

Time to Loss of Disease Control following Guselkumab Withdrawal in Relation to Initial Speed of Response: A post hoc Analysis of the VOYAGE 2 Trial

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Keywords

Guselkumab · Psoriasis · VOYAGE 2 · Treatment withdrawal · Maintenance of response

Abstract

Background: Psoriasis is a chronic inflammatory skin disorder typically requiring lifelong treatment. As such, patients may occasionally need treatment breaks. Understanding factors predicting maintenance of disease control during treatment breaks could improve long-term disease management. This post hoc analysis of data from the phase 3 VOYAGE 2 clinical trial evaluates how initial speed of response to guselkumab treatment affects time to loss of disease control following treatment withdrawal and identifies baseline characteristics corresponding with maintenance of disease control. **Methods:** Patients with moderate-to-severe plaque psoriasis were assigned to treatment withdrawal following achievement of a Psoriasis Area and Severity Index (PASI) 90 response after two or four guselkumab doses. Loss of disease control was defined as time

to PASI ≥ 3 and was assessed using Kaplan-Meier analysis. The relationship between baseline characteristics and maintenance of response was evaluated using a Cox proportional hazards model. **Results:** Of patients who were randomized to placebo and switched to guselkumab at week 16, 149/248 (60%) achieved PASI90 after two guselkumab doses (week 28). Of patients who were randomized to guselkumab, 377/496 (76%) had a PASI90 response after four guselkumab doses (week 28), of whom 182 were then re-randomized to withdrawal. Of these, 131 had achieved PASI90 after two guselkumab doses (week 12) and 51 had achieved PASI90 after four guselkumab doses (week 28). Maintenance of disease control following guselkumab withdrawal was longer in patients who achieved PASI90 after two versus four guselkumab doses. Lower body mass index, biologic-naïve status, and shorter disease duration at baseline corresponded with a longer time to PASI ≥ 3

Clinical trial registration number and trial register: NCT02207244 (ClinicalTrials.gov identifier).

following withdrawal. **Conclusion:** Faster initial response to guselkumab resulted in longer maintenance of disease control after treatment withdrawal. These findings may be used to inform personalized dosing strategies with guselkumab, which may increase patient compliance to treatment and improve long-term treatment outcomes.

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Plain Language Summary

Psoriasis is a long-term inflammatory disease primarily associated with red, scaly, itchy plaques of skin. Owing to the long-term nature of psoriasis, patients usually require life-long treatment, although occasional breaks from the treatment may be required, e.g., for travel or health-related reasons. In this analysis using data from a large clinical trial, VOYAGE 2, we assessed patients with psoriasis who were treated with the injectable biologic drug guselkumab to improve their condition. Among patients whose skin greatly improved ($\geq 90\%$ improvement in affected psoriatic skin) with guselkumab treatment, we report on factors linked to recurrence of psoriasis after patients stopped receiving treatment. After stopping guselkumab treatment, the skin remained clear of psoriasis for longer in patients who initially had the quickest response to treatment (patients whose skin achieved $\geq 90\%$ clearance after just two doses of guselkumab, compared with those who required four doses to achieve the same response). The skin also remained clear of psoriasis for longer in patients who had a shorter duration of psoriasis (from symptom onset to starting guselkumab treatment), those who had not previously received a biologic therapy for their psoriasis, and those with a lower body mass index. Although it is recommended that guselkumab should be injected only every 8 weeks for the treatment of psoriasis, these findings may help healthcare providers identify suitable candidates for dose reduction and inform individual patient-tailored dosing strategies. This may increase the likelihood of patients continuing to receive their treatment and improve long-term treatment outcomes.

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Introduction

Psoriasis is a chronic, immune-mediated disease [1] managed with a broad spectrum of treatments, including ultraviolet light, topical corticosteroids, systemics, and biologic therapies [2]. Guselkumab is a fully

human monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23 [3] and was approved in Europe in November 2017 for the treatment of moderate-to-severe plaque psoriasis [4]. Approval was based on the VOYAGE 1 and 2 phase 3 clinical trials, which demonstrated that guselkumab was superior to placebo and adalimumab for the coprimary endpoints of achieving $\geq 90\%$ improvement in Psoriasis Area and Severity Index (PASI90) and Investigator's Global Assessment (IGA) score of 0 or 1 at week 16 [5, 6]. VOYAGE 2 had a randomized withdrawal and re-treatment phase – patients treated with guselkumab who achieved a PASI90 response at week 28 were randomized 1:1 to continue guselkumab treatment or withdraw from guselkumab and receive placebo. For patients randomized to the withdrawal group, the median time to loss of PASI90 response was 15.2 weeks (23 weeks after the last guselkumab dose) [6]. A multivariate analysis suggested that maintenance of PASI90 response during the withdrawal phase was associated with shorter disease duration, lower body mass index (BMI), and lower serum levels of IL-17F and macrophage inflammatory protein 1- β at baseline [7].

There is currently no cure for psoriasis; treatment to maintain disease control is typically a lifelong endeavor. Inevitably, patients with psoriasis may require occasional treatment breaks, e.g., during travel or for health-related reasons [8]. Further understanding of the dynamics of loss of disease control during treatment breaks and the baseline characteristics associated with patients who are more likely to maintain disease control after treatment withdrawal could help improve long-term compliance and treatment outcomes.

Patients with fast and exceptional improvement in psoriasis following treatment may be considered super responders [9, 10]. In the GUIDE clinical trial, super responders were defined as those achieving an absolute PASI of 0 at weeks 20 and 28 following treatment with guselkumab [11, 12]. It was hypothesized that patients with short disease duration (≤ 2 years from symptom onset) and fast complete skin clearance in response to guselkumab treatment (i.e., super responders) might maintain long-term, drug-free disease control [11].

To further our understanding of super response, maintenance of disease control, and the associated baseline characteristics, this post hoc analysis of VOYAGE 2 data was conducted to evaluate whether the initial speed of response to guselkumab treatment (PASI90 response after two vs. four doses of guselkumab) affects maintenance of disease control (time to PASI ≥ 3) upon discontinuation of treatment. A multivariable regression

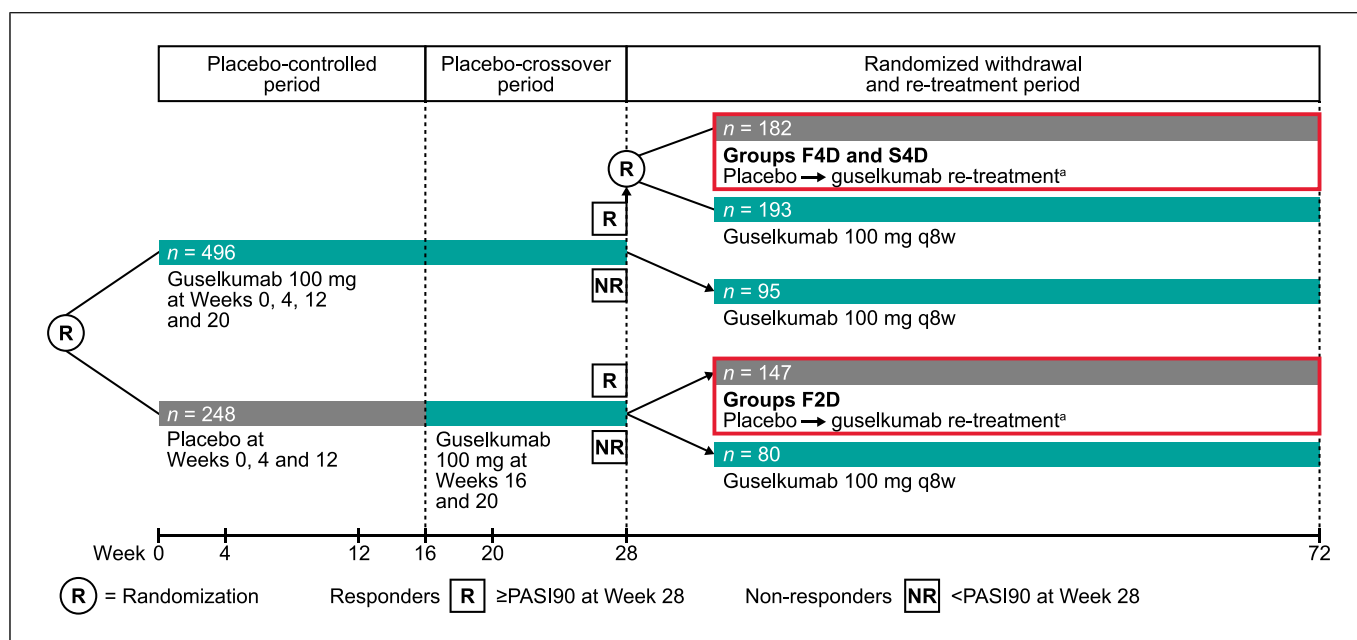


Fig. 1. Study design. The adalimumab arm and open-label portions of VOYAGE 2 are not included in the figure. The red boxes indicate the portion of the randomized withdrawal and retreatment period of VOYAGE 2 included in this post hoc analysis. Of those randomized to guselkumab at week 0, 18 and 8 patients discontinued during weeks 0–16 and weeks 16–28, respectively; of those randomized to placebo at week 0, 15 and 6

patients discontinued during weeks 0–16 and weeks 16–28, respectively. ^aIn VOYAGE 2, with loss of ≥50% of PASI response achieved at week 28, or if at week 72 the prerequisite loss of PASI response was not observed, patients reinitiated treatment with guselkumab. F2D, fast responders – two doses; F4D, fast responders – four doses; q8w, every 8 weeks; S4D, slow responders – four doses.

analysis was conducted to assess the relationship between baseline patient and disease characteristics and time to loss of disease control (PASI ≥3).

Methods

Trial Design

The VOYAGE 2 trial design has been described previously [6]. In summary, VOYAGE 2 was a phase 3, multicenter, randomized, double-blind, placebo- and adalimumab comparator-controlled clinical trial (NCT02207244) conducted across 115 global sites from November 2014 to May 2016. VOYAGE 2 consisted of a placebo-controlled period (weeks 0–16), an active comparator-controlled period (weeks 0–28), a randomized withdrawal and retreatment period (weeks 28–72), and an open-label treatment period (weeks 76–252) [3, 6]. At the beginning of the study, patients were randomized in a 2:1:1 ratio to receive subcutaneous injections of guselkumab 100 mg ($n = 496$) at weeks 0, 4, 12, and 20; placebo ($n = 248$) at weeks 0, 4, and 12, followed by guselkumab 100 mg at weeks 16 and 20; or adalimumab

80 mg ($n = 248$) at week 0, 40 mg at week 1, then 40 mg q2w through to week 23 [6]. This post hoc analysis focuses on the randomized withdrawal period of VOYAGE 2 (shown in Fig. 1). The study protocol was approved by Investigational Review Boards at each site (online suppl. material; for all online suppl. material, see <https://doi.org/10.1159/000542344>), and written informed consent was provided by all patients. VOYAGE 2 was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice.

Patients

Patients eligible for VOYAGE 2 were ≥18 years of age, had moderate-to-severe plaque psoriasis (i.e., IGA score ≥3, PASI ≥12, body surface area involvement ≥10%) for at least 6 months, and were candidates for systemic therapy or phototherapy [6]. Patient exclusion criteria have been described previously [5, 6]. Patients eligible for this post hoc analysis were those initially randomized to guselkumab or placebo (patients randomized to adalimumab were not included) who achieved a PASI90 response relative to baseline and were

subsequently withdrawn from treatment at week 28 (shown in Fig. 1).

Patients included in this post hoc analysis were divided into three groups. Group F2D (fast responders – two doses) comprised patients randomized to placebo who achieved a PASI90 response at week 28 following crossover with two doses of guselkumab (one at week 16 and one at week 20). Group F4D (fast responders – four doses) comprised patients randomized to guselkumab who achieved a PASI90 response at week 12 after two doses at weeks 0 and 4 and maintained PASI90 response at week 28, after two more doses at weeks 12 and 20. Group S4D (slow responders – four doses) comprised patients randomized to guselkumab who did not achieve a PASI90 response at week 12 but did achieve a PASI90 response at week 28 after doses of guselkumab at weeks 0, 4, 12, and 20.

Assessments

Time to worsening of psoriasis to PASI ≥ 1 , PASI ≥ 3 , and PASI ≥ 5 after withdrawal from treatment was assessed for patients in groups F2D, F4D, and S4D who achieved a PASI90 response and PASI < 1 or a PASI90 response and PASI = 0 at week 28. In addition, the relationship between baseline characteristics and time to loss of disease control (PASI ≥ 3) following guselkumab withdrawal was assessed for patients in each group (F2D, F4D, and S4D) that achieved a PASI 90 response and PASI < 1 at week 28.

Statistical Analysis

Kaplan-Meier analysis was conducted to determine median time to loss of disease control, using as observed data. The association between baseline characteristics and time to loss of disease control was based on a multivariable regression (Cox proportional hazards) model. This post hoc analysis was not powered for statistical significance; therefore, *p* values are not presented.

Results

Response at Week 28 and Baseline Characteristics

In total, 992 patients were randomized in the VOYAGE 2 clinical trial, of whom 329 were included in this post hoc analysis. Of the patients initially randomized to placebo who switched to guselkumab at week 16 (*n* = 248), 149 (60%) achieved a PASI90 response at week 28 after two doses of guselkumab, 147 of whom were withdrawn from treatment (group F2D). Of these, 99 patients also achieved PASI < 1 and 59 patients

achieved PASI = 0 at week 28. The remaining 48 patients had a mean PASI of 1.8. Among patients initially randomized to guselkumab (*n* = 496), 377 (76%) achieved a PASI90 response at week 28, and 182 of these were re-randomized to withdrawal. Of these, 131 patients had achieved a PASI90 response at week 12 after two doses of guselkumab and maintained their PASI90 response at week 28 after four doses of guselkumab (group F4D); 110 of these patients had also achieved PASI < 1 and 88 patients had achieved PASI = 0. The remaining 21 patients had a mean PASI of 1.5. Of the 182 patients who were initially randomized to guselkumab and were later randomized to withdrawal, 51 had achieved a PASI90 response at week 28 after a total of four doses of guselkumab (group S4D). Of these, 31 patients had also achieved PASI < 1 and 19 patients had achieved PASI = 0. The remaining 20 patients had a mean PASI of 1.6.

Patient demographics and disease characteristics for the overall VOYAGE 2 population and for each analysis group are shown in Table 1. Baseline characteristics were generally well balanced between groups F2D and F4D, though there were numerically higher percentages of males and patients with overweight BMI, and lower percentages of smokers and patients with normal BMI in group S4D, compared with groups F2D and F4D.

Time to Loss of Disease Control in Relation to Speed of Response to Guselkumab

Time to loss of disease control (PASI ≥ 3) following withdrawal of guselkumab at week 28 was assessed for groups F2D, F4D, and S4D. Among those who achieved a PASI90 response and PASI < 1 at week 28, time to PASI ≥ 3 was longer for patients in group F2D {median (95% confidence interval [CI]) = 27.9 (20.3–31.9) weeks; hazard ratio (HR) (95% CI) = 0.489 (0.319–0.749)} and group F4D (median [95% CI] = 23.3 [20.6–27.4] weeks; HR [95% CI] = 0.645 [0.426–0.977]) versus group S4D (median [95% CI] = 16.9 [15.4–29.0] weeks) (shown in Fig. 2a). Of those in groups F2D, F4D, and S4D who achieved a PASI90 response and PASI = 0 at week 28, the median time (95% CI) to PASI ≥ 3 was 28.5 (24.0–35.1), 23.0 (20.3–27.4), and 21.9 (16.3–36.0) weeks, respectively (shown in Fig. 2b).

Further analyses assessed time to PASI ≥ 1 and PASI ≥ 5 . For patients in groups F2D, F4D, and S4D who achieved a PASI90 response and PASI < 1 at week 28, time to PASI ≥ 1 was longer for patients in group F2D (median [95% CI] = 19.0 [16.0–20.3] weeks; HR [95% CI] = 0.487 [0.320–0.741]) and group F4D (median [95% CI] = 16.3 [14.9–19.9] weeks; HR [95% CI] = 0.588 [0.390–0.887])

Table 1. Patient baseline demographic and disease characteristics

Baseline characteristic ^a	Overall (N = 992)	Group F2D (n = 147)	Group F4D (n = 131)	Group S4D (n = 51)
Age, years	43.5 (12.2)	42.2 (12.4)	41.6 (11.8)	44.6 (11.2)
Male, %	69.8	68.7	68.7	88.2
Current cigarette smokers, %	33.2	36.7	45.0	15.7
BMI, kg/m ²	29.6 (6.5)	28.7 (5.8)	28.7 (6.9)	29.0 (4.7)
Normal (BMI <25 kg/m ²), %	23.5	27.2	32.8	13.7
Overweight (BMI ≥25–<30 kg/m ²), %	36.3	36.1	35.9	47.1
Obese (BMI ≥30 kg/m ²), %	40.1	36.7	31.3	39.2
Psoriasis duration, years	17.8 (11.9)	17.8 (11.4)	18.2 (12.0)	16.1 (11.4)
Baseline PASI	21.8 (8.6)	21.7 (7.8)	22.4 (8.8)	22.2 (8.9)
hf-pPGA score, 0–4, n	262	34	37	17
hf-pGA ≥2, %	88.9	91.2	97.3	88.2
Biologic experienced, %	20.6	23.8	19.1	17.6
Comorbid PsA, %	18.3	16.3	18.3	19.6

BMI, body mass index; F2D, fast responders – two doses; F4D, fast responders – four doses; PASI, Psoriasis Area and Severity Index; hf-pGA, Physician's Global Assessment of hands and/or feet; PsA, psoriatic arthritis; S4D, slow responders – four doses.
^aValues are presented as mean (standard deviation) unless otherwise indicated.

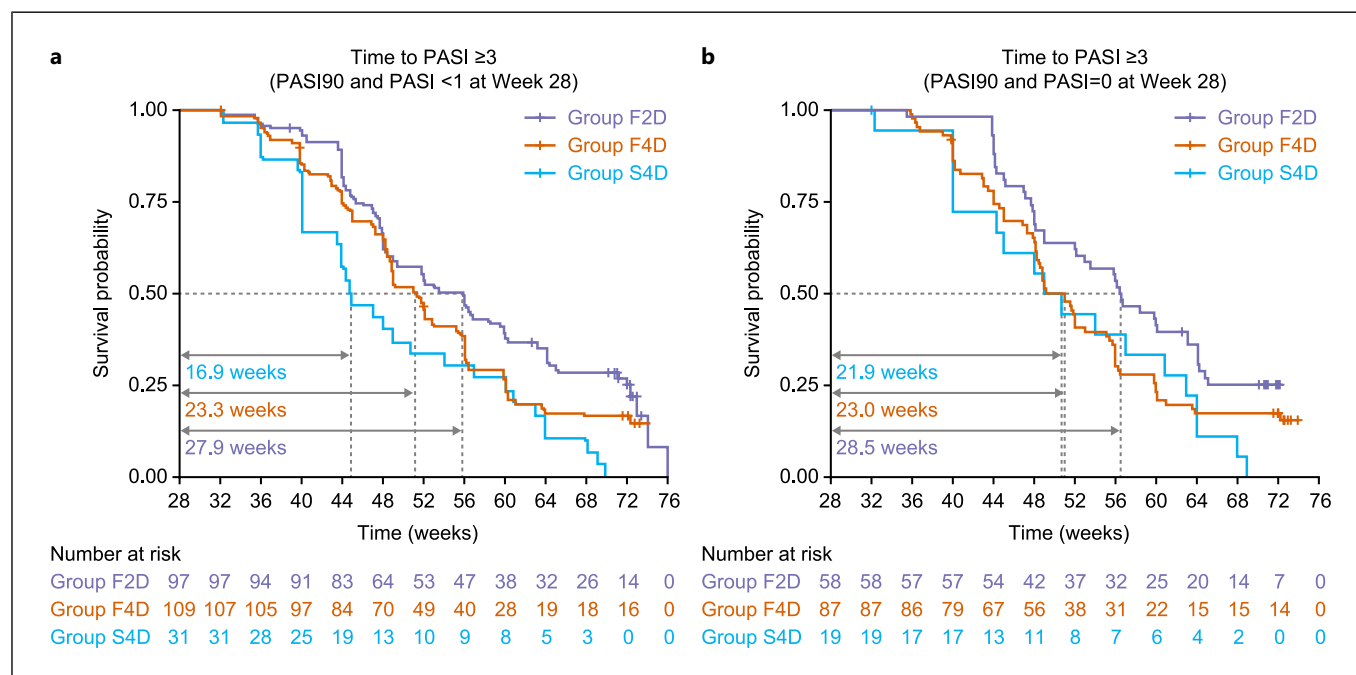


Fig. 2. Survival analysis of time to PASI ≥3 for patients achieving a PASI90 and PASI <1 (a) or PASI = 0 (b) response at week 28. Time to loss of disease control was assessed by Kaplan-Meier analysis. F2D, fast responders – two doses; F4D, fast responders – four doses; PASI, Psoriasis Area and Severity Index; S4D, slow responders – four doses.

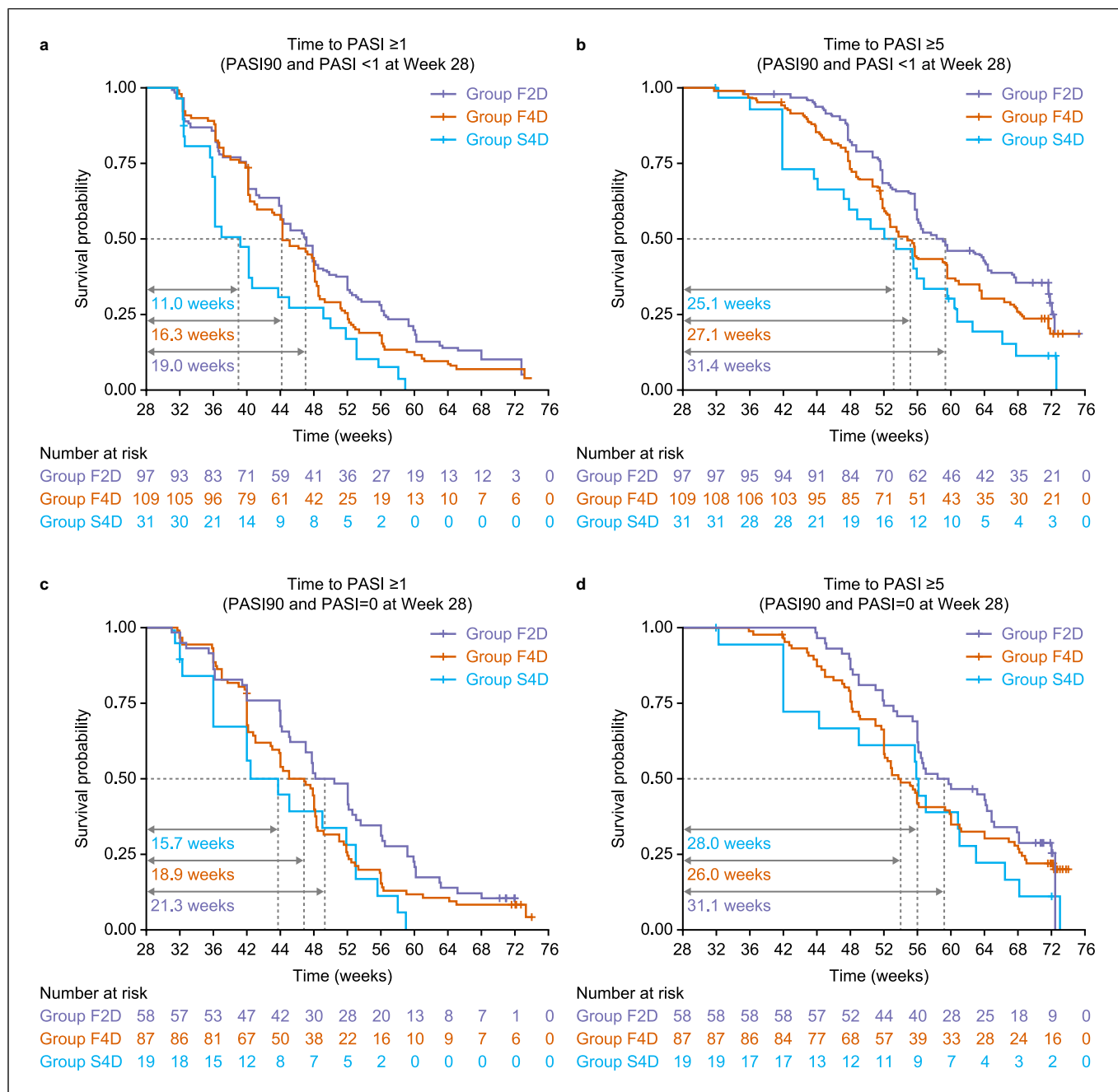


Fig. 3. Survival analysis of time to PASI ≥ 1 (a) or PASI ≥ 5 (b) for patients achieving a PASI90 and PASI < 1 response at week 28, and time to PASI ≥ 1 (c) or PASI ≥ 5 (d) for patients achieving a PASI90 and PASI = 0 response at week 28. Time to loss of disease control was assessed by Kaplan-Meier analysis. F2D, fast responders – two doses; F4D, fast responders – four doses; PASI, Psoriasis Area and Severity Index; S4D, slow responders – four doses.

versus group S4D (median [95% CI] = 11.0 [8.0–17.0] weeks; shown in Fig. 3a). For those who achieved a PASI90 response and PASI < 1 at week 28, time to PASI ≥ 5 was also longer for patients in group F2D

(median [95% CI] = 31.4 [28.0–36.9] weeks; HR [95% CI] = 0.517 [0.330–0.809]) and group F4D (median [95% CI] = 27.1 [24.4–32.0] weeks; HR [95% CI] = 0.691 [0.448–1.066]) versus group S4D (median [95% CI] = 25.1

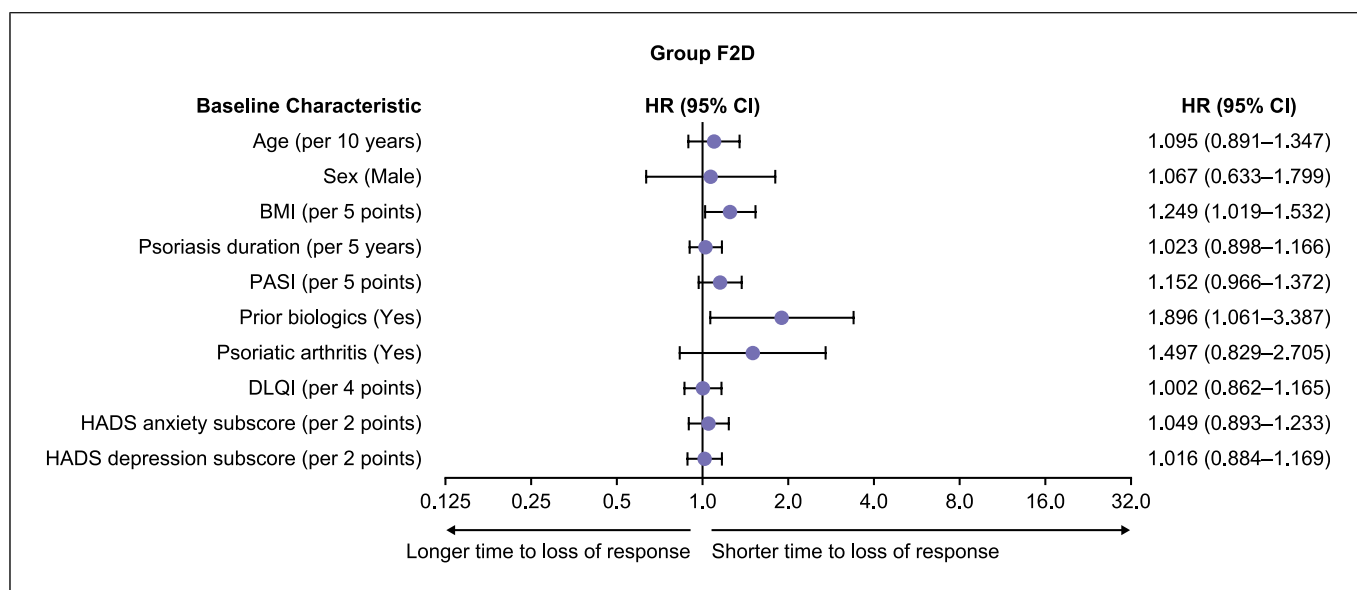


Fig. 4. Baseline characteristics corresponding with time to PASI ≥ 3 for patients in group F2D ($n = 97$). Log base 2 was used as the x-axis scale. BMI, body mass index; CI, confidence interval; DLQI, Dermatology Life Quality Index; F2D, fast responders – two doses; HADS, Hospital Anxiety and Depression Scale; PASI, Psoriasis Area and Severity Index.

[19.4–32.9] weeks) (shown in Fig. 3b). Similar trends were observed regarding patients with a PASI90 response and PASI = 0 at week 28: the median time to PASI ≥ 1 and PASI ≥ 5 was longer for patients in groups F2D and F4D versus group S4D (shown in Fig. 3c, d).

Relationships between Time to Loss of Disease Control and Baseline Characteristics

The relationship between time to loss of disease control (PASI ≥ 3) and baseline characteristics was assessed using a multivariable Cox proportional hazards model for patients in groups F2D, F4D, and S4D with a PASI90 response and PASI < 1 at week 28. For patients in group F2D, higher baseline BMI (per 5 points, HR [95% CI] = 1.249 [1.019–1.532]) and prior use of biologics (HR [95% CI] = 1.896 [1.061–3.387]) corresponded with shorter time to loss of disease control (shown in Fig. 4). For patients in group F4D, higher baseline BMI (per 5 points, HR [95% CI] = 1.270 [1.093–1.476]) and longer psoriasis duration (per 5-year increase, HR [95% CI] 1.157 [1.045–1.281]) corresponded with shorter time to loss of disease control (shown in Fig. 5). For patients in group S4D, higher baseline BMI (per 5 points, HR [95% CI] = 1.865 [1.094–3.181]) and prior use of biologics (HR [95% CI] = 4.174 [1.101–15.830]) corresponded with shorter time to loss of disease control (shown in Fig. 6).

Discussion

To our knowledge, this post hoc analysis of VOYAGE 2 data is the first to assess whether the initial speed of response to treatment (PASI90 response after two versus four doses of guselkumab) affects time to loss of disease control in patients with moderate-to-severe plaque psoriasis. There are some similarities between this analysis and the GUIDE clinical trial, which proposed that super responders who achieve clear skin at weeks 20 and 28 may maintain disease control with an extended q16w dosing interval [11]. Both this analysis and the GUIDE clinical trial defined loss of disease control as PASI ≥ 3 , aligning with the treat-to-target recommendation of PASI ≤ 2 proposed by the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) [13].

Previous analyses of VOYAGE 2 showed PASI90 response was well maintained during the withdrawal phase [6]. In the current analysis, maintenance of disease control after withdrawal was longer for patients who achieved a PASI90 response after two doses of guselkumab than for patients who achieved a PASI90 response after four doses of guselkumab. Therefore, faster initial response correlated with longer time to loss of disease control.

The results of this post hoc analysis are consistent with results from GUIDE, which demonstrated that PASI

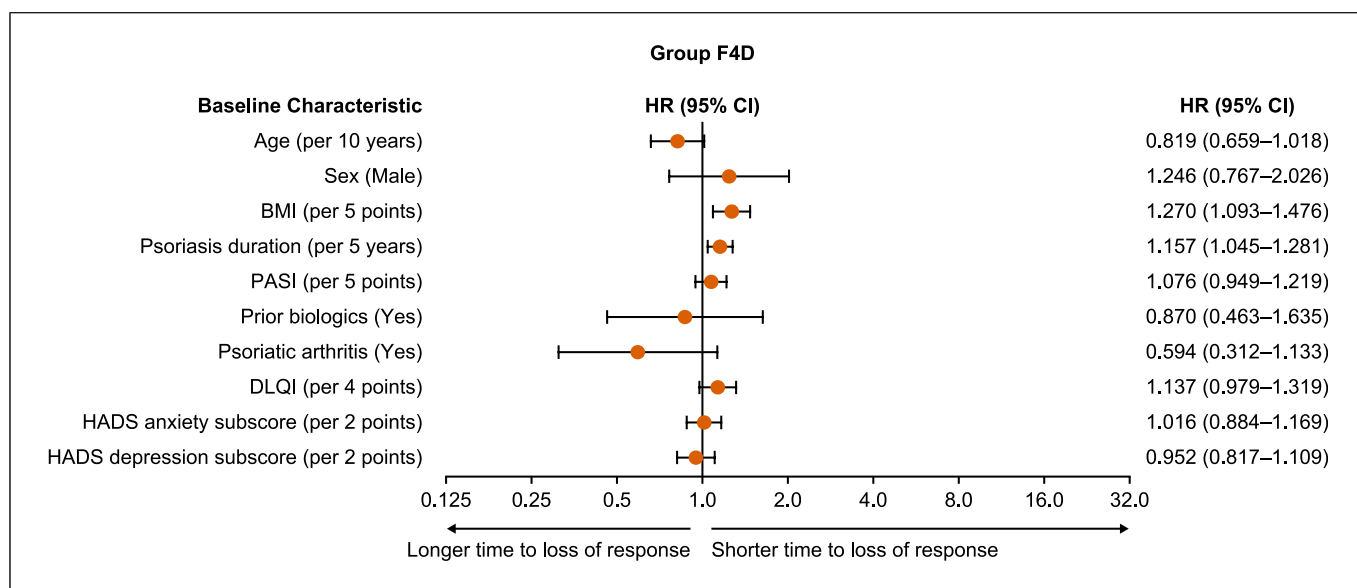


Fig. 5. Baseline characteristics corresponding with time to PASI ≥ 3 for patients in group F4D ($n = 109$). Log base 2 was used as the x-axis scale. BMI, body mass index; CI, confidence interval; DLQI, Dermatology Life Quality Index; F4D, fast responders – four doses; HADS, Hospital Anxiety and Depression Scale; PASI, Psoriasis Area and Severity Index.

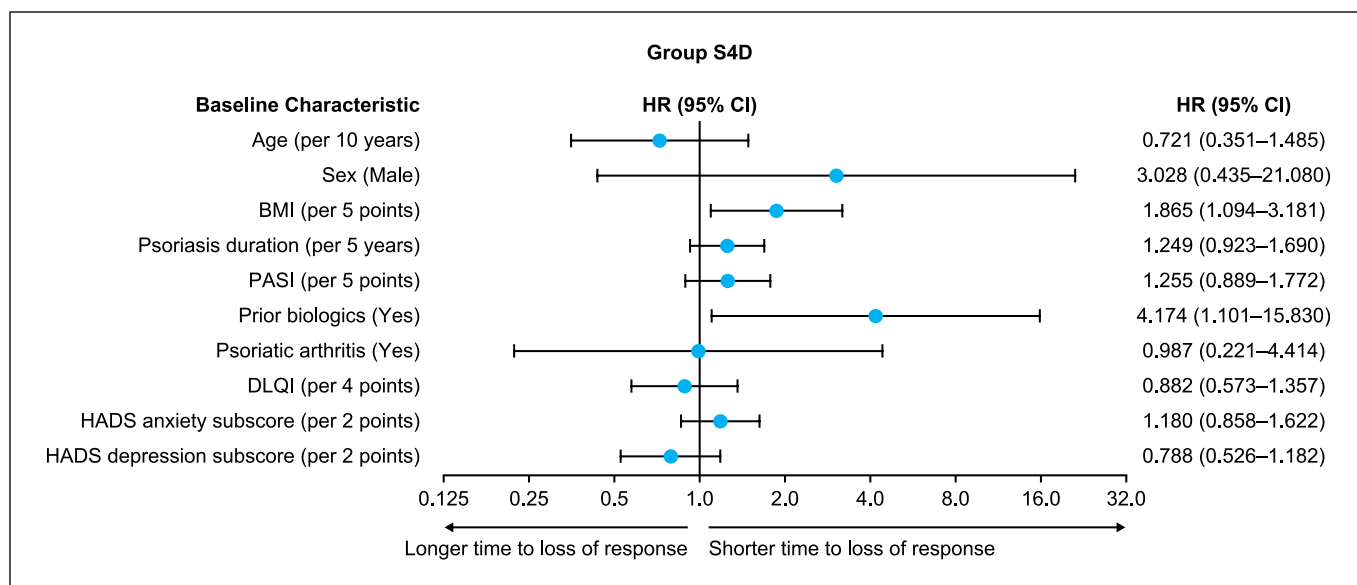


Fig. 6. Baseline characteristics corresponding with time to PASI ≥ 3 for patients in group S4D ($n = 31$). Log base 2 was used as the x-axis scale. BMI, body mass index; CI, confidence interval; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; PASI, Psoriasis Area and Severity Index; S4D, slow responders – four doses.

response rates were higher among super responder patients than non-super responders, and that super responders maintained disease control with an extended

q16w dosing interval [14]. Our post hoc analysis results are also consistent with other studies, which propose that patients with psoriasis and an exceptional response to

treatment may be suitable candidates for dose reduction [15] or dosing on an as-needed basis [16].

This post hoc analysis also examined baseline characteristics corresponding with time to loss of disease control in patients with differing initial speeds of treatment response. In previous analyses of patients with psoriasis, baseline characteristics associated with an exceptional response to guselkumab treatment or long-term maintenance of disease control included younger age, lower BMI ($<30 \text{ kg/m}^2$), shorter disease duration, lower PASI, biologic-naïve status, fewer comorbidities, and lower serum levels of IL-17F and macrophage inflammatory protein 1- β [7, 9, 12, 17]. This post hoc analysis demonstrated similarities with these findings; lower baseline BMI and biologic-naïve status corresponded with longer time to loss of disease control (PASI ≥ 3). Additionally, shorter disease duration corresponded with a longer time to loss of disease control in patients with a particularly fast response to guselkumab (PASI90 after two doses of guselkumab).

These findings reflect those observed in GUIDE, which showed that patients who were biologic-naïve at baseline and patients with short disease duration (≤ 2 years from symptom onset) were more likely to be super responders than patients who had received prior biologic therapies and patients with long disease duration (>2 years) [12]. However, comparison between these studies is confounded by the fact that disease duration was assessed in 5-year increments in this post hoc analysis, while GUIDE assessed patients with short (≤ 2 years) or long disease duration (>2 years) [12].

These results offer insights into baseline characteristics that might affect time to loss of disease control if treatment with guselkumab is interrupted and, therefore, which patients may achieve long-term, drug-free disease control or represent candidates for dosing interval flexibility. However, additional confirmatory studies are needed because of the post hoc nature of this analysis and the relatively small number of patients in some groups.

In summary, faster initial response to treatment corresponded with longer maintenance of disease control during the treatment withdrawal period. This finding may be helpful to inform approaches to personalized dosing with guselkumab, which might increase patient compliance to treatment regimens. Furthermore, among patients achieving a PASI90 response after two or four doses of guselkumab, lower baseline BMI, biologic-naïve status, and shorter disease duration may be indicative of a longer time to loss of disease control and longer drug-free time. Limiting the chronicity of disease [11], and potentially the comorbidities associated with chronic dis-

ease, may therefore increase success in long-term disease management. Importantly, the data presented here relate only to guselkumab, a p19-targeted IL-23 inhibitor; further analyses would be required to determine whether these findings are applicable to other treatments, particularly those with other modes of action.

Key Message

Psoriasis patients with faster initial response to guselkumab had longer maintenance of response during treatment withdrawal.

Acknowledgments

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Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. This study protocol was reviewed and approved by the ethics committees at each of the 115 participating sites. The full list of participating site and ethics committees can be found as online supplementary material. Written informed consent was provided by all patients.

Conflict of Interest Statement

The authors disclose that B.K. has received grants and/or honoraria from AbbVie, Almirall, Amgen, Eli Lilly, Janssen, LEO Pharma, Merck, MoonLake, MC2 therapeutics, Novartis, Pfizer, UCB, and Union; that A.C. has served as an advisory board member and consultant, has received fees and speaker's honoraria, or participated in clinical trials for AbbVie, Almirall, LEO Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme; that P.G. is an employee of Janssen-Cilag Ltd, High Wycombe, UK; that J.B. is an employee of Janssen Pharmaceutica NV, Beerse, Belgium; that R.P. is an employee of Janssen-Cilag, Issy-les-Moulineaux, France; that S.W. is an employee of Janssen-Cilag GmbH, Neuss, Germany; and that L.P. has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius Kabi, Gebro, Janssen, JS BIOCAD, LEO Pharma, Lilly, Merck Serono, Merck Sharp and Dohme, Mylan, Novartis, Pfizer, Regeneron, Roche, Samsung Bioepis, Sandoz, Sanofi, and UCB.

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Author Contributions

B.K., A.C., and L.P. assisted in the collation of data. B.K., A.C., P.G., R.P., S.W., and L.P. provided significant contributions to the concept and design, as well as the drafting of the manuscript. J.B. provided significant contributions to the analysis, and all authors assisted in interpretation of the data and review and editing of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available but are available from the authors upon reasonable request. The data sharing policy of Johnson & Johnson Innovative Medicine is available at <https://www.janssen.com/clinical-trials/transparency>. As noted on this website, requests for access to the study data can be submitted through the Yale Open Data Access Project website at <http://yoda.yale.edu>.

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