ORIGINAL REPORT

Guselkumab in Patients with Scalp Psoriasis: A *post hoc* Analysis of the VOYAGE 2 Phase III Randomized Clinical Trial

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Scalp psoriasis affects approximately 80% of patients with psoriasis and can negatively impact their quality of life. This *post hoc* analysis of the VOYAGE 2 Phase III randomized clinical trial evaluated scalp response to guselkumab treatment and its association with skin response and patient-reported outcomes. The study included patients with moderate-to-severe plaque psoriasis and baseline scalp psoriasis who were initially randomized to receive guselkumab. Patients were divided into 3 groups based on their achievement of a Psoriasis Area and Severity Index 90 response at week 28: responder continuation, non-responder continuation and responder withdrawal. In all 3 groups, mean Psoriasis Area and Severity Index head and scalp-specific Investigator's Global Assessment scores improved through week 28. In the responder withdrawal group, these scores worsened after treatment withdrawal at week 28, but remained stable through week 48 in both continuation groups. Trends in Dermatology Life Quality Index and Psoriasis Symptoms and Signs Diary itch scores mirrored those of mean scalp-specific Investigator's Global Assessment scores through week 48. Within-subject correlations were 0.83 between scalp-specific Investigator's Global Assessment and Psoriasis Area and Severity Index head scores and 0.78 between scalp-specific Investigator's Global Assessment and Psoriasis Symptoms and Signs Diary itch scores. Through week 252, Psoriasis Area and Severity Index head scores remained stable in the responder continuation group, improved in the non-responder continuation group and rapidly improved by week 84 in the responder withdrawal group after retreatment.

Key words: antibodies, monoclonal; dermatologic agents; psoriasis; quality of life; scalp dermatoses; severity of illness index.

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SIGNIFICANCE

Scalp psoriasis affects approximately 80% of patients with psoriasis and negatively impacts their quality of life. Data from the VOYAGE 2 clinical trial were used in this study to analyse the speed and level of scalp response to guselkumab treatment. Improvements were seen in skin and scalp psoriasis, as well as in measures of itch and quality of life over 48 weeks. Characteristics associated with the achievement of a good scalp response after 24 and 48 weeks of guselkumab treatment were also identified. Improvements in scalp psoriasis were maintained for 5 years, including for patients who stopped and restarted treatment.

Scalp involvement affects approximately 80% of patients with psoriasis, and often represents the first manifestation of the disease (1–3). Scalp psoriasis is associated with a severe disease course, an increased risk of psoriatic arthritis (PsA) and decreased quality of life (QoL) (1, 3–5). Despite recent progress and guidance from EuroGuiDerm on treating moderate-to-severe plaque psoriasis with biologic therapies, scalp psoriasis remains challenging to treat (6–8).

Multiple types of therapies have been used to treat scalp psoriasis with mixed success, including topical agents, phototherapy, conventional systemic therapy, oral small molecules and biologics (6, 9). Guselkumab is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23 and blocks it from signalling through its receptor (10, 11). Efficacy in a broad patient population with moderate-to-severe plaque psoriasis was confirmed in the VOYAGE 2 trial; improvements in scalp-specific Investigator's Global Assessment (ss-IGA) scores were greater in patients receiving guselkumab vs placebo (through week 16) and similar in the guselkumab and adalimumab treatment groups (through week 24) (10). Furthermore, skin response (assessed using the Psoriasis Area and Severity Index; PASI) was maintained after the withdrawal of guselkumab treatment (10). In a combined analysis of VOYAGE 1 and 2, treatment with guselkumab led to statistically greater improvements in near-complete and complete clearance of scalp psoriasis vs adalimumab at month 6 (12).

This *post hoc* analysis of VOYAGE 2 data evaluated the dynamics of scalp response and its association with skin response and patient-reported outcomes (PROs) over 48 weeks of guselkumab treatment, including the impact of a randomized withdrawal period followed by

retreatment. The long-term correlation between ss-IGA and PASI head and neck scores through week 48 and the factors associated with complete or near-complete clearance of scalp psoriasis following guselkumab treatment have also been analysed.

MATERIALS AND METHODS

Trial design

Full details of the VOYAGE 2 trial (NCT02207244) have been published previously; the study design is shown in Fig. S1 (10). In brief, VOYAGE 2 was a Phase III, multicenter, randomized, double-blind clinical trial of guselkumab that was conducted in 115 sites globally. The trial consisted of a placebo-controlled period (weeks 0–16), active-comparator-controlled period (weeks 0–28), randomized withdrawal and retreatment period (weeks 28–72) and open-label long-term extension (weeks 76–252). Eligible patients were aged ≥18 years, had moderate-to-severe plaque psoriasis (absolute PASI ≥12, Investigator's Global Assessment score ≥3 and body surface area (BSA) involvement ≥10%) for ≥6 months before the first administration of the study agent and were candidates for phototherapy or conventional systemic therapy. All patients provided written informed consent; the study was approved by the relevant review boards/ethics committees at each site and was compliant with applicable guidelines.

This analysis focuses on 3 groups of patients with scalp psoriasis at baseline who were initially randomized to receive guselkumab: the (*i*) responder continuation group (patients who achieved a PASI90 response at week 28 and were subsequently re-randomized to receive guselkumab); (*ii*) non-responder continuation group (patients who did not achieve a PASI90 response at week 28 and were subsequently re-randomized to receive guselkumab); and (*iii*) responder withdrawal group (patients who achieved a PASI90 response at week 28 and were subsequently re-randomized to receive placebo). Patients in the responder withdrawal group were retreated with guselkumab either after a ≥50% loss of their week 28 PASI response or when they reached week 72.

Assessments

Overall skin efficacy was assessed using total PASI scores; these were evaluated at weeks 0, 2 and 4, then every 4 weeks until week 76, from which point assessments were performed every 8 weeks until the final visit. Scalp efficacy was assessed at weeks 0, 16, 24 and 48 using the ss-IGA. Scalp outcomes were also assessed using the regional PASI head and neck scores, which were obtained as part of the assessment of total PASI scores through to the end of the study (13).

The Psoriasis Symptoms and Signs Diary (PSSD) is a patient-reported questionnaire that was used to evaluate the severity of psoriasis. As itch is known to impact the QoL of patients with psoriasis, itch was assessed using the 24-h recall version of the PSSD itch score at weeks 0, 16, 24 and 48 (14, 15).

PROs were assessed using the 7-day recall version of the Dermatology Life Quality Index (DLQI) at weeks 0, 16, 24 and 48 (16). Details of the assessment methods for PASI, ss-IGA and PSSD are included in Appendix S1

To gain insight into the durability of outcomes (including after treatment withdrawal), changes in scalp and overall skin response, as well as PROs, were measured through week 48, with PASI head scores being evaluated through week 252.

Statistical analysis

To determine whether long-term PASI data could be used to assess scalp outcomes through week 252, the evolution of ss-IGA scores, PSSD itch scores and PROs were assessed during guselkumab treatment and withdrawal. A within-subject correlation coefficient for ss-IGA vs PASI head scores through week 48 was calculated using a method reported by Bland & Altman (17). 95% confidence intervals (95% CI) were calculated using 500 bootstrap samples.

To establish which factors may be associated with achieving an ss-IGA score of 0 or 1 at weeks 24 and 48, multivariable logistic regression analyses of baseline patient and clinical characteristics (age, body mass index (BMI), sex, smoking status, presence of PsA, presence of nail psoriasis, PASI score, BSA involvement, ss-IGA score, duration of psoriasis and prior use of biologics, phototherapy or conventional systemic therapies) were performed.

The results of all efficacy assessments and PROs are summarized with descriptive statistics. Comparative statistics in this *post hoc* analysis are descriptive and based on numerical differences. All analyses used observed data.

RESULTS

Patient disposition and baseline characteristics

Of the 496 patients in VOYAGE 2 who were randomized to receive guselkumab from baseline, 67 patients did not have scalp psoriasis at baseline and were excluded from this analysis. An additional 22 patients discontinued guselkumab treatment before week 28; therefore, a total of 407 patients were included in this analysis. Baseline patient demographics and disease characteristics of the analysed subgroups are shown in **Table I**; these were consistent with those seen in the total study population of VOYAGE 2 (10).

Efficacy

Efficacy measures through week 24 (before the withdrawal period). Consistent with the overall results from VOYAGE 2 (10), total PASI scores improved between baseline and week 24 in all 3 subgroups (**Fig. 1**, Table SI). In the responder continuation group and responder withdrawal group, mean ss-IGA, total PASI and PASI head scores improved in a similar way from week 0 through week 24. In the non-responder continuation group, all scores also improved, but the improvements in mean total PASI and PASI head scores were smal-

Table I. Baseline patient demographics and disease characteristics

Baseline characteristic	Responder continuation ($n=159$)	Non-responder continuation ($n=84$)	Responder withdrawal* ($n=164$)
Age, years, mean (SD)	43.3 (12.7)	44.0 (11.2)	42.5 (11.5)
Male, %	65.4	76.2	73.8
Body mass index, kg/m^2, mean (SD)	29.5 (6.1)	31.1 (6.6)	28.7 (6.3)
Current or former smoker, %	51.6	44.0	51.8
Previous biologic use, %	17.6	28.6	20.1
Comorbid psoriatic arthritis, %	15.7	20.2	19.5
Psoriasis duration, years, mean (SD)	18.1 (11.9)	18.2 (11.1)	17.8 (11.8)
PASI, mean (SD)	21.9 (8.6)	21.5 (9.1)	22.6 (9.0)
ss-IGA, mean (SD)	2.9 (0.7)[a]	2.8 (0.7)[c]	2.9 (0.7)[d]
DLQI, mean (SD)	14.9 (6.3)[b]	15.3 (7.9)	14.8 (6.5)

Data only include patients with scalp psoriasis at baseline. Guselkumab response was defined as a patient achieving a PASI90 response at week 28.
In the responder withdrawal group, 14 patients were re-treated with guselkumab (2 at week 36, 3 at week 40 and 9 at week 44) following a ≥50% loss of their week 28 total PASI response; [a]$n=157$; [b]$n=158$; [c]$n=83$; [d]$n=162$.
DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; SD: standard deviation; ss-IGA: scalp-specific Investigator's Global Assessment.

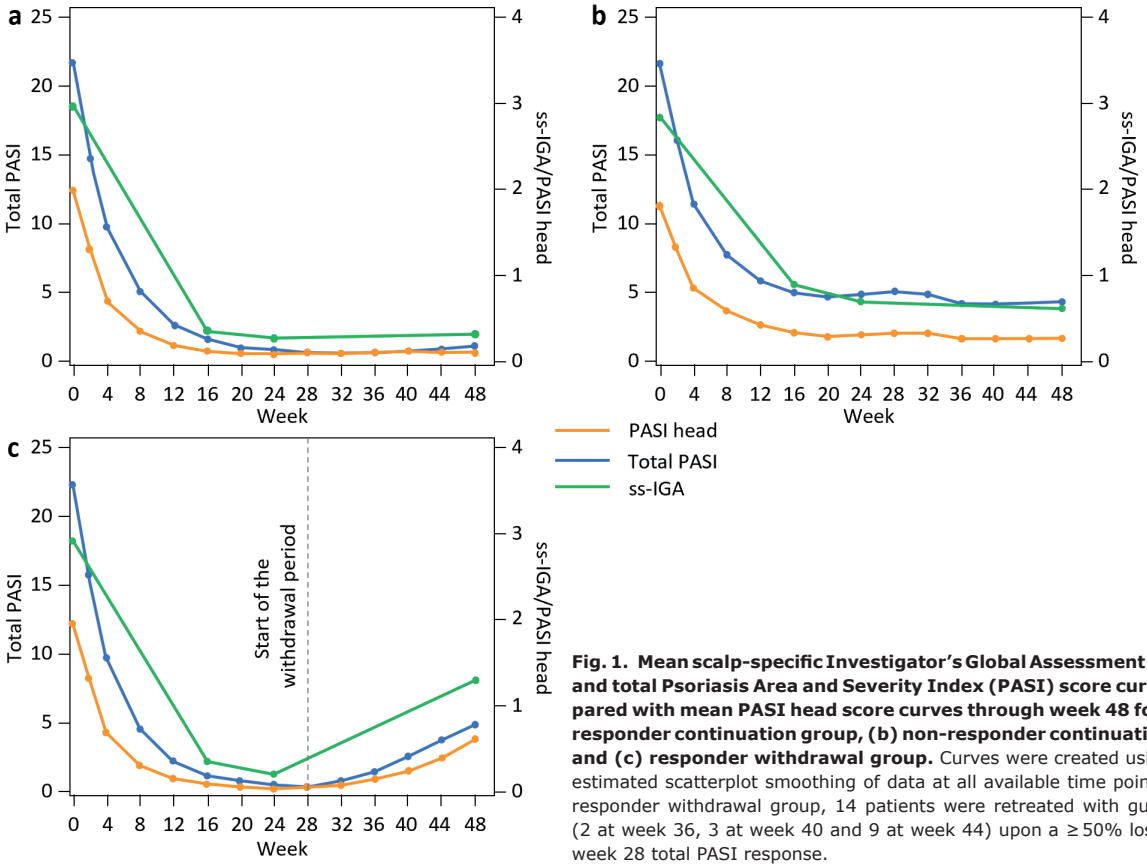

Fig. 1. Mean scalp-specific Investigator's Global Assessment (ss-IGA) and total Psoriasis Area and Severity Index (PASI) score curves compared with mean PASI head score curves through week 48 for the (a) responder continuation group, (b) non-responder continuation group and (c) responder withdrawal group. Curves were created using locally estimated scatterplot smoothing of data at all available time points. In the responder withdrawal group, 14 patients were retreated with guselkumab (2 at week 36, 3 at week 40 and 9 at week 44) upon a ≥ 50% loss of their week 28 total PASI response.

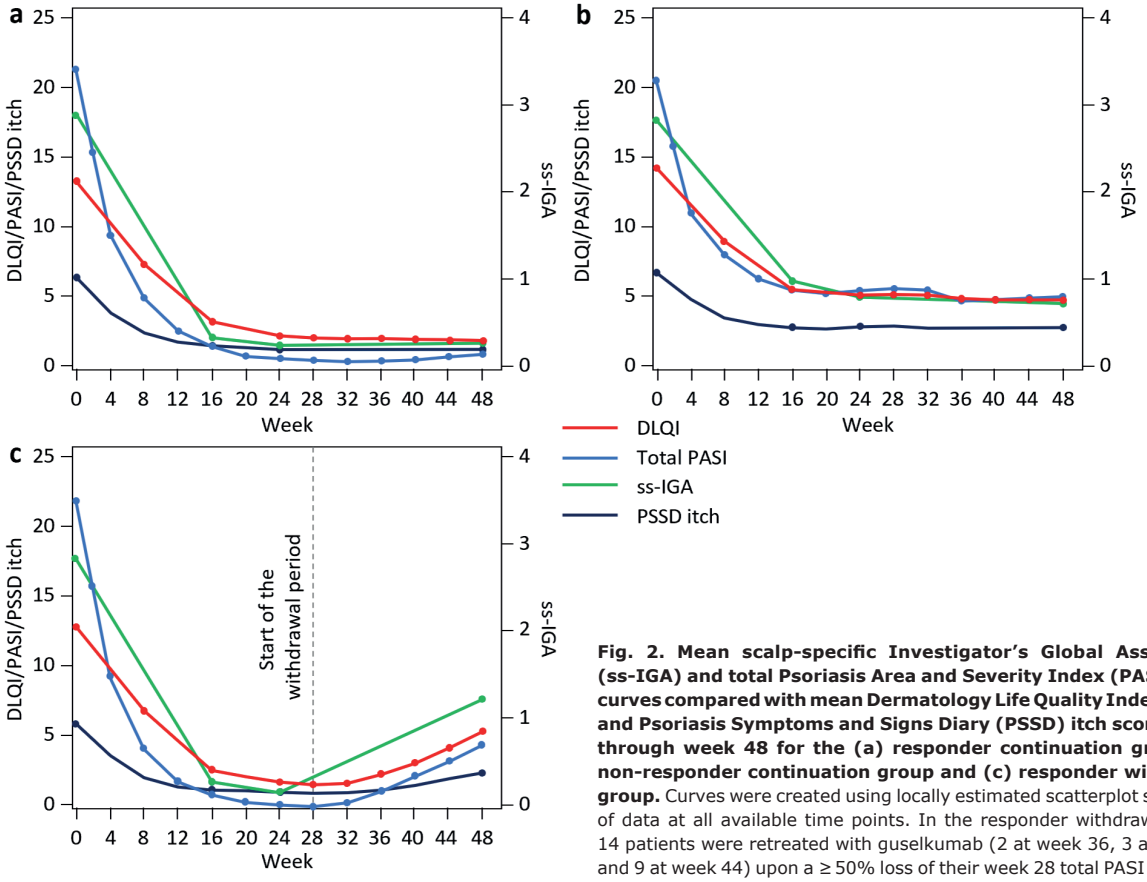

Fig. 2. Mean scalp-specific Investigator's Global Assessment (ss-IGA) and total Psoriasis Area and Severity Index (PASI) score curves compared with mean Dermatology Life Quality Index (DLQI) and Psoriasis Symptoms and Signs Diary (PSSD) itch score curves through week 48 for the (a) responder continuation group, (b) non-responder continuation group and (c) responder withdrawal group. Curves were created using locally estimated scatterplot smoothing of data at all available time points. In the responder withdrawal group, 14 patients were retreated with guselkumab (2 at week 36, 3 at week 40 and 9 at week 44) upon a ≥ 50% loss of their week 28 total PASI response.

ler than in the responder continuation and responder withdrawal groups.

Efficacy measures between weeks 24 and 48 (the withdrawal period). Mean ss-IGA, total PASI and PASI head scores remained stable from week 28 through week 48 in the responder continuation and non-responder continuation groups (Fig. 1, Table SI). Mean ss-IGA, total PASI and PASI head scores in the responder withdrawal group began to worsen from week 24 (0.2, 0.6 and 0.1, respectively), following treatment withdrawal, through week 48 (1.3, 4.8 and 0.6, respectively).

Patient-reported outcomes through week 48 and their association with efficacy outcomes. Across all 3 subgroups, trends in mean DLQI and PSSD itch scores mirrored those in mean ss-IGA scores through week 48 (**Fig. 2**, Table SI). In the responder continuation group, mean DLQI and PSSD itch scores improved from week 0 through week 24 before remaining stable through week 48. In the non-responder continuation group, mean DLQI and PSSD itch scores improved from week 0 through week 24 and continued to improve through week 48. In the responder withdrawal group, mean DLQI and PSSD itch scores improved from week 0 through week 24; however, after week 24, they (2.2 and 1.1, respectively) began to worsen during treatment withdrawal, increasing to 5.9 and 2.6 at week 48, respectively.

Long-term outcomes

*Association between ss-IGA and PASI head and PSSD itch scores***.** Based on data through week 48, the within-subject correlation between ss-IGA and PASI head scores was 0.83 (n=407; 95% CI: 0.81, 0.85) and 0.78 between ss-IGA and PSSD itch scores (n=398; 95% CI: 0.75, 0.81).

Efficacy through week 252. Changes in mean PASI head scores through week 252 are shown in **Fig. 3**. In the responder continuation group, mean PASI head scores remained stable from week 48 through week 252 (0.1 and 0.1 at weeks 48 and 252, respectively). In the non-responder continuation group, mean PASI head scores continued to improve slightly from week 48 and were comparable to those in the responder continuation group through week 252 (0.3 and 0.1 at weeks 48 and 252, respectively). In the responder withdrawal group, mean PASI head scores worsened after treatment withdrawal at week 28 through week 48 (from 0.1 to 0.6), then improved slightly from week 48 through week 72 (from 0.6 to 0.5). Following retreatment with guselkumab at week 72, scores improved rapidly through week 84 and remained stable through week 252 (0.1 and 0.1 at weeks 84 and 252, respectively).

Characteristics associated with scalp response

The logistic regression analysis of factors associated with achieving an ss-IGA score of 0 or 1 at week 24 (n=398) and week 48 (n=391) in patients receiving guselkumab from baseline is shown in **Fig. 4**. Only receipt of no or 1 prior biologic therapy was associated with a higher probability of achieving an ss-IGA score of 0 or 1 at week 24 vs receipt of 2 or more prior biologic therapies (odds ratio (OR) 4.720; 95% CI: 1.367, 16.300 and OR 5.593; 95% CI: 1.112, 28.140, respectively).

Factors associated with a lower probability of achieving an ss-IGA score of 0 or 1 at week 48 were a higher baseline ss-IGA score (OR 0.480; 95% CI: 0.301, 0.764), the absence of PsA at baseline (OR 0.269; 95% CI: 0.115, 0.630) and a BMI in the obese range compared with one in the normal or overweight ranges (OR 4.668; 95% CI: 1.996, 10.910 and OR 2.569; 95% CI: 1.325, 4.979, respectively). There was no association between achieving an ss-IGA score of 0 or 1 at week 48 and any other parameters assessed.

In a second logistic regression analysis that included PASI scores at week 16 as an independent variable, higher PASI scores at week 16 were associated with a lower probability of achieving an ss-IGA score of 0 or 1 at week 24 (OR 0.830; 95% CI: 0.752, 0.917; Fig. S2).

DISCUSSION

To the best of our knowledge, this is the first time the trajectory of scalp response to a biologic therapy over 5 years has been evaluated, while including a randomized withdrawal and retreatment period. Guselkumab improved scalp outcomes (PASI head scores) in patients with moderate-to-severe plaque psoriasis, and these improvements were maintained through week 252. Although long-term ss-IGA data were not assessed in VOYAGE 2, the correlation between ss-IGA and PASI head scores observed in week 48 data suggests that PASI head scores are indicative of scalp response, which were maintained with long-term guselkumab treatment.

Guselkumab improved PROs and psoriasis-specific measures of QoL in patients with scalp psoriasis. This included PSSD itch scores that, though not a scalp-specific measure of itch, strongly correlated with ss-IGA scores and showed a similar evolution to PASI and DLQI scores. These results are valuable, as scalp psoriasis has a negative impact on patient QoL (1, 6). Overall, these results support the previously published results from VOYAGE 1 and 2, which demonstrated improvements in PASI and PSSD itch scores through week 48 in patients with plaque psoriasis who were treated with guselkumab (10, 18, 19). Real-world evidence for the use of guselkumab for scalp psoriasis is limited; however, in the PERSIST trial, guselkumab improved health-related QoL and scalp-specific Physician's Global Assessment scores through week 28 (15). Real-world data also showed improvements in scalp outcomes in patients who were treated with IL-23 inhibitors (20).

Some guidelines on the treatment of psoriasis include specific considerations for scalp psoriasis (21, 22). More

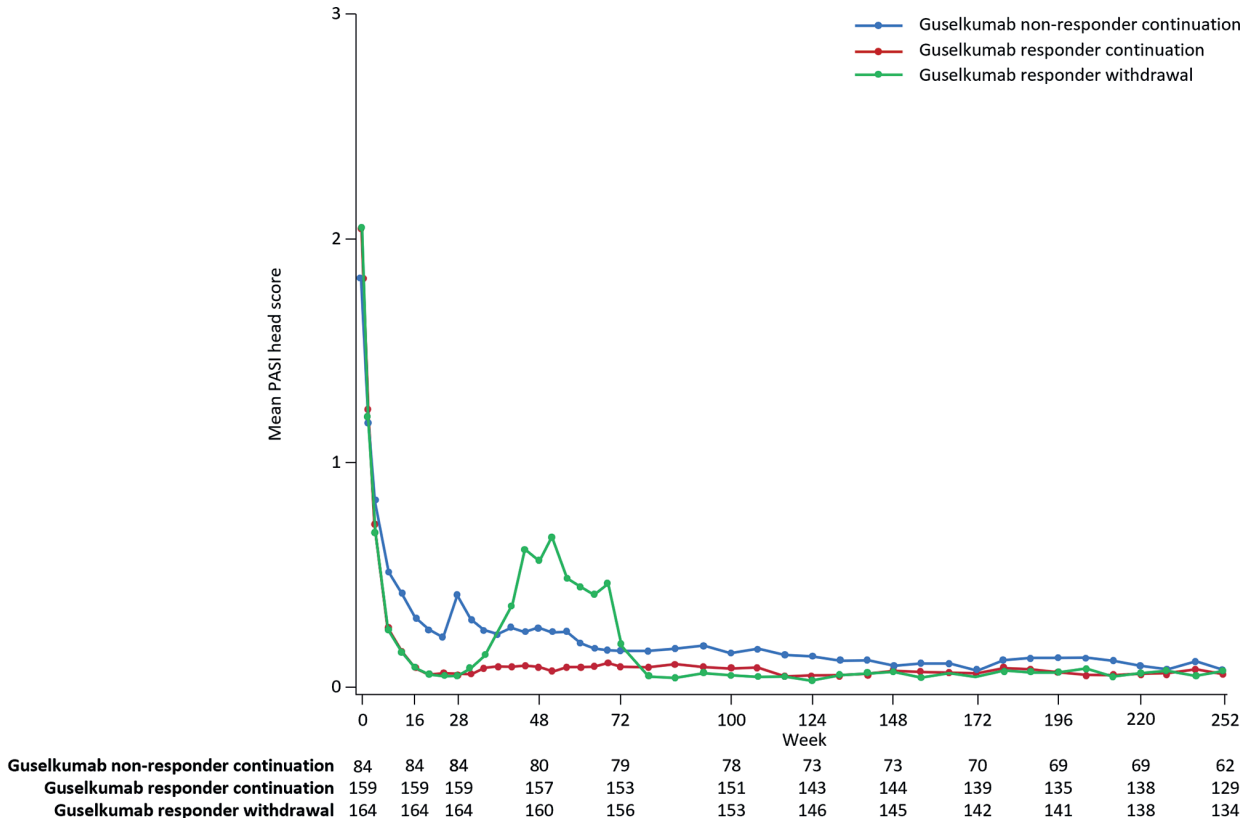

Fig. 3. Mean Psoriasis Area and Severity Index (PASI) head scores through week 252 by treatment subgroup. The maximum possible PASI head score was 7.2. Patients in the responder withdrawal group were retreated with guselkumab at week 76 through week 252.

recent guidelines now incorporate the consensus that significant scalp involvement conduces the reclassification of mild disease to moderate-to-severe disease (7, 23, 24). Although a range of biologics have been shown to be efficacious in scalp psoriasis (25–28), recommendations are limited by the strength of available evidence, particularly regarding long-term treatment (21, 22).

Furthermore, there is a lack of long-term data on the efficacy of IL-23 inhibitors in scalp psoriasis. The reSURFACE 1 trial ($n=463$) demonstrated that tildrakizumab improved PASI head scores at weeks 12 and 28 (29). A retrospective analysis of patients treated with tildrakizumab ($n=18$) showed improvement in the Psoriasis Scalp Severity Index (PSSI) by week 4, with improvements continuing through weeks 12 and 28 (30). In a randomized, head-to-head, dose-ranging, Phase II trial where patients received risankizumab or ustekinumab ($n=166$), 90% receiving risankizumab and 82% receiving ustekinumab achieved a mean PSSI reduction at week 12. This reduction was maintained through week 48 in the risankizumab group but not in the ustekinumab group (31). Ustekinumab has not been investigated specifically as a treatment for scalp psoriasis in any randomized trials; however, in a retrospective analysis of patients with scalp psoriasis receiving ustekinumab ($n=41$), patients achieved a mean PSSI reduction of 61.7% at week 4 and 94.9% at week 48 (26).

This 5-year analysis substantially extends our understanding of scalp response to IL-23 inhibitors. Long-term data are important because patients with psoriasis may require treatment breaks. Our results show, for the first time, that in the event of treatment withdrawal, patients with scalp psoriasis who were early responders to guselkumab treatment are likely to recapture and maintain their response for up to 5 years when treatment is resumed.

In this analysis, the absence of PsA at baseline was associated with a decreased probability of achieving complete or near-complete clearance of scalp psoriasis at week 48. While previous studies have shown a relationship between PsA and severe psoriasis, those studies did not use scalp-specific measures of disease severity (32, 33). Furthermore, as the result was marginal and the analysis retrospective, this association should not be over-interpreted. No association was found between BMI and the probability of achieving an ss-IGA score of 0 or 1 at week 24, although a BMI in the normal range was associated with a higher chance of achieving an ss-IGA score of 0 or 1 at week 48. Data from existing clinical trials and real-world evidence on the use of biologics have shown that obesity correlates with increased rates of treatment discontinuation due to a loss or lack of skin efficacy (34–36). For guselkumab specifically, results from a pooled analysis of VOYAGE 1 and 2 at week 24 (18) and the ECLIPSE study at week 48 (37) confirmed

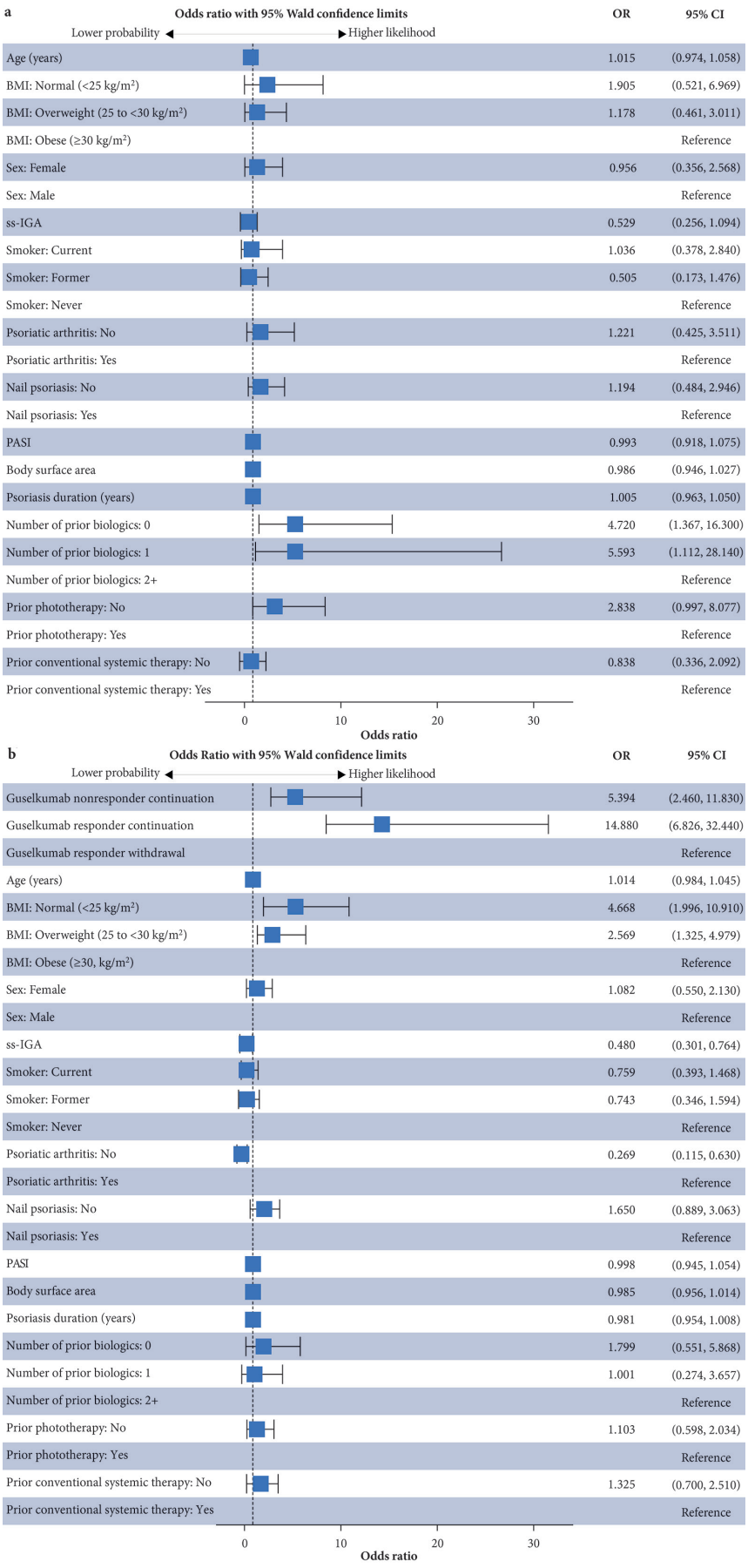

Fig. 4. Logistic regression analysis of factors associated with achieving a scalp-specific Investigator's Global Assessment (ss-IGA) score of 0 or 1 at (a) week 24 (*n* = 398) and (b) week 48 (*n* = 391). This analysis includes all patients with scalp psoriasis at baseline who were randomized to receive guselkumab from baseline. BMI: body mass index; 95% CI: 95% confidence interval; OR: odds ratio; PASI: Psoriasis Area and Severity Index.

that it was effective and more effective than comparators despite smaller proportions of patients with high BMIs achieving efficacy and PRO endpoints. Within the IL-23 inhibitor class, a similar worsening in the proportion of patients with BMIs in the obese and non-obese ranges achieving efficacy and PRO endpoints was seen in long-term (up to 3 years) pooled results from the reSURFACE 1 and 2 trials (38). These clinical observations may be partially explained by data from a prospective, observational, registry-based study, which found that over a 1-year follow-up period of patients receiving guselkumab, although those with a BMI in the obese or overweight range were less likely to meet endpoints such as a PASI90 response or an ss-IGA score of 0 or 1, absolute improvement was similar across weight groups. The difference between achieving an absolute improvement and meeting treatment targets can be attributed to known predictors of response to therapy, such as baseline disease severity, that differ by BMI status (39). It is important to note that scalp efficacy was not specifically investigated in the aforementioned studies; although the current results seem broadly consistent with research on overall psoriasis outcomes, further studies may be warranted.

These analyses are limited by their *post hoc* nature and the use of predominantly descriptive statistics. Furthermore, the use of observed data in this analysis may mean that the results appear more positive than could be expected in the clinic. The very small amount of missing data through week 48 means the influence of this should be minimal through this time point. However, the missing data could have skewed week 252 results due to an increasing proportion of patients who dropped out of the study over time (82 patients across 252 weeks). In addition, in the logistic regression analyses in which PASI scores at week 16 were an independent variable, they may have been influenced by the baseline variables included, thus complicating interpretation of the association between baseline variables and scalp outcomes. As such, these models should only be used to assess the association between achieving an ss-IGA score of 0 or 1 and PASI scores at week 16, after adjusting for the influence of other variables in the model. In the logistic regression analyses, scalp psoriasis was considered a single variable without regard to different facets of the disease (itching, erythema, etc.). If these facets were examined individually, different correlations with treatment response to those from this analysis may have been shown. In addition, the PASI head score is not a scalp-specific measure, as it also involves the face and neck; however, the score predominantly reflects scalp psoriasis as facial involvement is less common. This is also supported by the correlation shown between PASI head and ss-IGA scores.

These findings have the potential to support clinical decisions in psoriasis management, as they indicate that patients receiving guselkumab are likely to achieve and maintain high levels of skin clearance, both overall and specific to their scalp psoriasis, in the long term.

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Data availability statement. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA).

Ethics statement. VOYAGE 2 was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by ethics committees at each site. All participants provided written informed consent.

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Conflicts of interest. ES has received research grants from Pfizer and consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Janssen, LEO Pharma, Novartis, Sanofi and UCB. JTM has served as an advisor for, received speaker fees from or been involved in clinical trials sponsored by AbbVie, Almirall, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, LEO Pharma, Merck Sharp and Dohme, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi and UCB. MM has received speaker or consulting fees from AbbVie, Almirall, Amgen, Eli Lilly, Janssen, LEO Pharma, Novartis and UCB. PG is an employee of Janssen-Cilag Ltd, High Wycombe, UK. EC is an employee of Janssen-Cilag BV, Breda, The Netherlands. JB is an employee of Janssen Pharmaceutica NV, Beerse, Belgium. LS has received research grants from Janssen and Pfizer and consulting fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck Sharp and Dohme, Novartis, Pfizer, Sanofi, Takeda and UCB.

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