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Noninferiority of 16-Week vs 8-Week Guselkumab Dosing in Super Responders for Maintaining Control of Psoriasis
The GUIDE Randomized Clinical Trial

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IMPORTANCE Psoriasis is a chronic inflammatory skin disease with unmet needs for tailored treatment and therapy de-escalation strategies.

OBJECTIVE To evaluate early intervention with and prolonging the dosing interval for guselkumab, a p19 subunit-targeted interleukin (IL)-23 inhibitor, in patients with moderate to severe psoriasis.

DESIGN, SETTING, AND PARTICIPANTS The GUIDE clinical trial is an ongoing phase 3b, randomized, double-blinded trial conducted across 80 centers in Germany and France comprising 3 parts evaluating the impact of early disease intervention, prolonged dosing interval, and maintenance of response following treatment withdrawal among adults with moderate to severe plaque psoriasis. In study part 2, reported herein, first and last patient visits were September 2019 and March 2022, respectively.

INTERVENTIONS In GUIDE part 1 (week [W]0-W28), patients received guselkumab, 100 mg, at W0, W4, W12, and W20. Those achieving a Psoriasis Area and Severity Index (PASI) of 0 at both W20 and W28 were termed *super responders* (SRes). In part 2 (W28-W68), SRes were randomized to guselkumab, 100 mg, every 8 weeks or every 16 weeks; non-SRes continued open-label guselkumab every 8 weeks.

MAIN OUTCOMES AND MEASURES Primary objective was to demonstrate noninferiority (with a 10% margin) of guselkumab every 16 weeks vs every 8 weeks dosing among SRes for maintenance of disease control (PASI <3 at W68). Biomarker substudies assessed immunologic effects in skin and blood.

RESULTS Overall, 822 patients received guselkumab in part 2 (297 [36.1%] SRes [every 8 weeks/every 16 weeks; n = 148/n = 149] and 525 [63.9%] non-SRes). Among SRes, mean (SD) age was 39.4 (14.1) years, 95 (32.0%) were female, and 202 (68.0%) were male. The primary end point of noninferiority for guselkumab every 16 weeks vs every 8 weeks in SRes was met (P = .001), with 91.9% (137/149; 90% CI, 87.3%-95.3%) of SRes receiving every 16 weeks and 92.6% (137/148; 90% CI, 88.0%-95.8%) of SRes receiving dosing every 8 weeks having PASI lower than 3 at W68. Clinical effects corresponded with immunologic changes; skin CD8-positive tissue-resident memory T (TRM)–cell count decreased quickly from baseline, remaining low in both dosing groups. Similarly, serum IL-17A, IL-17F, IL-22, and β defensin (BD)–2 levels decreased significantly from baseline, remaining low in both dosing groups to W68. Guselkumab was well-tolerated; no new safety signals were identified.

CONCLUSIONS AND RELEVANCE Psoriasis treatment guidelines lack or provide inconsistent advice on patient stratification and treatment de-escalation. We present the first randomized trial providing evidence that, in patients with early complete skin clearance at 2 consecutive visits (W20 and W28), extending the guselkumab dosing interval may control disease activity.

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Visual Abstract
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Psoriasis is a chronic, systemic immune-mediated disease, predominately characterized by skin plaques.[1,2] Owing to the chronic and often progressive nature of the disease,[2] long-term treatment is required, and the timing of targeted intervention plays a crucial role in the ensuing response to therapy.[3,4] Though treatment de-escalation of biologic therapies for psoriasis is commonly applied in daily practice, evidence-based treatment guidelines and algorithms are lacking.[5]

Guselkumab is a fully human monoclonal antibody that targets the p19 subunit of interleukin (IL)-23, and is approved for the treatment of moderate to severe psoriasis and psoriatic arthritis (100 mg maintenance doses administered every 8 weeks after 2 initial doses 4 weeks apart).[6-8] The ongoing GUIDE clinical trial is the first prospective, randomized, double-blinded, controlled phase 3b clinical trial to stratify patients with psoriasis based on early and complete skin clearance at 2 consecutive visits (Psoriasis Area and Severity Index [PASI] of 0 at both week [W]20 and W28; patients achieving this response are defined as *super responders* [SRes]), and to assess the long-term impact of subsequent treatment de-escalation at the clinical and immunologic levels.[4] The primary objective was to demonstrate noninferiority of extended guselkumab dosing every 16 weeks vs every 8 weeks in SRes for maintenance of disease control (PASI <3) at W68. The GUIDE trial secondary objectives include evaluation of early intervention with guselkumab on long-term disease outcomes, as well as clinical response in SRes following drug withdrawal. Exploratory analyses will assess immunologic markers in the serum and skin, including tissue-resident memory T (TRM) cells.

Based on previous findings from GUIDE,[9] as well as the phase 3 VOYAGE 2[10] and ECLIPSE clinical trials,[11] we hypothesized that patients with psoriasis who achieve early and complete skin clearance in response to treatment with guselkumab, accompanied by rapid reduction in skin TRM cell numbers, represent a distinct patient population. In these patients, disease activity may be suppressed and modified in a manner that may allow for long-term disease control with an extended dosing interval.[4,12-14] Herein, we present primary end point data, supported by other clinical and immunologic findings, to evaluate whether de-escalation of guselkumab treatment by dosing interval extension to every 16 weeks is noninferior to dosing every 8 weeks for maintaining clinical response in SRes. The overarching aim of the ongoing GUIDE clinical trial is to provide clinical and molecular insights into disease modification and durable remission.[4]

Key Points

Question Is guselkumab dosing every 16 weeks noninferior to standard dosing every 8 weeks for maintenance of psoriasis disease control, defined as a Psoriasis Area and Severity Index lower than 3 at week (W)68, in super responders (SRes)?

Findings This phase 3b clinical trial randomized 149 guselkumab SRes to guselkumab every 16 weeks dosing and 148 SRes to every 8 weeks dosing at W28 and demonstrated noninferiority of every 16 weeks dosing for maintenance of disease control, meeting the primary end point; clinical effects corresponded with immunologic changes.

Meaning The GUIDE randomized clinical trial is the first to demonstrate that disease activity in patients with early complete skin clearance may be controlled with an extended guselkumab dosing interval.

Methods

Study Design

The trial protocol and the statistical analysis plan are available in Supplement 1 and Supplement 2, respectiveley. The GUIDE trial[4] is an ongoing phase 3b, randomized, double-blinded, parallel-group, multicenter study of adults (aged ≥18 years) with moderate to severe plaque psoriasis (eMethods in Supplement 3).[4] The study has 3 parts (eFigure 1 in Supplement 3): in part 1 (W0 to W28), patients received guselkumab, 100 mg, at W0, W4, W12, and W20. In part 2 (W28-W68, the focus of this study), SRes were randomized to continue receiving guselkumab, 100 mg, every 8 weeks (group 2A) or every 16 weeks (group 2B). Non-SRes continued open-label guselkumab every 8 weeks treatment (group 2C). In part 3 (W68 to W220), SRes from groups 2A and 2B with PASI lower than 3 at W68 were withdrawn from guselkumab and followed to W220 (group 3A or 3B, respectively). SRes with PASI of 3 or higher at W68 or PASI higher than 5 at any visit during part 2 or 3 would receive retreatment with guselkumab (group 2D or 3C) at that visit, and then 8 and 16 weeks later.

The GUIDE trial was designed and conducted in accordance with the Harmonized Tripartite Guidelines for Good Clinical Practice from the International Conference on Harmonization, with applicable local regulations, and in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board of the Paul-Ehrlicher-Institut; Germany. All patients provided written informed consent. Data are presented according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients

Key inclusion criteria (eMethods in Supplement 3) include having moderate to severe plaque-type psoriasis, defined by PASI higher than 10 or affected body surface area (BSA) greater than 10%, and Dermatology Life Quality Index (DLQI) greater than 10 at baseline. A ratio of 40:60 for short disease duration (SDD; ≤2 years from symptom onset to screening): long disease duration (LDD; >2 years) patients was planned based on previous analyses.[6,7] All patients were eligible for biologic therapy.

Randomization and Blinding

At W28, SRes were assigned 1:1 to receive guselkumab every 8 weeks (at W28, W36, W44, W52, and W60) or every 16 weeks (at W36 and W52) based on a computer-generated randomization schedule, using randomly permuted blocks. The interactive web-response system stratified patients in groups 2A and 2B by disease duration (SDD/LDD; eMethods in Supplement 3). Patients, investigators, and the study sponsor were blinded throughout study part 2.

Clinical End Points and Assessments

The primary end point was the percentage of patients achieving absolute PASI lower than 3 at W68 to demonstrate noninferiority (with a margin of 10%) of guselkumab every 16 weeks vs every 8 weeks dosing for maintenance of disease control in SRes. Secondary end points presented include absolute PASI lower than 3, PASI 1 or lower, and PASI of 0 rates at W68 and over time, rates of DLQI 0/1 (and DLQI <5 [non-SRes only]) response, mean PASI, BSA, and Psoriasis Symptoms and Signs Diary (PSSD) scores over time, and PASI 75/90 responses at W68. Safety was assessed through 12 weeks after the last administration of guselkumab by evaluating adverse events (AEs) using the Medical Dictionary for Regulatory Activities-defined terms. The safety set population comprised all patients treated with 1 or more doses of the study agent.

Biomarker Analyses

Optional exploratory biomarker substudies were conducted to assess CD8-positive TRM (CD3 positive, CD8 positive, CD103 positive, and/or CD49a positive) cell count and IL-17A, IL-17F, IL-22, and β defensin (BD)-2 serum levels by every 8 weeks/every 16 weeks dosing group and SRe status, using flow cytometry and immunoassay, respectively. For CD8-positive TRM cell count, skin biopsies were collected from nonlesional (at W0) and lesional (at W0, W4, W28, and W68) skin samples for fluorescence-activated cell sorting (FACS) analysis (eMethods in Supplement 3). For serum cytokine analyses, blood samples were collected at W0, W4, W28, and W68 (and from an independently procured healthy control cohort) and measured using immunoassays (Millipore Sigma and MesoScale Discovery).

Statistical Analyses

Statistical analyses in GUIDE[4] are detailed in the eMethods in Supplement 3. The primary end point was powered for statistical significance; other *P* values are considered nominal and no adjustments for multiplicity were performed. Confidence intervals (CIs) and risk differences for secondary end points are provided in eTable 1 in Supplement 3.

In study part 2, patients were analyzed according to the treatment group in which they were randomized regardless of the treatment received (the intention-to-treat [ITT] analysis set), and if they received 1 or more doses of the study agent in study part 2. If not otherwise specified, the ITT set was used for tabulations of clinical data. A predefined per-protocol (PP) analysis was conducted for the primary end point (population defined in eMethods in Supplement 3). The program used for analyses was SAS statistical software (version 9.4; SAS Institute), and all tests for significance were conducted at the 5% level. The date of analysis was June 24, 2022.

Results

Of 880 patients enrolled, 822 received treatment in study part 2 and were included in the ITT population; 297 (36.1%) were SRes (eFigure 2 in Supplement 3). Among SRes, mean (SD) age was 39.4 (14.1) years, 95 (32.0%) were female, and 202 (68.0%) were male. Among SRes, 148 (49.8%) were randomized to receive guselkumab every 8 weeks and 149 (50.2%) to receive guselkumab every 16 weeks. A total of 525 (63.9%) non-SRes received every 8 weeks treatment in part 2.

Comparison of baseline characteristics for the SRe every 8 weeks and every 16 weeks dosing groups in study part 2 showed similar median (IQR) values for disease duration (2.1 [1.4-16.0]/2.0 [1.1-17.6] years), age (36.5 [27.5-49.5]/37.0 [29.0-50.0] years), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared; 26.7 [23.0-29.5]/26.2 [23.2-30.1]), PASI (16.7 [13.5-21.6]/16.7 [13.3-22.8]), and DLQI (20.0 [15.0-23.0]/18.0 [15.0-22.0]), respectively. The proportion of patients who had received prior biologic therapy was lower in the every 8 weeks group than the every 16 weeks group (7/148 [4.7%] vs 14/149 [9.4%], respectively; **Table 1**). In comparison with non-SRes, SRes in study part 2 had median (IQR) shorter disease duration (2.0 [1.3-16.0] vs 10.0 [1.7-22.0] years), were younger (age 37.0 vs 44.0 years), had slightly lower BMI (26.5 vs 28.3), and were less likely to have received a prior biologic therapy (7.1% vs 17.7%; Table 1). Median baseline PASI were similar between SRes and non-SRes (16.7 vs 16.8, respectively).

The primary end point of noninferiority of guselkumab every 16 weeks vs every 8 weeks dosing for maintenance of disease control in SRes was met, with PASI less than 3 at 68 weeks achieved by 137 of 149 patients treated with guselkumab every 16 weeks (91.9%; 90% CI, 87.3%-95.3%) and 137 of 148 patients treated with guselkumab every 8 weeks (92.6%; 90% CI, 88.0%-95.8%; odds ratio [OR] 0.92; 90% CI, 0.45-1.87; *P* = .001 for noninferiority; **Figure 1**A), with a corresponding risk difference of -0.6 (90% CI, -5.7 to 4.5; *P* = .84). This finding was confirmed by a PP analysis (eTable 1 in Supplement 3). Overall, a high proportion of SRes maintained PASI lower than 3 over time, independent of the treatment interval.

SRes maintained high rates of PASI of 1 or lower and PASI of 0 response over time and at W68, with higher response rates with every 8 weeks vs every 16 weeks dosing (PASI ≤1 at W68: 133/148 every 8 weeks [89.9%], and 118/149 patients [79.2%] doesed every 16 weeks; *P* = .01; PASI = 0 at W68: 120/148 every 8 weeks [81.1%], and 103/149 patients [69.1%] dosed every 16 weeks; *P* = .02; Figure 1B and Figure 1C, eTable 2 in Supplement 3). Mean PASI and affected BSA (%) improved rapidly from baseline and remained low to W68 with both dosing intervals in SRes (Figure 1D; eFigure 3, eTable 3 in Supplement 3). SRes also achieved high rates of PASI 75 (137/148 every 8 weeks [92.6%], and 140/149 patients [94.0%] dosed every 16 weeks; *P* = .63) and PASI 90 (136/148 every 8 weeks [91.9%], and 128/149 patients [85.9%] dosed every 16 weeks; *P* = .10) responses at W68, with no statistically significant differences observed between every 8 weeks and 16 week dosing intervals (eFigure 4, eTable 2 in Supplement 3). Similarities in PASI responses between dosing groups were also observed using individual patient data (eFigure 5 in Supplement 3).

Observed skin improvements were consistent with a substantial and positive impact on patient-reported quality-of-life outcomes, independent of dosing interval. High DLQI 0/1 response rates were maintained at W68 in SRes (123/148 every 8 weeks [83.1%], and 116/149 patients [77.9%] dosed every 16 weeks; *P* = .25; Figure 1E, eTable 2 in Supplement 3);

Table 1. Patient Demographic, Disease Characteristics, and Prior Therapies at Baseline (Intention-to-Treat [ITT] Population)[a]

Characteristic	Guselkumab, 100 mg, SRe patients randomized to every 8 wk vs every 16 wk (double-blinded)			Guselkumab, 100 mg, non-SRe patients, group 2C, every 8 wk (n = 525)
	Group 2A, every 8 wk (n = 148)	Group 2B, every 16 wk (n = 149)	Groups 2A and 2B (n = 297)	
Age, median (range), y	36.5 (18.0-84.0)	37.0 (18.0-77.0)	37.0 (18.0-84.0)	44.0 (18.0-79.0)
Age at first diagnosis, median (range)	26.0 (3.0-78.0)	28.0 (2.0-76.0)	27.0 (2.0-78.0)	27.0 (0.0-78.0)
Sex, No. (%)				
Female	53 (35.8)	42 (28.2)	95 (32.0)	145 (27.6)
Male	95 (64.2)	107 (71.8)	202 (68.0)	380 (72.4)
BMI (categorical), No. (%)[b]				
Normal (≤25)	58 (39.2)	60 (40.3)	118 (39.7)	145 (27.6)
Overweight (>25 to 30)	57 (38.5)	49 (32.9)	106 (35.7)	179 (34.1)
Obese (>30)	33 (22.3)	40 (26.8)	73 (24.6)	200 (38.1)
Disease duration, median (range), y	2.1 (0.2-59.0)	2.0 (0.1-46.0)	2.0 (0.1-59.0)	10.0 (0.1-67.0)
PASI at baseline[c]				
Mean (SD)	18.9 (8.1)	18.7 (7.1)	18.8 (7.6)	19.2 (8.1)
Median (range)	16.7 (10.0-59.2)	16.7 (9.2-43.2)	16.7 (9.2-59.2)	16.8 (6.3-60.0)
DLQI at baseline[c]				
Mean (SD)	19.4 (5.3)	18.5 (4.7)	18.9 (5.0)	19.2 (5.2)
Median (range)	20.0 (11.0-30.0)	18.0 (11.0-29.0)	19.0 (11.0-30.0)	19.0 (11.0-30.0)
Prior psoriasis therapy (hierarchized), No. (%)[d]				
Any therapy	146 (98.6)	145 (97.3)	291 (98.0)	516 (98.3)
Topical	57 (38.5)	45 (30.2)	102 (34.3)	140 (26.7)
Phototherapy	31 (20.9)	27 (18.1)	58 (19.5)	92 (17.5)
Nonbiologic systemic	51 (34.5)	59 (39.6)	110 (37.0)	191 (36.4)
Biologic	7 (4.7)	14 (9.4)	21 (7.1)	93 (17.7)

Abbreviations: BMI, body mass index; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; SRe, super responder.

[a] This Table was previously presented at the European Academy of Dermatology & Venereology Congress 2022 and used with permission from Prof Knut Schäkel, MD.

[b] Calculated as weight in kilograms divided by height in meters squared. Documentation of BMI was not recorded for one patient in the non-SRe group at baseline.

[c] Screening data were used for baseline DLQI and PASI if W0 data were missing.

[d] In the hierarchical analysis, patients were counted in only 1 therapeutic regimen group according to the following procedure: topical, phototherapy, nonbiologic systemic, and biologic.

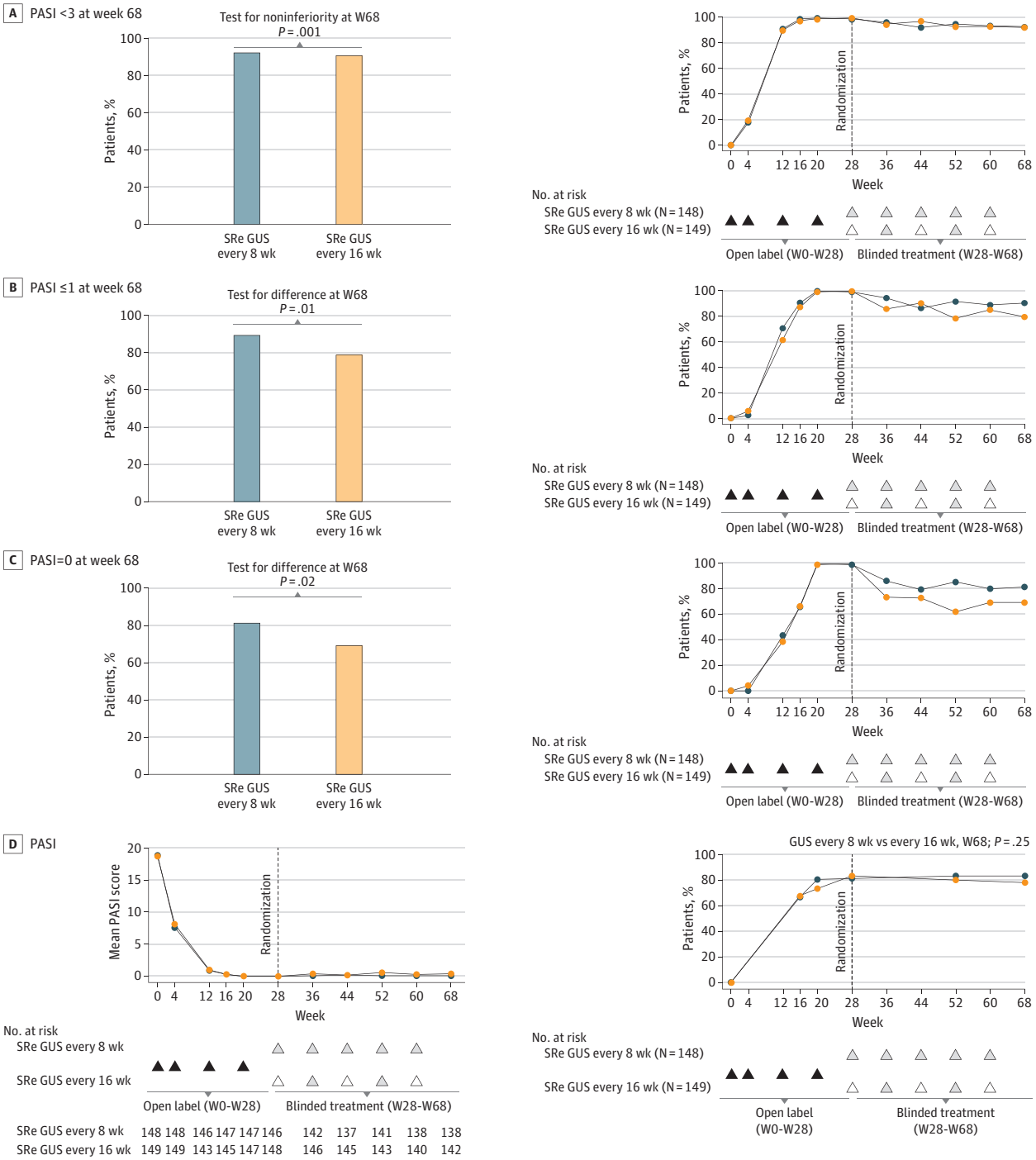
similarly, mean PSSD scores improved rapidly from baseline and remained low to W68 with both dosing intervals (eFigure 6 in Supplement 3).

Non-SRes also achieved high PASI less than 3 (435/525 [82.9%]), PASI of 1 or lower (325/525 [61.9%]), and PASI of 0 (200/525 [38.1%]) response rates over time to W68 (**Figure 2**A), although lower than those achieved by SRes. Consistent with absolute PASI response findings, non-SRes achieved high rates of PASI 75 (462/525 [88.0%]) and PASI 90 (387/525 [73.7%]) responses at W68 (eFigure 7 in Supplement 3), and maintained low affected BSA (%) to W68 (eFigure 8 in Supplement 3). Notable improvements were also observed for patient-reported quality-of-life outcomes in non-SRes, with high DLQI less than 5 and DLQI 0/1 (Figure 2B) response rates over time and at W68 (DLQI <5, 414/525 [78.9%]; DLQI 0/1, 325/525 [61.9%]). PSSD scores similarly decreased from baseline to W28 in non-SRes and continued to improve to W68 (eFigure 9 in Supplement 3).

Serum cytokine levels and skin effector T-cell subsets were assessed in exploratory substudies,[4] and findings align with the clinical and patient-reported outcome data observed. Guselkumab treatment decreased serum IL-17A, IL-17F, IL-22, and BD-2 levels from baseline to W28, and continued suppression of these biomarkers was observed with both every 8 weeks and every 16 weeks dosing from W28 to W68 (**Figure 3**A, Figure 3B, Figure 3C, and Figure 3D). No statistically significant differences were observed between dosing groups, except for baseline BD-2 levels (Figure 3). No differences were observed in IL-17A, IL-17F, and IL-22 levels between the SRe and non-SRe groups from baseline to W68, while BD-2 levels were lower in SRes compared with non-SRes at W4 and W28 (eFigure 10 in Supplement 3). Overall, CD8-positive TRM cell count in lesional skin was elevated, compared with nonlesional skin, at baseline and decreased over time with guselkumab treatment (Figure 3E). Among SRes, CD8-positive TRM cell count continued to be suppressed from W28 to W68 regardless of dosing interval (eFigure 11 in Supplement 3). Reduction of CD8-positive TRM cell count in lesional skin to nonlesional skin levels was observed at W28 in SRes and at W68 in non-SRes.

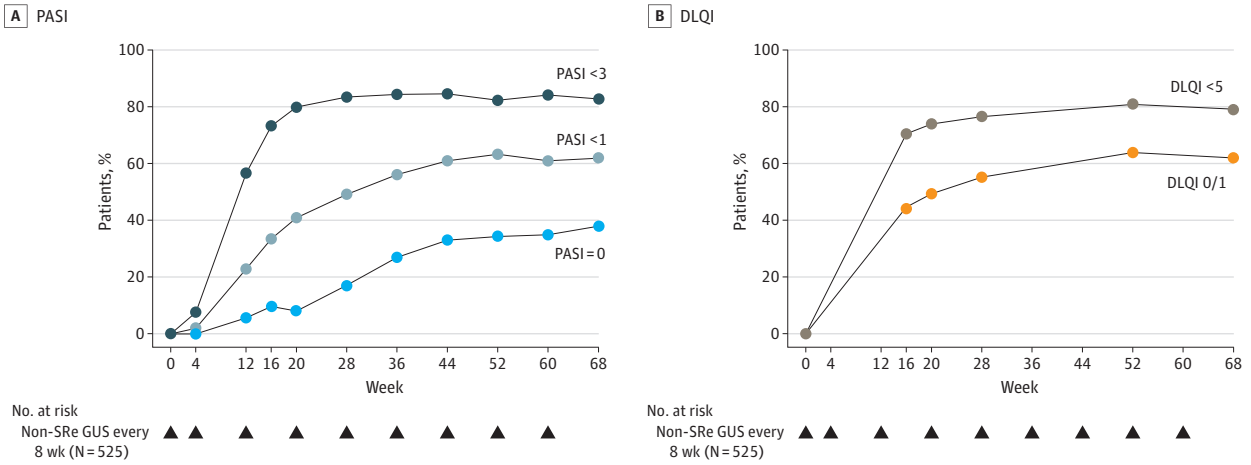
Overall, 577 patients (70.2%) experienced a treatment-emergent adverse event (TEAE; **Table 2**) during part 2 of the GUIDE trial. The most common TEAEs were nasopharyngitis and headache (>5.0% per group). TEAEs that led to treatment discontinuation were reported for 11 patients (1.3%) and the overall incidence of treatment-emergent serious AEs was similar across groups (7 [4.7%], SRe every 8 weeks; 6 [4.0%], SRe every 16 weeks; 33 [6.3%], non-SRe every 8 weeks; Table 2; eTable 4 in Supplement 3). The rates of candidiasis and major adverse cardiovascular events were low, and there were no

Figure 1. Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) Response Rates at Week 68 (W68) or Over Time Among Super Responders (SRes)



Proportion of patients achieving (A) PASI lower than 3 (primary end point), (B) PASI of 1 or lower, and (C) PASI of 0 at W68 or from baseline to W68, (D) mean PASI from baseline to W68, and (E) DLQI 0/1 response from baseline to W68, among SRes randomized to guselkumab every 8 weeks vs every 16 weeks dosing (intention-to-treat population). In panels A to C, the percentages at W20 and W28 are less than 100.0 because some patients who had a PASI of 0 had their assessment outside of the predefined visit window; these patients were imputed as nonresponders in this analysis but still considered SRes. Black arrowheads represent open-label guselkumab injections (W0 to W28), gray arrowheads represent blinded guselkumab injections in the every 8 weeks and every 16 weeks groups (W28 to W60), and white arrowheads represent placebo injections. Patients in the every 16 weeks dosing group received placebo injections at W28, W44, and W60. Nonresponder imputation was used for missing data with the exception of mean PASI assessment, for which as-observed data are shown. GUS indicates guselkumab. Panels A to E previously presented at the European Academy of Dermatology & Venereology Congress 2022 and used with permission from Prof Knut Schäkel.

Figure 2. Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) Response Rates in Non-Super Responders (SRes) Over Time to Week 68 (W68)



Proportion of non-SRe patients achieving (A) PASI lower than 3, PASI of 1 or lower, and PASI of 0, and (B) DLQI lower than 5 and DLQI 0/1 responses from baseline to W68 (intent to treat population). Nonresponder imputation was used for missing data. GUS indicates guselkumab. This Figure was previously presented at the European Academy of Dermatology & Venereology Congress 2022 and used with permission from Prof Knut Schäkel, MD.

cases of tuberculosis or inflammatory bowel disease (Table 2). The incidence of drug-related TEAEs was similar across groups (26 [17.6%], SRe every 8 weeks; 21 [14.1%], SRe every 16 weeks; 102 [19.4%], non-SRe every 8 weeks; eTable 5 in Supplement 3).

Discussion

The GUIDE trial, to our knowledge, is the first randomized clinical trial providing evidence that guselkumab-treated patients with early and complete skin clearance can maintain control of psoriasis with an extended dosing interval. We demonstrated that guselkumab dosing every 16 weeks was noninferior to the standard every 8 weeks dosing interval for maintenance of disease control at W68 in SRes, meeting the primary end point. Of note, disease control in the GUIDE trial was defined as PASI lower than 3, similar to treat-to-target goals proposed by national treatment guidelines.[15,16]

Further supporting the primary end point findings, a high level of response was observed in SRes with no significant differences between every 16 weeks and every 8 weeks guselkumab dosing with regard to clinical outcomes such as PASI 90 at W68, or patient-reported outcomes such as DLQI 0/1 response over time. For the highest treatment goals, every 8 weeks maintenance dosing appeared to be favorable, with more than 80% of SRes maintaining completely clear skin at W68 compared with almost 70% of SRes receiving dosing every 16 weeks. A similar difference was observed between dosing groups for PASI of 1 or lower response. Nevertheless, only small differences between the every 8 weeks and dosing every 16 weeks groups for mean PASI (0.1 vs 0.4, respectively) and affected BSA (%; 0.2 vs 0.4, respectively) values were observed at W68.

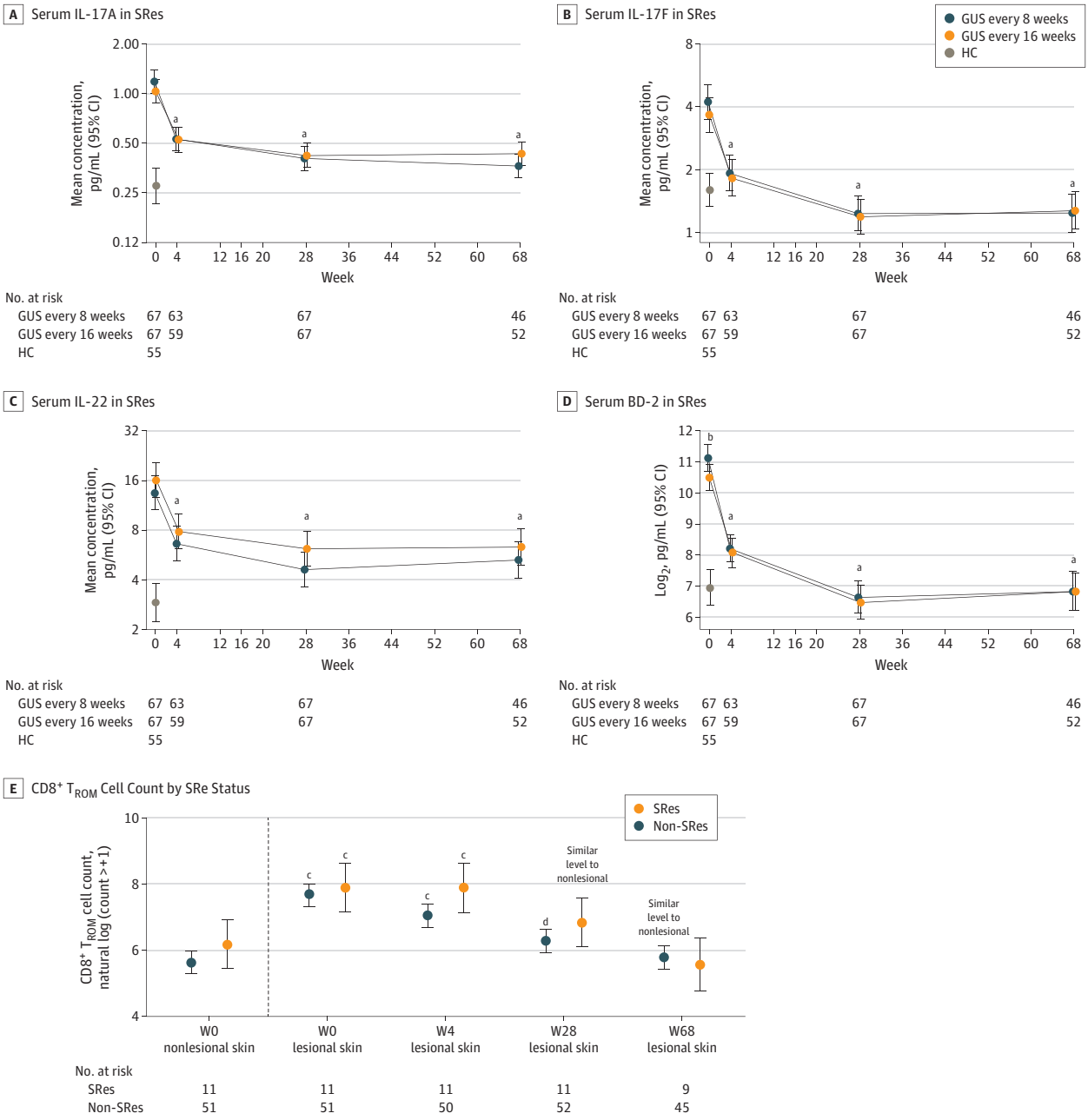
Clinical findings in SRes were supported through assessment of immunologic parameters, including blood and skin biomarkers associated with psoriasis. The cytokines IL-17A, IL-17F, and IL-22, together with the keratinocyte-derived antimicrobial peptide BD-2, represent markers of disease activity and clinical response.[9,12,17] We showed that IL-17A, IL-17F, IL-22, and BD-2 serum levels were reduced as early as W4 with guselkumab treatment, and remained suppressed to W68. In turn, lesional skin CD8-positive TRM cells were normalized to nonlesional skin levels by W28. In line with clinical and patient-reported outcomes, no differences in immunologic parameters were observed between the every 8 weeks and every 16 weeks dosing groups at W68.

Our findings suggest that early skin clearance with guselkumab is accompanied by rapid and sustained suppression of TRM cells in lesional skin, after which an extended dosing interval effectively controlled disease activity in SRes. Importantly, the 16-week dosing interval evaluated in the GUIDE clinical trial corresponds to a duration far greater than 5 half-lives of guselkumab.[18] Although it is currently unknown whether some SRes had higher blood levels of guselkumab throughout the dosing randomization period, our data suggest a link between TRM cells and maintenance of clinical response.

A new Delphi consensus[19] defines disease modification as sustained improvement in the disease course of psoriasis resulting from changes in pathophysiology that minimize the need for treatment. Based on this definition, data from the GUIDE trial suggest the potential for achieving disease modification with guselkumab treatment in SRes.

Although skin and quality-of-life improvements were generally greater in SRes than non-SRes, non-SRes also achieved highly favorable skin, quality-of-life, and immunologic outcomes, with 82.9% of non-SRes achieving the treatment goal of PASI lower than 3 at W28 and maintaining this level of re-

Figure 3. Interleukin (IL)–17A, IL-17F, IL-22, and B Defensin-2 (BD-2) Serum Levels and Skin CD8-Positive Tissue-Resident Memory (TRM) Cell Count From Baseline to Week 68 (W68)



Mean serum concentration (pg/mL; 95% CI) for (A) IL-17A, (B) IL-17F, and (C) IL-22, and averaged $\log_2$ concentration for (D) BD-2, from baseline to W68, among SRes randomized to guselkumab every 8 weeks vs every 16 weeks dosing; E, CD8-positive TRM cell count ($\log_e$, 95% CI) by SRe status. Normalization was defined as a cell count that was not statistically significantly different compared with W0 nonlesional skin. Variation in the number of patients analyzed across visits is the result of patient withdrawals, and (E) the availability of obtaining bead counts. Log cell count represents natural log (cell count of plus 1). BD-2 indicates β defensin-2; GUS, guselkumab; HC, healthy control; IL, interleukin; SRe, super responder. Panel E was previously presented at the International Societies for Investigative Dermatology Congress 2023 and used with permission from Dr Julianty Angsana, PhD.

[a]vs W0, $P < .001$.

[b]vs W0 nonlesional skin, $P < .01$.

[c]vs W0 nonlesional skin, $P < .001$.

sponse to W68. For more stringent clinical (eg, PASI = 0) and patient-reported outcomes, response rates continued to improve after W28; however, non-SRes generally took longer to achieve treatment targets than SRes. Consistent with this, normalization of CD8-positive TRM cell count was observed by W28 in SRes but not until W68 in non-SRes.

Whether non-SRes are capable of maintaining long-term disease control with an extended dosing interval was not stud-

Table 2. Safety Events During W28 to W68 (Safety Set Population)[a]

Event	Guselkumab, 100 mg, randomized SRe patients		Guselkumab, 100 mg, non-SRe patients, group 2C, every 8 wk (n = 525)
	Group 2A, every 8 wk (n = 148)	Group 2B, every 16 wk (n = 149)	
Total AEs, No.	314	251	1015
Patients with ≥1 AE, No. (%)	102 (68.9)	104 (69.8)	378 (72.0)
Total SAEs, No.	8	6	45
Patients with ≥1 SAE, No. (%)	7 (4.7)	6 (4.0)	36 (6.9)
Death, No (%)	0	0	1 (0.2)[b]
AESI, No. (%)			
Acute TB or reactivation[c]	0	0	0
Nonmelanoma skin cancer	0	1 (0.7)	1 (0.2)
Melanoma/lymphoma	0	0	0
Transitional cell carcinoma	0	0	1 (0.2)
TEAEs, No. (%)[d]			
Patients with ≥1 event	102 (68.9)	103 (69.1)	372 (70.9)
Nasopharyngitis	26 (17.6)	23 (15.4)	97 (18.5)
Headache	8 (5.4)	9 (6.0)	29 (5.5)
Back pain	6 (4.1)	8 (5.4)	13 (2.5)
Arthralgia	5 (3.4)	5 (3.4)	29 (5.5)
Influenza	5 (3.4)	5 (3.4)	6 (1.1)
Hypertension	4 (2.7)	5 (3.4)	31 (5.9)
Increased blood creatine phosphokinase	3 (2.0)	6 (4.0)	8 (1.5)
Diarrhea	5 (3.4)	1 (0.7)	13 (2.5)
Injection-site erythema	6 (4.1)	0	5 (1.0)
Treatment-emergent SAEs, No. (%)	7 (4.7)	6 (4.0)	33 (6.3)
Selected TEAEs, No. (%)			
Hypersensitivity	1 (0.7)	1 (0.7)[e]	0
Infections			
COVID-19	4 (2.7)	3 (2.0)	13 (2.5)
Candidiasis[f]	2 (1.4)	2 (1.3)	6 (1.1)
Major adverse cardiovascular event	1 (0.7)[g]	0	6 (1.1)[h]
Chronic cholecystitis	1 (0.7)	0	0
Thrombosis	0	0	2 (0.4)
Inflammatory bowel disease	0	0	0
Suicidal behavior	1 (0.7)	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event; SRe, super responder; TB, tuberculosis; TEAE, treatment-emergent adverse event.

[a] This Table was previously presented at the European Academy of Dermatology & Venereology Congress 2022 and used with permission from Prof Knut Schäkel, MD.

[b] Cause of death unknown (doubtfully related to treatment).

[c] There were 6 patients with latent TB at baseline.

[d] Reported in ≥3% of patients in any group.

[e] Hypersensitivity pneumonitis.

[f] Includes all cases of skin candida, oral candidiasis, esophageal candidiasis, balanitis candida, and candida infection.

[g] Myocardial infarction.

[h] Included 5 cases of myocardial infarction and 1 case of unintentional cerebrovascular injury.

ied in the GUIDE clinical trial. Achievement of early and complete skin clearance at 2 consecutive visits, representing a high level of stability of response to treatment, may be a critical indicator for effective control of disease activity with an extended dosing interval.

Overall, guselkumab was well tolerated in the GUIDE trial, with no new safety signals identified. The low rates of TEAEs in the every 16 weeks dosing group were comparable to those observed in the every 8 weeks dosing group and in previous studies.[6,7] Our data further complement the favorable benefit-risk profile for guselkumab in the treatment of psoriasis.

Across a range of immunologic disorders, including psoriasis, there remains a large unmet medical need for personalized treatment and dosing strategies. With the availability of highly effective biologic therapies, high treatment goals have become attainable for many patients in recent years, providing opportunities to address individual treatment goals. Although long-term maintenance of response after de-escalation of biologic therapy has been evaluated in psoriasis to some degree, the body of scientific evidence is relatively limited and not as robust compared with other disease areas, such as rheumatoid arthritis.[20,21]

Michielsens et al[21] identified 19 studies evaluating tapering of biologic therapy in psoriasis. One of these was the large-scale phase 3b OPTIMISE trial, which determined that the treatment interval for secukinumab (an IL-17 inhibitor) could not be extended from every 4 weeks to every 6 weeks without impacting efficacy and overall persistence.[20] Meanwhile, a post hoc exploratory analysis of the phase 3 PSTELLAR clinical trial demonstrated that patients who achieved a Physician's Global Assessment score of 0 after 28 weeks of ustekinumab (an IL-12/23 inhibitor) treatment were able to maintain high levels of clinical response following dosing interval extension up

to every 24 weeks.[22] Similarly, in a clinical study of patients who achieved a PASI of 0 after the third administration of guselkumab, extension of the dosing interval did not result in loss of disease control.[23] Together, these results suggest that early response to IL-23 inhibition may be a key determinant of effective disease control with dosing interval extension. However, given the molecular and pathomechanistic differences of approved IL-23 inhibitors,[24] further studies are needed to address this possibility for other agents in this class. These data also suggest that maintenance of efficacy following dose de-escalation may vary across biologic treatment classes as a result of their differential therapeutic impact on pathogenic mechanisms.[11] Specifically, IL-17–producing CD8-positive TRM cells are known to be responsible for the recurrence of psoriasis skin lesions in previously affected areas,[3,25,26] and that IL-23, but not IL-17, has a key role in the differentiation, expansion, and survival of TRM cells.[11,27] Reflective of our findings in the GUIDE trial, the ECLIPSE trial[11] demonstrated that guselkumab decreased the frequency of CD8-positive TRM cells in lesional skin at W24 relative to baseline, whereas treatment with the IL-17 inhibitor secukinumab did not. Therefore, the effect of guselkumab on TRM cells may explain how SRes can maintain high levels of response with an extended dosing interval. This may also account for the long-term maintenance of response typically observed with guselkumab treatment, even after withdrawal of guselkumab.[12] Maintenance of response after withdrawal of guselkumab will be further evaluated in part 3 of the GUIDE trial.

Though treatment de-escalation of biologics for psoriasis may be attempted in daily practice, evidence-based treatment guidelines and algorithms for suitable patients are limited.[5] As part of a recent modified Delphi procedure, van der Schoot et al[5] highlighted the importance of clear criteria, supported by existing evidence, for clinicians to consider treatment de-escalation. The authors also noted the small volume of evidence on de-escalation of newer biologic therapies, such as IL-23 inhibitors.[5] Similarly, Michielsens et al[21] concluded that further research into dose reduction is required, highlighting the need for randomized clinical trials including a standard-of-care treatment arm, such as in the GUIDE trial.

In the GUIDE trial, we identified a population of SRes who maintained psoriasis disease control with treatment de-escalation through dosing interval extension to every 16 weeks. Previous findings from GUIDE demonstrated that SDD and biologic-naive patients were more likely to achieve super response than those with LDD or prior biologic exposure.[9] A post hoc analysis of pooled VOYAGE 1 and 2 clinical trial data also determined that SRes tended to be younger and have lower body weight and less severe disease at baseline.[28] Nonetheless, further analyses of GUIDE data may provide insights into clinical and biomarker parameters predictive of super response. Our current findings suggest that early intervention with guselkumab increases the likelihood of achieving super response,[9] and thus subsequently may be important to accommodate therapeutic strategies through dosing interval flexibility. The GUIDE clinical trial contributes critical prospective data to help address individual patient needs in everyday practice, and potentially improve long-term disease management and patient compliance with treatment.

Limitations

A potential limitation of this trial is the absence of a non-SRe dosing interval extension group to serve as a comparator. Consequently, it remains unclear whether dosing flexibility is feasible in this patient group. In addition, some biomarker analyses comprised only small groups of patients, such as the CD8-positive TRM cell count by dosing group analysis, which may affect the reliability of the findings.

Conclusion

Following achievement of early and complete clearance of psoriasis, guselkumab dosing at an extended every 16 weeks interval was noninferior to every 8 weeks dosing for maintaining disease control. Patient-reported outcomes and findings for key immunologic parameters support the clinical observations. Data from the GUIDE trial add new insights into the concepts of disease modification and long-term maintenance of efficacy. Future analyses from the GUIDE trial will assess the association between clinical response and biomarker and pharmacokinetic data, and further evaluate maintenance of long-term response after treatment withdrawal.

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