{RM} cells in their lesions have thicker plaques and more severe psoriasis compared with those with fewer T_{RM} cells.^{40,42} As IL-23 is involved in the differentiation and survival of these pathogenic T_{RM} cells,⁴³ inhibition of IL-23 may have broader implications beyond the clearance of psoriatic plaques.³⁶ Mehta et al.¹¹ demonstrated that guselkumab, but not the IL-17A inhibitor secukinumab, decreased the proportion of T_{RM} cells in healed psoriatic skin 6 months after initiation of treatment. Depletion of T_{RM} cells by guselkumab may account for the long-term disease remissions observed following drug withdrawal.¹⁹ Importantly, patients with a longer duration of psoriasis have greater proportions of T_{RM} cells in their skin compared with patients with a shorter duration of disease.⁴¹ Therefore, early intervention that targets these cells could allow for disease modification with curative intent,^{36,44} and this may explain the benefits observed in SDD compared with LDD patients receiving guselkumab in GUIDE. Specifically, SDD patients achieved higher rates of completely clear skin compared with LDD patients. Though GUIDE is the largest study to date to assess the efficacy of biologic treatment in psoriasis based on disease duration, other studies are also evaluating the impact of early treatment intervention in psoriasis. For example, the STEPIn study is assessing the impact of secukinumab on clinical outcomes and the natural course of disease in patients with new-onset (≤ 12 months) psoriasis.⁴⁵ STEPIn demonstrated that early biologic treatment resulted in high levels of sustained skin clearance at W52,⁴⁵ and that lesional skin transcriptomes were reverted to a non-lesional state more rapidly in patients with new-onset compared with chronic (≥ 5 years) psoriasis.⁴⁶

Finally, our W28 analysis of GUIDE demonstrated that guselkumab was well tolerated, and no new safety findings were identified.

In summary, early treatment with guselkumab in psoriasis patients with an SDD was associated with an increased likelihood of becoming a SRe. Patients with a SDD also

achieved complete skin clearance faster and at a higher rate than patients with a LDD. Together with other clinical findings,³⁴ early intervention with guselkumab appears to lead to a better clinical response, which is associated with a greater reduction in the inflammatory marker BD2 as early as W4. This could translate to improved long-term control of a patient's psoriasis and eventually, sustainable maintenance of response following drug withdrawal. Further analyses in GUIDE will assess the relationship between disease memory (represented by T_{RM} and T_{reg} /Th17 cell frequencies) and clinical response.

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CONFLICT OF INTEREST STATEMENT

The authors disclose that they were an advisor and/or received speakers' honoraria and/or received grants and/or participated in clinical trials of the following companies: KS, AbbVie, Almirall, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Janssen-Cilag GmbH, LEO Pharma, Novartis, Pfizer and UCB; KR, AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Forward Pharma, Gilead, Galderma, Janssen-Cilag GmbH, Kyowa Kirin, LEO Pharma, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi and UCB and is co-founder of Moonlake Immunotherapeutics; KA, AbbVie, Almirall, Antabio, Bayer, BMS, Euroimmune, Emphasis, Emeriti Pharma, Galderma, Janssen-Cilag GmbH, La Roche-Posay, LEO Pharma, L'Oréal, Novartis, Parexel International, Pierre Fabre, Roxall, RG, Sanofi Genzyme, TFS Trial Form Support and UCB; AP, AbbVie, Almirall Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Galderma, GSK, Hexal, Janssen-Cilag GmbH, Klinge Pharma, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering-Plough, Tigercat Pharma and UCB Pharma; DJ, Abbott Laboratories, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius Medical Care, Janssen Pharmaceuticals Inc., LEO Pharma, Lilly ICOS LLC, Medac Pharma Inc., Novartis, Pfizer, Sanofi and UCB; PW, AbbVie, Almirall, Biogen, Eli Lilly, Janssen-Cilag GmbH, LEO Pharma, Medac, Novartis, Pfizer and UCB; CP, AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen-Cilag GmbH, LEO Pharma, Merck, Mylan,

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DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

GUIDE was designed and will be conducted in accordance with the Harmonised Tripartite Guidelines for Good Clinical Practice from the International Conference on Harmonisation, with applicable local regulations, and in accordance with the Declaration of Helsinki. All patients provided written informed consent.

ORCID

K. Schäkel  <https://orcid.org/0000-0001-6344-7799>

K. Reich  <https://orcid.org/0000-0001-5248-4332>

A. Pinter  <https://orcid.org/0000-0002-1330-1502>

D. Jullien  <https://orcid.org/0000-0002-2995-7928>

Y. Personke  <https://orcid.org/0000-0002-8631-518X>

Y. Chen  <https://orcid.org/0000-0002-9534-6199>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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