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Anxiety and depression in patients with moderate-to-severe psoriasis and comparison of change from baseline after treatment with guselkumab versus adalimumab: Results from the Phase 3 VOYAGE 2 study

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ABSTRACT

Background: Anxiety and depression are clinically significant comorbidities associated with psoriasis. Improvements in psoriasis are known to decrease anxiety and depression.

Guselkumab, an anti-interleukin-23 monoclonal antibody, has demonstrated efficacy/safety for the treatment of moderate-to-severe psoriasis.

Objective: Assess improvements in anxiety/depression with guselkumab vs. placebo and adalimumab using the Hospital Anxiety and Depression Scale (HADS).

Methods: In VOYAGE 2, a Phase 3, randomised, double-blind, placebo- and adalimumab-controlled study, patients received placebo (through wk16 then crossover to guselkumab), guselkumab, or adalimumab through wk24. HADS consists of two subscales measuring anxiety (HADS-A) and depression (HADS-D), with scores ranging from 0-21 and higher scores indicating more severe symptoms. Scores ≥ 8 indicate instrument-defined anxiety/depression. Severity of psoriasis was assessed using the Psoriasis Area and Severity Index (PASI).

Results: Among 989 patients randomised (with baseline HADS measurements), mean HADS-A and HADS-D scores were 6.8 ± 4.2 and 5.3 ± 4.2 , respectively; 38.6% of patients reported HADS-A ≥ 8 and 27.7% HADS-D ≥ 8 at baseline. At wk16, a significantly greater proportion of guselkumab patients with baseline HADS-A or -D ≥ 8 reported HADS-A < 8 (51.4% vs. 25.9%; $p < 0.001$) or HADS-D < 8 (59.2% vs 27.0%; $p < 0.001$) vs. placebo patients. At wk24, a greater proportion of guselkumab patients with baseline HADS-A or -D ≥ 8 reported HADS-A < 8 (58.4% vs. 42.9%; $p = 0.028$) or HADS-D < 8 (59.8% vs. 46.4%; $p = 0.079$) vs. adalimumab patients. PASI improvements correlated with improvement in anxiety ($r = 0.27$; $p < 0.0001$) and depression ($r = 0.25$; $p < 0.0001$) scores in patients with baseline HADS-A or -D ≥ 8 . Greater improvements in HADS were also observed at wk16 in guselkumab-treated patients vs. placebo using a more stringent cut-off of HADS ≥ 11 .

Conclusion: Guselkumab treatment was associated with greater improvements in symptoms of anxiety/depression scores in psoriasis patients compared with placebo and adalimumab.

Introduction

Psoriasis, a chronic immune-mediated disorder, not only affects skin-related symptoms and signs, but can also negatively impact a patient's quality of life.¹⁻⁵ The burden of psoriasis has even been categorised as a cumulative disability, which can negatively impact a patient throughout their lifetime.^{6,7} Patients with psoriasis have a significantly higher prevalence of psychiatric disorders, including anxiety and depression, compared with the general population and with other dermatology patient populations.^{2,3,8-13} In addition, psoriasis patients with psychiatric disorders have higher health care costs than psoriasis patients without these disorders.¹⁴

Improvement in psoriasis has been associated with improvements in patients' quality of life. Guselkumab, a human interleukin (IL)-23 inhibitor, improves moderate-to-severe psoriasis.¹⁵⁻¹⁷ The VOYAGE 1 and VOYAGE 2 Phase 3, double-blind placebo- and active-comparator (adalimumab)-controlled studies, demonstrated high levels of efficacy for guselkumab in the treatment of moderate-to-severe plaque psoriasis through 48 weeks, with a favorable safety profile.^{16,17}

The analyses presented in this report evaluated if guselkumab improved the symptoms of anxiety and depression in patients from the VOYAGE 2 study¹⁷ compared with placebo and adalimumab using the Hospital Anxiety and Depression Scale (HADS).¹⁸ Possible correlations in changes from baseline anxiety and depression scores with efficacy measures were also assessed.

Materials and Methods

Patients and study design

VOYAGE 2 was a multicenter, randomised, double-blind, placebo- and active comparator- (adalimumab) controlled Phase 3 study evaluating the efficacy and safety of guselkumab in patients with moderate-to-severe plaque psoriasis.¹⁷ The detailed study design through week 48 has been previously reported.¹⁷ A total of 992 patients were randomised at baseline 2:1:1 to guselkumab 100 mg (n=496) at weeks 0, 4, 12, and 20; placebo (n=248) at weeks 0, 4, 12 followed by guselkumab 100 mg at weeks 16, 20; or

adalimumab 80 mg (n=248) at week 0, 40 mg at week 1, and 40 mg every-2-weeks through week 23. In this analysis, we report efficacy data through week 24.

Analyses

Here, HADS¹⁸ was used to assess anxiety and depression in patients from the VOYAGE 2 study population. The HADS is a patient-reported anxiety (HADS-A) and depression (HADS-D) assessment consisting of seven questions for each subscale (anxiety or depression), with responses for each question ranging from scores of 0-3 (totaling 0-21). A lower score indicates less severity. Scores consistent with anxiety or depression are each defined by subscale scores of 8 or greater, and categorised as normal (score of 0-7), mild (score of 8-10), moderate (score of 11-14), and severe (score of 15-21)¹⁹. We used HADS-A or HADS-D scores of ≥ 8 ^{20,21} to define patients with mild symptoms of anxiety or depression. Additionally, a more stringent cut-off of HADS scores ≥ 11 ^{22,23} was used to identify patients with more severe clinical symptoms of anxiety and depression. Among patients with baseline HADS-A or HADS-D scores ≥ 8 and HADS-A or -D scores ≥ 11 , correlations of improvement in anxiety and depression scores with percent improvement in Psoriasis Area and Severity Index (PASI) scores were also evaluated, respectively.

Statistical analyses

Analyses of HADS data from the VOYAGE 2 study were prespecified.¹⁷ The analysis population only included patients with baseline HADS measurements. Treatment failure rules were applied. Patients who discontinued study agent due to lack of efficacy or an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy that could improve psoriasis, were considered treatment failures. If a patient met at least one treatment failure criterion, baseline values were used after the occurrence of the first treatment failure criterion. For the shift table analyses, only patients with both baseline and post-baseline values were included. Continuous response parameters were compared based on an analysis of variance model stratified by investigator site. The Cochran-Mantel-Haenszel test was used to compare the proportion of patients responding to treatment stratified by investigator site (pooled).

In addition, multiple linear regression models were used to evaluate the independent effect of guselkumab treatment on anxiety and depression at week 16 by adjusting for disease severity (including PASI score at baseline and week 16), investigator site (pooled), and baseline HADS-A or HADS-D score for patients with baseline HADS-A or HADS-D scores ≥ 8 and ≥ 11 , respectively. All statistical testing was performed at the 2-sided 0.05 significance level. Nominal p-values are presented.

Posthoc analyses of the Spearman correlations between PASI improvements and improvement in HADS scores, with associated p-values, were conducted.

Results

Baseline demographics and disease characteristics

Baseline demographics and disease characteristics were comparable across treatment groups (Table 1); greater details have been previously reported.¹⁷ At baseline, 38.6% of patients had anxiety scores (HADS-A) of ≥ 8 and 27.7% had depression scores (HADS-D) of ≥ 8 . Additionally, 19.1% of patients had baseline HADS-A ≥ 11 and 13.2% had HADS-D ≥ 11 (Table 1). Approximately 8% of all patients had a self-reported history of depression. At baseline 3.7% used antidepressant prescription medications and 2.4%

used benzodiazepines (Table 1).

Change from baseline in HADS at weeks 8, 16, and 24

Patients treated with guselkumab had significantly greater decreases (improvement) in HADS-A and HADS-D scores compared with placebo-treated patients at week 8, and week 16 (both $p < 0.001$; Table 2; Fig. 1). At week 24, a significantly greater proportion of guselkumab-treated patients had improvements from baseline in HADS-A scores compared with adalimumab ($p < 0.001$; Table 2; Fig. 1). Greater improvements in HADS-D scores at week 24 were also observed in the guselkumab patients versus adalimumab patients ($p = 0.06$).

A significantly greater proportion of guselkumab patients with anxiety at baseline (HADS-A ≥ 8 ; 51.4%) changed their status to a HADS-A score of < 8 at week 16 compared with placebo (25.9%; $p < 0.001$; Table 3). Similarly, 59.2% of guselkumab patients with baseline HADS-D ≥ 8 achieved a HADS-D score < 8 at week 16 compared with 27.0% of placebo patients ($p < 0.001$). At week 24, a greater proportion of guselkumab patients no longer reported scores consistent with anxiety/depression (HADS-A < 8 [58.4% vs. 42.9%; $p = 0.028$] or HADS-D < 8 [59.8% vs. 46.4%; $p = 0.079$]) compared with adalimumab patients, respectively (Table 3). Consistent results were observed for patients with baseline HADS scores ≥ 11 (Table 4).

Correlation of PASI improvement with HADS

A correlation between percent improvement in PASI scores and improvements (decreased from baseline) in HADS-A scores ($r = 0.34$; $p < 0.0001$) and HADS-D scores ($r = 0.22$; $p < 0.0001$) was observed at week 16 among all patients (placebo, guselkumab, and adalimumab) with baseline HADS scores ≥ 8 (Table 5). Similar correlations with PASI improvement were observed at week 24 for HADS-A ($r = 0.27$; $p < 0.0001$) and HADS-D ($r = 0.25$; $p < 0.0001$). In addition, generally, the greater the percent improvement in PASI score, the lower the proportion of patients with HADS ≥ 8 (scores consistent with anxiety/depression). This finding was consistently observed across both time points (week 16 and week 24) as well. Similar correlations with PASI were reported

for patients with baseline HADS scores ≥ 11 (Table 6).

Results from multiple linear regression models based on baseline HADS scores ≥ 11 are shown in Table 7. After adjusting for baseline anxiety (HADS-A) and depression (HADS-D) scores, baseline and week-16 PASI scores, and investigator site (pooled), there was no significant treatment difference in change from baseline in HADS-A at week 16 for guselkumab (-3.6 [0.57]; $p=0.759$) compared with placebo (-3.2 [0.96]). However, for depression, guselkumab-treated patients had a trend towards greater improvement from baseline in HADS-D score at week 16 (-5.3 [0.65] vs. -2.8 [0.96]; $p=0.051$) compared with placebo-treated patients. No significant treatment differences were observed at week 16 for HADS-A or HADS-D in patients with baseline HADS scores ≥ 8 using similar linear regression models (data not shown).

Psychiatric adverse events

During the 16-week placebo-controlled period, 1/494 patients (0.2%) randomised to treatment with guselkumab reported an AE of generalised anxiety disorder, while 2/248 patients (0.8%) randomised to adalimumab and none (0.0%) in the placebo group reported an AE of anxiety. During this period, there was one event of suicide attempt (0.4%) in the adalimumab group, and no events of depression, suicidal ideation, or suicidal behavior in the placebo or guselkumab groups. Through the 28-week active comparator- (adalimumab) controlled period, there were no additional anxiety-related events among patients randomised to guselkumab, while there was one additional event of anxiety (total of 3 [1.2%]) and one event of a panic attack (0.4%) in the adalimumab group. There was one event of anxiety among 233 patients (0.4%) who crossed-over from placebo to guselkumab. Also, during the 28-week active comparator-controlled period, there was one event of suicidal ideation (0.2%) in the guselkumab group, and two events of depression (0.8%) in the adalimumab group. There were no additional events of depression, suicidal ideation, or suicidal behavior among patients in the placebo-crossover group.

The 2 psychiatric AEs in the guselkumab group (generalised anxiety disorder and suicidal ideation) and the 1 psychiatric event in the placebo-crossover group (anxiety) were all non-serious, moderate in severity, and did not result in treatment discontinuation. None of these 3 patients had a medical history of depression at baseline, and none were being treated with antidepressants or anti-anxiety medications at baseline. The guselkumab patient with the AE of generalised anxiety disorder had HADS-A and HADS-D scores <8 at baseline and did not receive any concomitant treatment for this AE, which was ongoing at the end of the 28-week follow-up period. The patient with the event of suicidal ideation experienced the AE for 3 days approximately 5 months after the first dose of guselkumab, did not receive any concomitant medications for this event, and had baseline HADS-A and HADS-D scores consistent with anxiety and depression (≥ 8). The patient in the placebo-crossover group with the AE of anxiety had a HADS-A score consistent with anxiety (≥ 8) at baseline, and initially reported this AE on the day of the first dose of guselkumab. Of note, the patient's psoriasis had been stable to slightly worse than baseline during the first 16 weeks of the study.

Discussion

This study confirms that high proportions of patients with moderate-to-severe psoriasis have anxiety and depression. Psoriasis affects not only the patient's skin, but can negatively effect their self-esteem,²⁴ work productivity,²⁵ and overall quality of life.²⁶ In addition, patients with long-term psoriasis and anxiety or depression may have cumulative life impairment, and restoration of their mental health may take time.^{6,7} It has also been reported that psoriasis patients with anxiety or depression may have additional treatment costs due to their psychiatric disorder.¹⁴

In this report, it was demonstrated that guselkumab treatment was associated with significant improvements in symptoms of anxiety and depression measured by HADS, which is an important comorbidity for patients with psoriasis. In the VOYAGE 2 study,¹⁷ a considerable proportion of patients had anxiety (approximately 40%) or depression (approximately 30%) at baseline as measured by the HADS, demonstrating the significant burden of psychiatric disorders for patients with psoriasis. These rates are

generally comparable to those reported in other psoriasis studies,^{2,3,8-13} and higher than the rates reported globally in patients without psoriasis.²⁷ Although there is no formal definition of clinically meaningful improvement in HADS scores, our findings show significant improvements in both anxiety and depression scores with guselkumab treatment compared with placebo at weeks 8 and 16 ($p<0.001$ for all). Guselkumab treatment also resulted in significantly better improvements in HADS-A ($p<0.001$) and numerically better improvements in HADS-D ($p=0.06$) scores compared with adalimumab treatment at week 24.

Thresholds for HADS scores defining anxiety and depression have been established (≥ 8 and ≥ 11) and in this study, we analysed the proportion of patients shifting across these thresholds (anxiety to no anxiety or depression to no depression). Following treatment with guselkumab, a significantly greater proportion of patients who had symptoms of anxiety or depression at baseline did not have symptoms of anxiety or depression at week 16 compared with patients receiving placebo. Similarly, a greater proportion of guselkumab-treated patients switched status from having symptoms of anxiety or depression at baseline to not having symptoms of anxiety or depression at week 24 compared with adalimumab-treated patients. Independent of treatment, a greater improvement in PASI was associated with a greater mean change in HADS-A or HADS-D from baseline. Few AEs of anxiety or depression were reported in any treatment group.

The multiple linear regression analysis demonstrated that after adjusting for factors including baseline HADS scores, baseline and week-16 PASI scores, and pooled investigator sites, guselkumab-treated patients with baseline HADS-D scores ≥ 11 had a trend towards greater improvement in HADS-D scores from baseline to week 16 compared with placebo-treated patients ($p=0.051$); however, no treatment difference was observed with HADS-A. It should be noted that the VOYAGE 2 study was not designed or powered for this posthoc analysis, with limited sample sizes for these subpopulations included in the analyses, especially for HADS-D.

Depression and anxiety can develop over time, as psoriasis is a chronic disease, and the average disease duration of this study population was approximately 18 years. Due to cumulative impairment, recovery from psychiatric disorders may be delayed despite significant improvements in clinical signs and symptoms with efficacious treatment. However, modest, but statistically significant correlations between improvements in PASI scores and improvement in symptoms of anxiety and depression were observed. Therefore, the results of this study suggest that concurrent improvement in symptoms of anxiety and depression can occur with improvement in psoriasis.

Theories have emerged regarding links between depression and inflammation. Increased levels of several cytokines, that play central roles in psoriasis, including IL-1, IL-6, and tumour necrosis factor-alpha, have been associated with depression; therefore, decreasing their levels may reduce the effects of these cytokines on depression symptoms.²⁸ It has therefore been hypothesized that treating inflammation could improve symptoms of depression, in addition to treating the psoriasis. Improvements in psoriasis through treatment with biologics that target specific cytokines, including the data presented herein for IL-23 blockade with guselkumab, have been shown to correlate with decreased anxiety and depression.^{11,29-33} However, it is difficult to assess how much of the improvements in anxiety and depression are directly related to the improvements in skin disease and how much may be an independent effect. The results of the multiple linear regression analysis summarized above suggest that at least among patients with more severe depressive symptoms, there may be an independent effect of guselkumab on these symptoms beyond its effect on patients' skin disease.

Limitations of this study include the limitations of the instrument to measure anxiety or depression. While the HADS has been used to assess the prevalence of anxiety and depression in clinical trials of many diseases,³⁴⁻³⁷ including moderate-to-severe plaque psoriasis,^{29,38-41} some studies have proposed that HADS is best suited for screening rather than assessment of severity of anxiety and depression over time.⁴²⁻⁴⁴ In addition, the optimal HADS score cut-off to define clinically important symptoms of anxiety or depression is still undertermined. Finally, the active comparator-controlled period in

VOYAGE 2 extended only through week 24 for HADS evaluation, which may be a relatively short period of time to assess HADS.

In summary, guselkumab treatment was associated with improvement in symptoms of anxiety and depression measured by HADS in patients with moderate-to-severe plaque psoriasis compared with placebo and adalimumab treatment. Anxiety and depression are important comorbidities in patients with moderate-to-severe psoriasis and it is essential for dermatologists and other health care providers to be aware of the impact of psoriasis treatments on these psychiatric disorders. Given the concerns of increased risks of depression/suicidal ideation with some of the currently available therapies for plaque psoriasis,^{45,46} the significant improvements in anxiety and depression scores observed with guselkumab treatment are reassuring. Additional HADS data will be evaluated in the long-term extension of this study to better understand the impact of long-term guselkumab treatment on anxiety and depression.

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References

1. Lamb RC, Matcham F, Turner MA, *et al.* Screening for anxiety and depression in people with psoriasis: a cross-sectional study in a tertiary referral setting. *Br J Dermatol* 2017;**176**:1028-34.
2. Fleming P, Roubille C, Richer V, *et al.* Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. *J Eur Acad Dermatol Venereol* 2015;**29**:1063-70.
3. Dowlatshahi EA, Wakkee M, Herings RM, Hollestein LM, Nijsten T. Increased antidepressant drug exposure in psoriasis patients: a longitudinal population-based cohort study. *Acta Derm Venereol* 2013;**93**:544-50.
4. Schmitt JM, Ford DE. Role of depression in quality of life for patients with psoriasis. *Dermatology* 2007;**215**:17-27.
5. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998;**139**:846-50.
6. Kimball AB, Gieler U, Linder D, Sampogna F, Warren RB, Augustin M. Psoriasis: is the impairment to a patient's life cumulative? *J Eur Acad Dermatol Venereol* 2010;**24**:989-1004.
7. Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *Br J Dermatol* 2011;**164 Suppl 1**:1-14.
8. Dalgard FJ, Gieler U, Tomas-Aragones L, *et al.* The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015;**135**:984-91.
9. Devrimci-Ozguven H, Kundakci TN, Kumbasar H, Boyvat A. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. *J Eur Acad Dermatol Venereol* 2000;**14**:267-71.
10. Gooderham M, Gavino-Velasco J, Clifford C, MacPherson A, Krasnoshtein F, Papp K. A review of psoriasis, therapies, and suicide. *J Cutan Med Surg* 2016;**20**:293-303.

11. Kimball AB, Leonardi C, Stahle M, *et al.* Demography, baseline disease characteristics and treatment history of patients with psoriasis enrolled in a multicentre, prospective, disease-based registry (PSOLAR). *Br J Dermatol* 2014;**171**:137-47.
12. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010;**146**:891-5.
13. Wu JJ, Penfold RB, Primatesta P, *et al.* The risk of depression, suicidal ideation, and suicide attempt in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis. *J Eur Acad Dermatol Venereol* 2017;**31**:1168-1175.
14. Han C, Lofland JH, Zhao N, Schenkel B. Increased prevalence of psychiatric disorders and health care-associated costs among patients with moderate-to-severe psoriasis. *J Drugs Dermatol* 2011;**10**:843-50.
15. Gordon KB, Duffin KC, Bissonnette R, *et al.* A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015;**373**:136-44.
16. Blauvelt A, Papp KA, Griffiths CEM, *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017;**76**:405-17.
17. Reich K, Armstrong A, Foley P, *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol* 2017;**76**:418-31.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-70.
19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale with the Irritability Depression-Anxiety Scale and the Leeds Situational Anxiety Scale Manual. London: GL Assessment Ltd. 1994.
20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;**52**:69-77.

21. Damen NL, Pelle AJ, Szabó BM, Pedersen SS. Symptoms of anxiety and cardiac hospitalizations at 12 months in patients with heart failure. *J Gen Intern Med* 2012;**27**:345-50.
22. Watson TM, Ford E, Worthington E, Lincoln NB. Validation of mood measures for people with multiple sclerosis. *Int J MS Care* 2014 Summer;**16**:105-9.
23. Hopwood P, Howell A, Maguire P. Psychiatric morbidity in patients with advanced cancer of the breast: prevalence measured by two self-rating questionnaires. *Br J Cancer* 1991;**64**:349-52.
24. Wojtyna E, Łakuta P, Marcinkiewicz K, Bergler-Czop B, Brzezińska-Wcisło L. Gender, body image and social support: biopsychosocial determinants of depression among patients with psoriasis. *Acta Derm Venereol* 2017;**97**:91-7.
25. Wu Y, Mills D, Bala M. Impact of psoriasis on patients' work and productivity: a retrospective, matched case-control analysis. *Am J Clin Dermatol* 2009;**10**:407-10.
26. Solovan C, Marcu M, Chiticariu E. Life satisfaction and beliefs about self and the world in patients with psoriasis: a brief assessment. *Eur J Dermatol* 2014;**24**:242-7.
27. Investing in treatment for depression and anxiety leads to fourfold return. 2016. at <http://www.who.int/mediacentre/news/releases/2016/depression-anxiety-treatment/en/>.
28. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol Clin Exp* 2004;**19**:397-403.
29. Langley RG, Feldman SR, Han C, *et al.* Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol* 2010;**63**:457-65.
30. Daudén E, Griffiths CEM, Ortonne JP, *et al.* Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol* 2009;**23**:1374-82.
31. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol* 2006;**54**:685-704.

32. Tying S, Gottlieb A, Papp K, *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006;**367**:29-35.
33. Fleming P, Bai JW, Pratt M, Sibbald C, Lynde C, Gulliver WP.
The prevalence of anxiety in patients with psoriasis: a systematic review of observational studies and clinical trials. *J Eur Acad Dermatol Venereol* 2017;**31**:798-807.
34. ■ Turner J, Kelly B, Clarke D, *et al.* A tiered multidisciplinary approach to the psychosocial care of adult cancer patients integrated into routine care: the PROMPT study (a cluster-randomised controlled trial). *Support Care Cancer* 2017;**25**:17-26.
35. Deterding K, Gruner N, Buggisch P, *et al.* Symptoms of anxiety and depression are frequent in patients with acute hepatitis C and are not associated with disease severity. *Eur J Gastroenterol Hepatol* 2016;**28**:187-92.
36. Gracie DJ, Williams CJM, Sood R, *et al.* Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. *Am J Gastroenterol* 2016;**111**:541-51.
37. Traki L, Rostom S, Tahiri L, *et al.* Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. *Clin Rheumatol* 2014;**33**:1055-60.
38. Tee SI, Lim ZV, Theng CT, Chan KL, Giam YC. A prospective cross-sectional study of anxiety and depression in patients with psoriasis in Singapore. *J Eur Acad Dermatol Venereol* 2016;**30**:1159-64.
39. Mrowietz U, Chouela EN, Mallbris L, *et al.* Pruritus and quality of life in moderate-to-severe plaque psoriasis: post hoc explorative analysis from the PRISTINE study. *J Eur Acad Dermatol Venereol* 2015;**29**:1114-20.
40. Martínez-García E, Arias-Santiago S, Valenzuela-Salas I, Garrido-Colmenero C, García-Mellado V, Buendía-Eisman A. Quality of life in persons living with psoriasis patients. *J Am Acad Dermatol* 2014;**71**:302-7.
41. Gniadecki R, Robertson D, Molta CT, *et al.* Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol* 2012;**26**:1436-43.

42. Golden SH, Shah N, Naqibuddin M, *et al.* The prevalence and specificity of depression diagnosis in a clinic-based population of adults with type 2 diabetes mellitus. *Psychosomatics* 2017;**58**:28-37.
43. Poole NA, Morgan JF. Validity and reliability of the Hospital Anxiety and Depression Scale in a hypertrophic cardiomyopathy clinic: the HADS in a cardiomyopathy population. *Gen Hosp Psychiatry* 2006;**28**:55-8.
44. ■ Silverstone PH. Poor efficacy of the Hospital Anxiety and Depression Scale in the diagnosis of major depressive disorder in both medical and psychiatric patients. *J Psychosom Res* 1994;**38**:441-50.
45. OTEZLA [package insert]. Summit, NJ: Celgene Corporation; 2014-2017.
46. SILIQ [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2017.

Figure Legends

Fig. 1. Proportion of patients with (a) anxiety (HADS-A ≥ 8) or (b) depression (HADS-D ≥ 8) at weeks 0, 8, 16, and 24 by treatment group. HADS, Hospital Anxiety and Depression Scale.

Table 1. Baseline demographics and disease characteristics

	Placebo	Guselkumab	Adalimumab	Total
Patients randomised, n	248	496	248	992
Age, years				
Mean $\pm$ SD	43.3 $\pm$ 12.4	43.7 $\pm$ 12.2	43.2 $\pm$ 11.9	43.5 $\pm$ 12.2
Men	173 (69.8)	349 (70.4)	170 (68.5)	692 (69.8)
White	206 (83.1)	408 (82.3)	200 (80.6)	814 (82.1)
Weight (kg)				
Mean $\pm$ SD	88.6 $\pm$ 20.0	89.2 $\pm$ 20.8	87.6 $\pm$ 21.0	88.7 $\pm$ 20.7
BMI (kg/m ²)				
Mean $\pm$ SD	29.6 $\pm$ 6.6	29.6 $\pm$ 6.5	29.6 $\pm$ 6.6	29.6 $\pm$ 6.5
Duration of psoriasis, years				
Mean $\pm$ SD	17.9 $\pm$ 11.9	17.9 $\pm$ 12.0	17.6 $\pm$ 11.7	17.8 $\pm$ 11.9
BSA, %				
Mean $\pm$ SD	28.0 $\pm$ 16.5	28.5 $\pm$ 16.4	29.1 $\pm$ 16.7	28.5 $\pm$ 16.5
PASI				
Mean $\pm$ SD	21.5 $\pm$ 8.0	21.9 $\pm$ 8.8	21.7 $\pm$ 9.0	21.8 $\pm$ 8.6
IGA (0-4)				
Mild (2)	0	1 (0.2)	0	1 (0.1)
Moderate (3)	191 (77.0)	380 (76.6)	195 (78.6)	766 (77.2)
Severe (4)	57 (23.0)	115 (23.2)	53 (21.4)	225 (22.7)
HADS-A				
N	248	495	246	989

Mean $\pm$ SD	6.5 $\pm$ 4.1	6.9 $\pm$ 4.1	6.9 $\pm$ 4.5	6.8 $\pm$ 4.2
Score $\geq$ 8	86 (34.7)	192 (38.8)	104 (42.3)	382 (38.6)
Score $\geq$ 11	43 (17.3)	89 (18.0)	57 (23.2)	189 (19.1)
HADS-D				
N	248	495	246	989
Mean $\pm$ SD	5.1 $\pm$ 4.3	5.3 $\pm$ 4.2	5.3 $\pm$ 4.3	5.3 $\pm$ 4.2
Score $\geq$ 8	66 (26.6)	134 (27.1)	74 (30.1)	274 (27.7)
Score $\geq$ 11	36 (14.5)	61 (12.3)	34 (13.8)	131 (13.2)
Patients with a self-reported medical history of depression	18 (7.3)	38 (7.7)	19 (7.7)	75 (7.6)
Patients receiving antidepressant medications ^a	11 (4.4)	19 (3.8)	7 (2.8)	37 (3.7)
Patients receiving benzodiazepines ^a	5 (2.0)	16 (3.2)	3 (1.2)	24 (2.4)

Values are presented as n (%) unless otherwise indicated.

^aAntidepressant medications or benzodiazepines may not have been administered for the treatment of anxiety or depression, but for another medical condition.

BMI, Body mass index; BSA, Body surface area; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index, SD, standard deviation.

Table 2. Change from baseline in Hospital Anxiety and Depression Scale (HADS) scores at weeks 8, 16, and 24

	Placebo	Guselkumab	Adalimumab
Patients randomised and with HADS at baseline, n	248	495	246
HADS-A			
Week 8			
n	248	495	246
Mean $\pm$ SD	-0.2 $\pm$ 2.9	-1.6 $\pm$ 3.1	-1.0 $\pm$ 3.2
p-value vs. placebo		< 0.001	0.004
Week 16			
n	248	495	246
Mean $\pm$ SD	-0.2 $\pm$ 2.9	-1.7 $\pm$ 3.4	-1.1 $\pm$ 3.4
p-value vs. placebo		< 0.001	0.001
Week 24			
n	-	495	246
Mean $\pm$ SD	-	-2.0 $\pm$ 3.6	-1.0 $\pm$ 3.6
p-value vs. adalimumab	-	< 0.001	
HADS-D			
Week 8			
n	248	495	246
Mean $\pm$ SD	0.0 $\pm$ 2.9	-1.3 $\pm$ 3.3	-1.2 $\pm$ 3.0
p-value vs. placebo		< 0.001	< 0.001
Week 16			

n	248	495	246
Mean $\pm$ SD	-0.1 $\pm$ 2.9	-1.6 $\pm$ 3.6	-1.2 $\pm$ 3.4
p-value vs. placebo		< 0.001	< 0.001

Week 24

n	-	495	246
Mean $\pm$ SD	-	-1.7 $\pm$ 3.8	-1.1 $\pm$ 3.5
p-value vs. adalimumab	-	0.06	

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression; SD, standard deviation

Table 3. Hospital Anxiety and Depression Scale (HADS) scores at weeks 16 and 24 in patients with baseline HADS score < 8 or ≥ 8

	Placebo	Guselkumab	Adalimumab
Patients randomised and with HADS scores at baseline, n	248	496	248
Week 16			
HADS- A			
Patients with baseline HADS-A score ≥ 8, n	81	185	98
HADS-A score < 8 at week 16	21 (25.9)	95 (51.4)	44 (44.9)
p-value vs. placebo		< 0.001	0.075
Patients with baseline HADS-A score < 8, n	155	292	136
HADS-A score ≥ 8 at week 16	25 (16.1)	25 (8.6)	15 (11.0)
p-value vs. placebo		0.009	0.346
HADS-D			
Patients with baseline HADS-D score ≥ 8, n	63	130	70
HADS-D score < 8 at week 16	17 (27.0)	77 (59.2)	38 (54.3)
p-value vs. placebo		< 0.001	0.003
Patients with baseline HADS-D score < 8, n	173	347	164
HADS-D score ≥ 8 at week 16	17 (9.8)	24 (6.9)	19 (11.6)
p-value vs. placebo		0.156	0.537
Week 24			
HADS- A			
Patients with baseline HADS-A score ≥ 8, n	---	185	98
HADS-A score < 8 at week 24	---	108 (58.4)	42 (42.9)
p-value vs. adalimumab	---		0.028

	Placebo	Guselkumab	Adalimumab
Patients with baseline HADS-A score < 8, n		285	132
HADS-A score $\geq$ 8 at week 24	---	26 (9.1)	15 (11.4)
p-value vs. adalimumab	---		0.636
HADS-D			
Patients with baseline HADS-D score $\geq$ 8, n	---	127	69
HADS-D score < 8 at week 24	---	76 (59.8)	32 (46.4)
p-value vs. adalimumab	---		0.079
Patients with baseline HADS-D score < 8, n	---	343	161
HADS-D score $\geq$ 8 at week 24	---	26 (7.6)	13 (8.1)
p-value vs. adalimumab	---		0.834

Values are presented as n (%) unless otherwise indicated.

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression

Table 4. Hospital Anxiety and Depression Scale (HADS) scores at weeks 16 and 24 in patients with baseline HADS score < 11 or $\geq$ 11

	Placebo	Guselkumab	Adalimumab
Patients randomized and with HADS scores at baseline, n	248	496	248
Week 16			
HADS- A			
Patients with baseline HADS-A score $\geq$ 11, n	42	86	54
HADS-A score < 11 at week 16	14 (33.3)	54 (62.8)	31 (57.4)
p-value vs. placebo		0.002	0.092
Patients with baseline HADS-A score < 11, n	194	391	180
HADS-A score $\geq$ 11 at week 16	10 (5.2)	12 (3.1)	7 (3.9)
p-value vs. placebo		0.284	0.506
HADS-D			
Patients with baseline HADS-D score $\geq$ 11, n	35	59	32
HADS-D score < 11 at week 16	11 (31.4)	45 (76.3)	21 (65.6)
p-value vs. placebo		< 0.001	< 0.001
Patients with baseline HADS-D score < 11, n	201	418	202
HADS-D score $\geq$ 11 at week 16	10 (5.0)	14 (3.3)	9 (4.5)
p-value vs. placebo		0.238	0.706
Week 24			
HADS- A			
Patients with baseline HADS-A score $\geq$ 11, n	---	85	53
HADS-A score < 11 at week 24	---	58 (68.2)	31 (58.5)
p-value vs. adalimumab	---		0.166

	Placebo	Guselkumab	Adalimumab
Patients with baseline HADS-A score < 11, n		385	177
HADS-A score $\geq$ 11 at week 24	---	10 (2.6)	10 (5.6)
p-value vs. adalimumab	---		0.078
HADS-D			
Patients with baseline HADS-D score $\geq$ 11, n	---	56	31
HADS-D score < 11 at week 24	---	39 (69.6)	19 (61.3)
p-value vs. adalimumab	---		0.730
Patients with baseline HADS-D score < 11, n	---	414	199
HADS-D score $\geq$ 11 at week 24	---	12 (2.9)	7 (3.5)
p-value vs. adalimumab	---		0.690

Values are presented as n (%) unless otherwise indicated.

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression

Table 5. Correlation of PASI improvements in all patients with improvement in Hospital Anxiety and Depression Scale (HADS) scores at weeks 16 and 24 in patients with baseline HADS score ≥ 8

		PASI response				
		< 50	50 to < 75	75 to < 90	90 to <100	100
HADS-A of patients with baseline score ≥ 8:						
Week 16	N	80	43	53	98	90
	Mean ± SD change from baseline in HADS-A score	-0.6 ± 2.8	-1.2 ± 2.8	-3.3 ± 3.1	-4.1 ± 4.2	-3.6 ± 4.2
	% of patients with HADS-A score ≥ 8	82.5	65.1	49.1	45.9	43.3
	Correlation of improvement in PASI and improvement in HADS-A	r = 0.34 and p < 0.0001				
Week 24	N	21	31	68	114	129
	Mean ± SD change from baseline in HADS-A score	-0.8 ± 3.2	-2.2 ± 3.1	-2.8 ± 3.0	-3.5 ± 3.7	-4.3 ± 3.7
	% of patients with HADS-A score ≥ 8	85.7	51.6	64.7	47.4	36.4
	Correlation of improvement in PASI and improvement in HADS-A	r = 0.27 and p < 0.0001				
HADS-D of patients with baseline score ≥8:						
Week 16	N	69	28	40	71	55
	Mean ± SD) change from baseline in HADS-D score	-1.3 ± 3.4	-1.9 ± 4.1	-3.9 ± 3.2	-4.5 ± 5.2	-5.0 ± 4.2
	% of patients with HADS-D score ≥ 8	75.4	64.3	37.5	38.0	34.6

	Correlation of improvement in PASI and improvement in HADS-D	r = 0.22 and p < 0.0001				
Week 24	N	19	28	48	84	79
	Mean ± SD change from baseline in HADS-D score	-1.7 ± 3.8	-2.1 ± 3.1	-3.6 ± 4.2	-4.0 ± 4.8	-5.2 ± 4.7
	% of patients with HADS-D score ≥ 8	68.4	71.4	45.8	42.9	34.2
	Correlation of improvement in PASI and improvement in HADS-D	r = 0.25 and p < 0.001				

Correlation was calculated based on the improvement in PASI and improvement in HADS score from baseline (decrease is improvement)

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 6. Correlation of PASI improvements in all patients with improvement in Hospital Anxiety and Depression Scale (HADS) scores at weeks 16 and 24 in patients with baseline HADS scores ≥ 11

		PASI response				
		< 50	50 to < 75	75 to < 90	90 to <100	100
HADS-A of patients with baseline score ≥ 11:						
Week 16	N	45	20	24	48	45
	Mean ± SD change from baseline in HADS-A score	-1.1 ± 3.3	-1.3 ± 3.4	-3.7 ± 3.8	-5.6 ± 4.7	-4.6 ± 4.6
	% of patients with HADS-A score ≥ 11	68.9	65.0	45.8	25.0	35.6
	Correlation of improvement in PASI and improvement in HADS-A	r = 0.35 and p < 0.0001				
Week 24	N	13	12	38	55	60
	Mean ± SD change from baseline in HADS-A score	-1.5 ± 3.5	-2.9 ± 4.1	-3.3 ± 3.1	-4.7 ± 4.5	-5.2 ± 4.2
	% of patients with HADS-A score ≥ 11	61.5	33.3	31.6	38.2	30.0
	Correlation of improvement in PASI and improvement in HADS-A	r = 0.29 and p < 0.0001				
HADS-D of patients with baseline score ≥ 11:						
Week 16	N	32	6	13	20	17
	Mean ± SD change from baseline in HADS-D score	-1.4 ± 3.3	-3.2 ± 5.2	-4.8 ± 3.4	-7.9 ± 5.5	-6.9 ± 5.3
	% of patients with HADS-D score ≥ 11	78.1	66.7	30.8	25.0	17.7
	Correlation of improvement in PASI and improvement in	r = 0.52 and p < 0.0001				

	HADS-D					
Week 24	N	7	11	16	28	23
	Mean $\pm$ SD change from baseline in HADS-D score	-3.0 $\pm$ 5.6	-2.4 $\pm$ 3.0	-7.0 $\pm$ 3.9	-6.3 $\pm$ 5.4	-7.3 $\pm$ 5.6
	% of patients with HADS-D score $\geq$ 11	71.4	45.5	25.0	39.3	30.4
	Correlation of improvement in PASI and improvement in HADS-D	r = 0.28 and p < 0.0102				

Correlation was calculated based on the improvement in PASI and improvement in HADS score from baseline (decrease is improvement)

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 7. Summary of change in Hospital Anxiety and Depression Scale (HADS) scores from baseline to week 16 with baseline HADS scores ≥ 11

	Anxiety (HADS-A)			Depression (HADS-D)		
	Placebo (n=43)	Guselkumab (n=89)	Adalimumab (n=57)	Placebo (n=36)	Guselkumab (n=61)	Adalimumab (n=57)
Baseline LS mean (SE) ^a	13.1 (0.43)	13.2 (0.30)	13.1 (0.35)	12.9 (0.46)	13.0 (0.36)	13.1 (0.35)
Week 16 LS mean (SE) ^b	10.1 (0.96)	9.7 (0.57)	9.6 (0.60)	10.2 (0.96)	7.8 (0.65)	7.7 (0.65)
Change from baseline LSmean (SE) ^b	-3.2 (0.96)	-3.6 (0.57)	-3.7 (0.60)	-2.8 (0.96)	-5.3 (0.65)	-5.4 (0.65)
LSmean difference (SE) ^b		-0.4 (1.22)	-0.5 (1.13)		-2.5 (1.26)	-2.6 (1.26)
95% CI ^b		(-2.79, 2.04)	(-2.74, 1.73)		(-4.99, 0.01)	(-5.04, 0.01)
p-value ^b		0.759	0.657		0.051	0.049

CI, confidence interval; HADS-A, Hospital Anxiety and Depression Score-Anxiety; HADS-D, Hospital Anxiety and Depression Score-Depression; LSmean, Least Squares Mean; SE, standard error.

^aBased on Analysis of Covariance (ANCOVA) model adjusting for baseline Psoriasis Area and Severity Index (PASI) score and investigator site (pooled).

^bBased on ANCOVA model adjusting for baseline depression/anxiety score, baseline PASI score, PASI score at week 16, and site (pooled); represents comparison of Guselkumab vs Adalimumab.

● Placebo ▲ Guselkumab ■ Adalimumab

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