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ORIGINAL RESEARCH

Direct and Indirect Effect of Guselkumab on Anxiety, Depression, and Quality of Life in Patients with Moderate-to-Severe Plaque Psoriasis: A Mediation Analysis

April W. Armstrong · Peter Foley · Yan Liu · Megan Miller · Rachel E. Teneralli · Anthony Bewley · Kenneth B. Gordon · Kim A. Papp · Chenglong Han

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ABSTRACT

***Introduction*:** Treating plaque psoriasis (PsO) with guselkumab (GUS) promotes skin clearance and is associated with improvements in health-related quality of life (HRQoL), anxiety, and depression. It is unclear whether improvements in patient-reported outcomes are due to resolution of skin symptoms or the direct result of GUS treatment.

***Methods*:** Two phase 3, placebo- and active-comparator-controlled studies randomized patients with moderate-to-severe PsO to GUS, placebo (crossing over to GUS at week 16), or adalimumab. Post hoc mediation analyses examined direct and indirect effects of GUS, versus adalimumab, on Dermatology Life Quality Index (DLQI) or Hospital Anxiety and Depression Scale (HADS) after adjusting for indirect effects mediated by skin clearance, evaluated via Psoriasis Area and Severity Index (PASI), to determine the direct effect of GUS on dermatology HRQoL, depression, and anxiety.

***Results*:** Compared with adalimumab, the natural direct effect (NDE) of GUS on change in DLQI from baseline was −2.04 ($P<0.001$), using PASI improvement as a mediator, indicating 89.2% of the total treatment effect was due to direct effects of GUS; using PASI 90 as a mediator, NDE of GUS was −1.43 ($P<0.001$), with 62.2% of the total treatment effect attributed to direct effects of GUS. Compared with adalimumab, 25.5% of change in HADS anxiety score was mediated through PASI improvement (NDE −0.74; $P=0.002$), indicating 74.5% of the total effect was independent of PASI improvement.

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A. W. Armstrong
University of California Los Angeles, Los Angeles, CA, USA

P. Foley
The University of Melbourne, St. Vincent's Hospital Melbourne and Probity Medical Research, Skin Health Institute, Carlton, VIC, Australia

Y. Liu · R. E. Teneralli · C. Han (✉)
Janssen Global Services, LLC, Horsham/Malvern, 200 Great Valley Pkwy, Malvern, PA, USA
e-mail: chan3@its.jnj.com

M. Miller
Janssen Research & Development, LLC, Spring House, PA, USA

A. Bewley
Barts Health NHS Trust and QMUL, London, UK

K. B. Gordon
Medical College of Wisconsin, Milwaukee, WI, USA

K. A. Papp
Alliance Clinical Trials and Probity Medical Research Inc, Waterloo, ON, Canada

Similarly, 24% of treatment effect was mediated through PASI 90 (NDE −0.76; $P=0.002$). Comparable proportions of the total improvement in HADS depression scores were due to direct and indirect effects of GUS mediated through PASI improvement (direct, 50.2%; indirect, 49.8%) or PASI 90 (direct, 59.5%; indirect, 40.5%).
Conclusions: GUS-mediated improvements in anxiety, depression, and overall HRQoL are not solely mediated by resolution of PsO signs, suggesting GUS use has a potential direct effect on anxiety and depression.

Keywords: Anxiety; Depression; Guselkumab; Health-related quality of life; Mediation analysis; Psoriasis

Key Summary Points

Why carry out this study?

Treatment of plaque psoriasis with guselkumab promotes skin clearance and is associated with improvements in health-related quality of life, anxiety, and depression.

This ad hoc analysis sought to determine the direct effect of guselkumab on dermatology health-related quality of life, depression, and anxiety, after adjusting for indirect effects mediated by skin clearance.

What was learned from the study?

Compared with adalimumab, <40% of change in Dermatology Life Quality Index (DLQI) was mediated through skin clearance (as measured by Psoriasis Area and Severity Index [PASI]), indicating that ≥60% of the total effect of guselkumab was independent of PASI improvement; approximately 50% of the effect of guselkumab on change in Hospital Anxiety and Depression Scale anxiety/depression scores was independent of PASI improvement.

Guselkumab-mediated improvements in anxiety, depression, and overall health-related quality of life are not solely mediated by resolution of psoriasis signs, suggesting guselkumab has a potential direct effect on anxiety and depression.

INTRODUCTION

Plaque psoriasis (PsO) is a chronic, immune-mediated inflammatory condition that manifests in skin-related signs (e.g., scaling, redness, and cracking) and symptoms (e.g., itch and pain) of disease. Patients with PsO also demonstrate impaired health-related quality of life (HRQoL), which may include feelings of anxiety or depression that, in turn, may negatively impact social interactions or self-esteem [1–4]. The prevalence of anxiety and depression is typically higher in patients with PsO than among the general population or among patients with other dermatologic disorders [5–7].

The impact of PsO on HRQoL may be influenced by a number of factors. Predictably, severity of PsO can contribute to impact on HRQoL [8]; for example, depression is more common in patients with more severe disease [5, 9, 10]. Severity of disease had traditionally been defined by the percentage of affected body surface area (BSA), but the location of psoriatic plaques on the body can also have a substantial effect on HRQoL [11]. For instance, PsO in certain locations, such as the face, genitals, or hands and/or feet, has a disproportionately negative impact on social interactions or self-esteem [11]. Further, the relationship between PsO and anxiety/depression may be reciprocal: while the signs and symptoms of PsO may contribute to feelings of depression and anxiety, stress may also exacerbate PsO [5]. Given the multiple, potentially interacting, factors that can contribute to impaired HRQoL in patients with PsO, it is important to determine how and to what extent treatments directly or indirectly improve HRQoL. In other words, do treatments improve overall HRQoL through the indirect effects of improving skin or can treatments directly affect

mental health and other aspects of HRQoL through direct action?

Treatment of PsO focuses on mitigating skin-related manifestations of disease, with the expectation that alleviating those signs and symptoms will improve HRQoL [11]. This idea is supported by the observed correlation between improvement in clinical endpoints, such as Psoriasis Area and Severity Index (PASI), and patient-reported outcomes (PRO), such as the Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HADS) scores [4, 12–16]. However, studies have shown that even complete clearance of PsO does not necessarily eliminate decrements in skin-related HRQoL. For example, in a pooled analysis of two phase 3 studies, a notable proportion of patients who achieved clear skin (PASI 100) still reported an impact of disease on HRQoL, as measured by a PsO-specific PRO [4]. Taken together, these observations suggest that, while skin-related signs and symptoms of PsO have a marked effect on daily life, other factors may also play a role in overall HRQoL.

Proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-12, and IL-23 are present in psoriatic lesions and play a key role in the pathogenesis of PsO [17, 18]. There is also growing evidence for a link between inflammatory pathways and mood disorders [19–22]. Biologics targeting inflammatory cytokines have demonstrated efficacy in evoking a clear skin response and have also been associated with benefits to HRQoL, including decreased anxiety and depression [12, 13, 23, 24].

Guselkumab (GUS), a monoclonal antibody that targets the p19 subunit of IL-23, is approved for the treatment of moderate to severe plaque PsO [25]. Two phase 3 studies, VOYAGE 1 and VOYAGE 2, confirmed the efficacy and safety of GUS in patients with moderate to severe PsO [23, 26]. In both studies, significantly greater proportions of GUS-treated patients achieved clear or nearly clear skin (an Investigator's Global Assessment [IGA] score of 0/1 or PASI 90 response) versus placebo or adalimumab. In VOYAGE 2, which evaluated PRO using HADS, a greater proportion of patients treated with GUS had significantly improved HADS-anxiety and HADS-depression scores versus patients treated with placebo or adalimumab [13]. Whether improvements in anxiety and depression are due to resolution of skin-related signs and symptoms of disease or the direct result of GUS treatment deserves further examination.

This study sought to determine the direct effect of GUS treatment on dermatology HRQoL, depression, and anxiety after adjusting for the indirect effect mediated by skin clearance (evaluated via PASI) to better understand the direct treatment effects of GUS on HRQoL in patients with PsO.

METHODS

VOYAGE 1 and VOYAGE 2 Study Designs

VOYAGE 1 and VOYAGE 2 were phase 3, randomized, double-blinded, placebo- and active-comparator-controlled studies of GUS; study designs for both trials have been reported in detail, elsewhere [23, 26]. Both studies enrolled adults (≥ 18 years of age) with moderate-to-severe plaque PsO for at least 6 months (defined as IGA score ≥ 3, PASI score ≥ 12, and BSA involvement ≥ 10%) and who were candidates for phototherapy or systemic therapy. In VOYAGE 1 ($N = 837$) and VOYAGE 2 ($N = 992$), patients were randomized to GUS 100 mg administered via subcutaneous injection (SC) at weeks 0 and 4, then every 8 weeks (q8w); or placebo at weeks 0, 4, and 12, followed by GUS 100 mg SC at weeks 16 and 20, then q8w; or adalimumab 80 mg SC at week 0, 40 mg at week 1, then 40 mg every 2 weeks. Through week 24, the study designs for VOYAGE 1 and VOYAGE 2 were identical. In VOYAGE 1, patients randomized to adalimumab continued to receive adalimumab every 2 weeks through week 47, then crossed over, at week 52, to received open-label GUS 100 mg q8w through week 252. In VOYAGE 2, PASI 90 responders at week 28 entered a randomized withdrawal and GUS re-treatment period (weeks 28–72), and then received open-label GUS (weeks 76–252).

In both VOYAGE 1 and VOYAGE 2, the coprimary endpoints were the proportion of patients reaching a ≥ 90% improvement in PASI (PASI 90)

and the proportion of patients achieving an IGA score of 0/1; primary results have been reported elsewhere [23, 26]. Impact of PsO on HRQoL, evaluated using DLQI, was a secondary endpoint in both studies [23, 26]. DLQI is a dermatology-specific instrument designed to assess the impact of the disease on a patient's HRQoL; scores range from 0 to 30, with higher scores indicating more impact of disease [27]. In addition, in VOYAGE 2, the emotional impact of PsO was measured using HADS to assess symptoms of anxiety and depression. HADS consists of two subscales, one for anxiety and one for depression, with scores ranging from 0 to 21. Higher scores indicate more severe symptoms, with scores ≥ 8 indicating anxiety or depression [28].

Ethical Approval

This article is based on data from previously conducted studies, VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT 02207244), which were conducted in accordance with the Declaration of Helsinki and were consistent with good clinical practices and regulatory requirements. Patients provided written informed consent prior to enrollment in either trial.

Mediation Analysis Scenarios

Post hoc mediation analyses to examine the direct and indirect effects of GUS treatment on DLQI were performed after adjusting for the indirect effects mediated by PASI, a clinician-reported measure of skin-related signs of PsO, using pooled data from VOYAGE 1 and VOYAGE 2 (Fig. 1a). The mediation analysis involved fitting two models: (1) a mediation model for modeling the mediator variable, given the treatment and covariates, and (2) an outcomes model for modeling the outcome of interest (e.g., DLQI), given the treatment, mediator variable, and covariates. Variables used in these mediation analyses included covariates (age, gender, body mass index, PsO duration, comorbidity of known psoriatic arthritis with joint pain, DLQI score at baseline, and IGA score at baseline), outcome (change from baseline in absolute DLQI score at week 24), mediator variables (absolute PASI improvement versus baseline or PASI 90 response at week 24), and treatment (GUS versus adalimumab).

In addition, mediation analyses were performed to examine the direct and indirect effects of GUS treatment on HADS after adjusting for the indirect effects mediated by PASI using data from VOYAGE 2 (Fig. 1b). The mediation analysis involved fitting two models: (1) a mediation model for modeling the mediator variable, given the treatment and covariates, and (2) an outcomes model for modeling the outcome of interest (e.g., HADS score), given the treatment, mediator variable, and covariates. Variables used in these mediation analyses included covariates (age, gender, body mass index, PsO duration, HADS scores at baseline, PASI at baseline, and race), outcome (change from baseline in absolute HADS score at week 24), mediator variables (absolute PASI improvement versus baseline at week 24 or PASI 90 response at week 24), and treatment (GUS versus adalimumab).

In both scenarios, estimates from the mediation analysis included control direct effect (independent treatment effect on the outcome when the mediator is set to a fixed level), natural direct effect (NDE; effect on the outcome after adjusting for the indirect effect exerted by the mediator), natural indirect effect (NIE; treatment effect on the outcome that is influenced by the mediator variable), and total effect (total treatment effect on the outcome = NDE + NIE).

RESULTS

Direct and Indirect Effects on DLQI

Compared with adalimumab, the NDE of GUS on change in DLQI score from baseline was −2.04 (95% CI −2.55, −1.53; $P<0.001$) using PASI improvement as the mediator; 89.2% of the total effect was attributed to a direct effect of GUS treatment. When PASI 90 response was used as the mediator, the NDE of GUS on change in DLQI was −1.43 (95% CI −1.95, −0.91; $P<0.001$), with 62.2% of the total effect attributed to a direct effect of GUS treatment (Table 1).

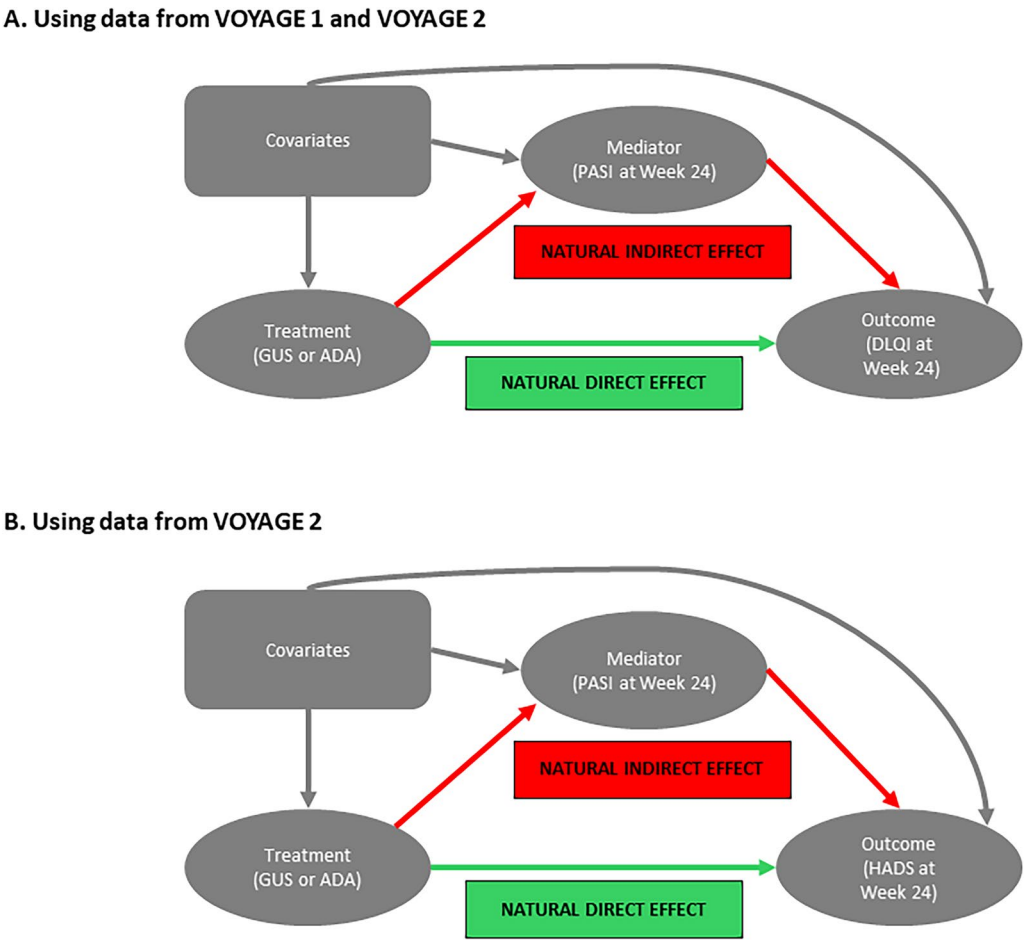

Fig. 1 Causal diagram of the mediation analyses. These models allow for exposure–mediator interactions. The natural direct effect is independent of the treatment effect on the outcome that is beyond its effect on the mediator; natural indirect effect is the treatment effect on the outcome that is mediated (explained) by its effect on the mediator. Models evaluated treatment effect on DLQI adjusting for PASI (**a**) and treatment effect on HADS (anxiety and depression) adjusting for PASI (**b**). *GUS* guselkumab, *ADA* adalimumab, *PASI* Psoriasis Area and Severity Index, *DLQI* Dermatology Life Quality Index, *HADS* Hospital Anxiety and Depression Scale

Direct and Indirect Effects on Anxiety

The NDE of GUS on change in HADS anxiety score mediated through PASI improvement was −0.74 (95% CI −1.22, −0.27; $P=0.002$), compared with adalimumab; 74.5% of the total effect at week 24 was independent of PASI improvement and 25.5% of the change in anxiety was mediated through PASI improvement (Table 2). Similarly, when PASI 90 was used as the mediator, the NDE of GUS (versus adalimumab) on change in HADS anxiety score was −0.76 (95% CI −1.24, −0.28; $P=0.002$), with 76.0% of the total effect on anxiety due to a direct effect of GUS (Table 2).

Direct and Indirect Effects on Depression

The direct effect of GUS on change in HADS depression score was more modest than the direct effect of GUS on HADS anxiety score (Table 3). Compared with adalimumab, the NDE of GUS on change in HADS depression

Table 1 Mediation analysis of change from baseline in DLQI score at week 24 in patients from VOYAGE 1 and VOYAGE 2

Effect	GUS versus ADA: estimated (95% CI)	*P* value[a]
With PASI improvement as a mediator		
Control direct effect[b]	− 2.08 (− 2.58, − 1.59)	< 0.001
Natural direct effect	− 2.04 (− 2.55, − 1.53)	< 0.001
Natural indirect effect	− 0.25 (− 0.38, − 0.12)	< 0.001
Total effect	− 2.29 (− 2.81, − 1.76)	< 0.001
Percent indirect effect[c]	10.8%	
Percent direct effect[d]	89.2%	
With PASI 90 response as a mediator		
Control direct effect (PASI 90: non-responder)	− 2.44 (− 3.34, − 1.55)	< 0.001
Control direct effect (PASI 90: responder)	− 0.66 (− 1.24, − 0.07)	0.029
Natural direct effect	− 1.43 (− 1.95, − 0.91)	< 0.001
Natural indirect effect	− 0.87 (− 1.14, − 0.61)	< 0.001
Total effect	− 2.30 (− 4.65, 0.04)	0.054
Percent indirect effect[c]	37.8%	
Percent direct effect[d]	62.2%	

The higher the DLQI score, the more health-related QoL was impaired

DLQI Dermatology Life Quality Index, *GUS* guselkumab, *ADA* adalimumab, *CI* confidence interval, *PASI* Psoriasis Area and Severity Index, *QoL* quality of life

[a]*P* value compares GUS versus ADA

[b]Level of mediator at which the controlled direct effect was estimated was 17.60 (median PASI improvement at week 24)

[c]Percent indirect effect = natural indirect effect/total effect

[d]Percent direct effect = natural direct effect/total effect

score, as mediated through PASI improvement, was − 0.29 (95% CI − 0.76, 0.19; *P* = 0.24); similar proportions of the total effect on depression at week 24 could be attributed to a direct treatment effect of GUS (50.2%) and an effect mediated through PASI improvement (49.8%). The NDE of GUS, mediated through PASI 90 response, was − 0.34 (95% CI − 0.82, 0.15; *P* = 0.17), with 59.5% of the total effect on HADS depression score resulting from a direct effect of GUS.

DISCUSSIONS

This study sought to determine the direct effect of GUS on HRQoL, independent of any benefits mediated through skin clearance using mediation analysis. Here, mediation analysis of pooled data from VOYAGE 1 and VOYAGE 2 showed a significant, direct effect of GUS treatment versus adalimumab, on dermatology-specific HRQoL (measure by DLQI) after adjusting for the indirect effect mediated through PASI improvement or PASI 90 response. This significant independent treatment effect of GUS indicates that GUS confers additional benefits

Table 2 Mediation analysis of change from baseline in HADS anxiety score at week 24 in VOYAGE 2 patients

Effect	GUS vs ADA: estimate (95% CI)	*P* value[a]
With PASI improvement as the mediator[b,c,d]		
Control direct effect[e]	− 0.75 (− 1.23, − 0.27)	0.002
Natural direct effect	− 0.74 (− 1.22, − 0.27)	0.002
Natural indirect effect	− 0.25 (− 0.40, − 0.11)	0.0005
Total effect	− 1.00 (− 1.47, − 0.52)	0.00004
Percent indirect effect[f]	25.5%	
Percent direct effect[g]	74.5%	
With PASI 90 response as the mediator[b,c]		
Control direct effect (PASI 90: non-responder)[h]	− 0.70 (− 1.49, 0.08)	0.078
Control direct effect (PASI 90: responder)[i]	− 0.80 (− 1.40, − 0.20)	0.009
Natural direct effect	− 0.76 (− 1.24, − 0.28)	0.002
Natural indirect effect	− 0.24 (− 0.39, − 0.09)	0.002
Total effect	− 1.00 (− 1.47, − 0.53)	0.000033
Percent indirect effect[f]	24.0%	
Percent direct effect[g]	76.0%	

The higher the HADS score, the worse the anxiety

HADS Hospital Anxiety and Depression Scale, *GUS* guselkumab, *ADA* adalimumab, *CI* confidence interval, *PASI* Psoriasis Area and Severity Index, *DLQI* Dermatology Life Quality Index, *QoL* quality of life

[a] *P* value compares GUS versus ADA

[b] The higher the PASI score, the worse the health condition

[c] The delta method was used to estimate standard error and confidence intervals

[d] PASI improvement at week 24 = PASI total score at baseline − PASI total score at week 24

[e] The level of mediator at which the controlled direct effect was estimated was 17.10 (median PASI improvement at week 24)

[f] Percent indirect effect = natural indirect effects/total effect

[g] Percent direct effect = natural direct effect/total effect

[h] PASI 90 non-responders had < 90% improvement in PASI from baseline

[i] PASI 90 responder had ≥ 90% improvement in PASI from baseline

to HRQoL, beyond those derived through improvement in skin appearance, as measured by PASI. Indeed, significant improvements in fatigue have been reported in GUS-treated patients, as measured by a short-form survey (SF-36), compared with patients who received adalimumab [29]. A direct effect of GUS on HRQoL is supported by results from a previous mediation analysis that demonstrated an effect of GUS on fatigue that was independent of improvement in clinical outcomes measures in patients with psoriatic arthritis [30].

Determining the direct effect of GUS on depression, beyond that associated with skin improvement, is important. Specifically, VOYAGE 2 collected PRO data using HADS, a measure of general depression and anxiety. In VOYAGE 2, the observed decrease in anxiety was not related to PASI 90 response alone, whereas the observed decrease in depression was more

Table 3 Mediation analysis of change from baseline in HADS depression score at week 24 in VOYAGE 2 patients

Effect	GUS vs ADA: Estimate (95% CI)	*P* value[a]
With PASI improvement as the mediator[b,c,d]		
Control Direct Effect[e]	− 0.29 (− 0.77, 0.20)	0.24
Natural Direct Effect	− 0.29 (− 0.76, 0.19)	0.24
Natural Indirect Effect	− 0.28 (− 0.43, − 0.13)	0.00022
Total Effect	− 0.57 (− 1.04, − 0.09)	0.019
Percent indirect effect[f]	49.8%	
Percent direct effect[g]	50.2%	
With PASI 90 response as the mediator[b,c]		
Control direct effect (PASI 90: non-responder)[h]	− 0.33 (− 1.12, 0.46)	0.41
Control direct effect (PASI 90: responder)[i]	− 0.35 (− 0.95, 0.26)	0.26
Natural direct effect	− 0.34 (− 0.82, 0.15)	0.17
Natural indirect effect	− 0.23 (− 0.38, − 0.08)	0.0024
Total effect	− 0.57 (− 1.04, − 0.09)	0.019
Percent indirect effect[f]	40.5%	
Percent direct effect[g]	59.5%	

HADS Hospital Anxiety and Depression Scale, *GUS* guselkumab, *ADA* adalimumab, *CI* confidence interval, *PASI* Psoriasis Area and Severity Index, *DLQI* Dermatology Life Quality Index, *QoL* quality of life

The higher the HADS score, the worse the depression

[a]*P* value compares GUS versus ADA

[b]The higher the PASI score, the worse the health condition

[c]Delta method was used to estimate the standard error and confidence interval

[d]PASI improvement at week 24 = PASI total score at baseline–PASI total score at week 24

[e]The level of mediator at which the controlled direct effect is estimated is 17.10 (median PASI improvement at week 24)

[f]Percent indirect effect = natural indirect effects/total effect

[g]Percent direct effect = natural direct effect/total effect

[h]PASI 90 non-responders had < 90% improvement in PASI from baseline

[i]PASI 90 responder had ≥ 90% improvement in PASI from baseline

strongly influenced by PASI improvement. After adjustment for the indirect effect mediated through PASI improvement or PASI 90 response, the NDE of GUS compared to adalimumab on anxiety was substantial (approximately 75%). The direct treatment effect of GUS on depression was not as robust as its effect on anxiety, with a moderate effect (approximately 50%) when adjusted for the indirect effect of change in PASI or PASI 90 response. Thus, GUS exerted an effect on anxiety and depression beyond its impact on skin clearance, although its direct effect on anxiety was more marked than its direct effect on depression.

There is growing evidence for a link between mood disorders, such as depression and anxiety, and inflammatory cytokines; these pathways present potential mechanisms through which GUS might exert a direct effect on mood-related QoL. High proportions

of inflammatory molecules are reported in patients with major depressive disorder [19, 20] and meta-analyses of clinically depressed patients have identified significantly elevated levels of TNFα, C-reactive protein (CRP), IL-1, and IL-6 compared to controls [21, 22]. Similarly, increased levels of TNFα, CRP, IL-2, and IL-6 were observed in meta-analyses of patients with panic disorders versus healthy controls [31]. Conversely, reduced depression and anxiety symptoms have been observed in patients treated with drugs/antibodies that inhibit inflammatory cytokines (e.g., IL-1, IL-6, and TNFα) [19, 32]. Further, inflammatory cytokines may affect neuropsychiatric function by activating the enzymes involved in the synthesis or metabolism of serotonin or dopamine or by modulating the receptors for these neurotransmitters, by activating pathways that promote excitotoxicity or oxidative stress, or by impairing neuroplasticity and antidepressant response via reduction of brain-derived neurotrophic factor (BDNF) [19, 20]. Thus, it is possible that, by targeting IL-23, GUS may also affect the pathways that contribute to mood disorders, such as anxiety and depression, and hence impact HRQoL in patients with PsO through a mechanism that is unrelated to skin clearance.

Mediation analysis can be used to estimate the direct and indirect treatment effects on an outcome of interest while adjusting for other mediators in the causal pathway of the treatment effect. This mediation analysis used the methodology from Valeri and VanderWeele, which allows for interaction between the treatment and mediator (i.e., exposure–mediator interaction) [33]. Mediation analysis clarifies the relationship between treatment and PRO and, by characterizing the extent to which a mediator contributes to overall treatment effect, may suggest the contribution of pathways not captured by other clinical assessments [33]. Mediation analyses are well established in psychology but their use in the clinical dermatology setting is more limited [34]. A mediation analysis in patients with atopic dermatitis concluded that the direct effect of treatment with a topical phosphodiesterase 4 inhibitor on QoL was largely mediated through its alleviation of pruritus [35]. In patients with PsO, a mediation analysis identified stigmatization and negative self-image as key drivers in the relationship between skin lesions and depression [36]. The mediation analysis described here suggests that GUS treatment impacts HRQoL in patients with PsO, in part, through a mechanism that is independent of skin clearance. Taken together, these studies suggest that further application of mediation analyses in dermatology will broaden the field's understanding of complex, multifactorial diseases.

Using combined data from two phase 3 studies provided a large data set from which to build the models used in these analyses. The similarities between the study designs in VOYAGE 1 and VOYAGE 2 facilitated pooling these data. However, the results from these analyses are limited by the patient populations enrolled in the VOYAGE studies and, therefore, extrapolation to other patient populations (e.g., those with mild PsO) may not be appropriate. This analysis was possible because the VOYAGE studies collected both clinical and PRO data. The findings from these analyses justify the importance of including PRO in future study designs and protocols. While several PRO tools exist, HADS is a widely available and well-validated measure of anxiety and depression in patients with PsO, which makes it a useful endpoint for future studies. Of note, these analyses focused on evaluation of HRQoL measures at a particular time point, week 28. To understand the cumulative direct and indirect effects of GUS on patient outcomes, the longitudinal impact of PsO on physiological, psychological, and social factors will need to be clarified. The VOYAGE studies did not include evaluation of alexithymia, which has been associated with PsO, particularly in those with anxiety and depression [37]. Further examination of alexithymia and neuroinflammation may be helpful in clarifying the interaction between depression, anxiety, and alexithymia in PsO. Additionally, while the focus of this analysis was to evaluate treatment effects of GUS on HADS after adjusting for clinician-reported outcomes based on PASI, other factors that could be related to improvement in HADS, such as

improvements in sexual or social life, should be investigated further.

CONCLUSIONS

These mediation analyses reveal that GUS-mediated improvements in anxiety, depression, and overall HRQoL cannot be explained solely by the resolution of PsO signs, as assessed by PASI, suggesting a direct, physiological effect of GUS on anxiety and depression. The mechanism of the direct effect of GUS on anxiety and depression, beyond its role in skin clearance, warrants additional research.

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Data Availability. 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 trial data can be submitted through Yale Open Data Access (YODA). Project site at http://yoda.yale.edu.

Declarations

Conflict of Interest. April W. Armstrong has served as a research investigator, scientific advisor, and/or speaker for AbbVie, Almirall, Arcutis, ASLAN, Beiersdoft, BI, BMS, EPI, Incyte, LEO, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, and Pfizer. Peter Foley has received grant support and/or travel grants and/or honoraria from and/or served as an investigator and/or advisory board member and/or consultant and/or speaker for AbbVie, Akaal, Amgen, Arcutis, Argenx, Aslan, AstraZeneca, Boehringer Ingelheim, Botanix, Bristol-Myers Squibb, Celgene, Celtaxsys, CSL, CSL Seqirus, Cutanea, Dermira, Eli Lilly, Evelo Biosciences, Galderma, Genentech, GenesisCare, GlaxoSmithKline, Hexima, Incyte, Janssen, Kymab, LEO Pharma, Mayne Pharma, MedImmune, Melaseq/Geneseq, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Reistone, Roche, Sanofi, Sun Pharma, Teva, UCB Pharma, and Valeant. Anthony Bewley has received ad hoc consultancy and/or travel bursaries from Abbvie, Almirall, Galderma, Leo Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi, and UCB. Kenneth B. Gordon has received research/grant support and/or honoraria for consultation from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Janssen, Novartis, and UCB Pharma. Kim A. Papp has received clinical research grants and/or honoraria as a consultant, and/or speaker, and/or investigator, and/or scientific officer, and/or advisory board member,

and/or Steering Committee member for AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, Avillion, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Can-Fite Biopharma, Celgene, Coherus, Dermavant, Dermira, Dow Pharma, Eli Lilly, Evelo, Galapagos, Galderma, Genentech, Gilead, GSK, Incyte, Janssen, Kyowa Hakko Kirin, Leo, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharma, Takeda and UCB. Rachel E. Teneralli, and Chenglong Han are employees of Janssen Global Services, LLC, Ya-Wen Yang is an employee of Immunology Global Medical Affairs, Janssen Pharmaceutical Companies of Johnson & Johnson, and Megan Miller is an employee of Janssen Research & Development, LLC; employees may own stock in Johnson & Johnson, of which Janssen is a subsidiary. Yan Liu was an employee of Janssen Global Services, LLC, at the time this study was conducted.

Ethical Approval. This article is based on data from previously conducted studies, VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT 02207244), which were conducted in accordance with the Declaration of Helsinki and were consistent with good clinical practices and regulatory requirements. Patients provided written informed consent prior to enrollment in either trial.

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