

Serious Gastrointestinal-Related Adverse Events Among Psoriasis Patients Treated With Guselkumab in VOYAGE 1 and VOYAGE 2

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ABSTRACT

Background: Anti-interleukin (IL)-17 biologic agents used to treat psoriasis are associated with onset/exacerbation of inflammatory bowel disease (IBD).

Objectives: To determine the incidence of IBD or serious gastrointestinal-related adverse events (GI SAEs) in patients with moderate-to-severe psoriasis treated with guselkumab, an IL-23p19 inhibitor that indirectly inhibits IL-17, through 4 years in the phase 3 VOYAGE 1 and VOYAGE 2 trials.

Methods: Patients were randomized to guselkumab 100 mg every-8-weeks or placebo → guselkumab (week 16), or adalimumab. In VOYAGE 1, all patients received open-label guselkumab starting at week 52. In VOYAGE 2, eligible patients were treated with guselkumab or placebo based on clinical response starting at week 28 and received open-label guselkumab starting at week 76. Cumulative incidence rates of IBD and other GI SAEs were calculated as events per 100 patient-years (PY) through week 204. IBD was defined as AEs of Crohn's disease or ulcerative colitis. Data were summarized for all guselkumab-treated patients for years 1-4.

Results: Of 1721 guselkumab-treated patients, 1612 were exposed for ≥1 year, 1545 for ≥2 years, 1454 for ≥3 years, and 661 for ≥4 years. For all patients through week 204, the cumulative rate of GI SAEs was 0.45/100PY. Event rates remained stable with longer duration of exposure, ranging from 0.36 to 0.57/100PY. No new or exacerbated cases of IBD were reported.

Conclusions: No cases of IBD were observed and rates of GI SAEs were low through 4 years of treatment with guselkumab in two large trials of patients with psoriasis.

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INTRODUCTION

Psoriasis is a systemic, immune-mediated, inflammatory disease manifested in the skin and associated with multiple comorbidities, including inflammatory bowel disease (IBD).¹ Psoriasis and IBD share a common pathogenic link based on mutual cellular mediators (eg, T17 helper cells), inflammatory pathways, and genetic factors.² Biologic agents targeting the interleukin (IL)-23/IL-17A signaling pathway have been used extensively to treat psoriasis. Some of these agents that target IL-17 have been associated with either new onset or exacerbation of IBD in the setting of skin disease.³⁻⁵

Furthermore, studies evaluating anti-IL-17 agents in IBD patients were terminated early due to a disproportionate number of cases of worsening of Crohn's disease (CD) or lack of efficacy.^{6,7}

Clinical studies of IL-23 and IL-12/23 inhibitors, which also target the IL-23/IL-17A axis for the treatment of psoriasis, have demonstrated efficacy and safety in patients with CD and/or ulcerative colitis (UC).⁸⁻¹⁰ In addition, IBD has not been identified as a safety concern in clinical studies of these biologic agents in psoriasis patients. A recent report focused specifically on

serious gastrointestinal adverse events (GI SAEs) showed that tildrakizumab (an IL-23 inhibitor) did not induce or worsen IBD through approximately one year (ie, 64 weeks).¹¹ This distinction from anti-IL-17 agents may affect treatment selection for patients with a history of IBD or pre-existing GI conditions.

Guselkumab, a fully human monoclonal antibody that also selectively binds and blocks the p19 subunit of IL-23, demonstrated significant efficacy in treating patients with moderate-to-severe plaque psoriasis in two pivotal phase 3 studies (VOYAGE 1 and VOYAGE 2) and in a phase 3 active comparator study with secukinumab (ECLIPSE).¹²⁻¹⁴ In VOYAGE 1 and VOYAGE 2, clinical response was maintained without additional safety concerns through 4 years of treatment.^{15,16} Here, we evaluated pooled safety data from both studies to determine the incidence of either IBD or GI SAEs in patients with moderate-to-severe psoriasis receiving continuous guselkumab treatment through 4 years.

MATERIALS AND METHODS

VOYAGE 1 and VOYAGE 2 are phase 3, multicenter, randomized, double-blinded, placebo- and active comparator-controlled studies evaluating the efficacy and safety of guselkumab for the treatment of adult patients with moderate-to-severe plaque-type psoriasis. The study designs of the two on-going trials have been presented in detail previously.^{12,13} Patients with a history or current signs of a severe, progressive, or uncontrolled medical condition were excluded; however, patients with GI symptoms or any pre-existing IBD conditions were not excluded. In VOYAGE 1, which evaluated continuous guselkumab treatment, patients were randomized at baseline to receive guselkumab 100 mg every-8-weeks, placebo, or adalimumab. Placebo- and adalimumab-randomized patients crossed over to receive guselkumab at weeks 16 and 52, respectively. During the subsequent open-label phase, all patients received guselkumab through the 4-year period studied here. The design of VOYAGE 2 was identical to that of VOYAGE 1 for the first 28 weeks, at which point patients entered the randomized withdrawal and retreatment period. Based on clinical response from week 28 to week 76, patients were treated with either guselkumab or placebo. The open-label phase began at week 76 when all eligible patients received guselkumab through week 204. In both studies, the trial will continue through 5 years.

Events of IBD were defined as the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of CD and UC within the system organ class (SOC) of GI disorders. All MedDRA PTs within the GI SOC that met the seriousness criteria of the International Council on Harmonization guidance document related to Good Clinical Practices were identified as GI SAEs. Nonserious AEs were reviewed to identify any events that could be considered to be IBD.

Through week 204, the number of GI SAEs adjusted by exposure (per 100 patient-year [PYs]) are presented by treatment group in the guselkumab (including placebo crossovers) and adalimumab→guselkumab groups. Additionally, these data are reported by exposure period over time: year 1 (within 52 weeks after the first administration of guselkumab), year 2 (between 52 and 104 weeks), year 3 (between 104 and 156 weeks), and year 4 (between 156 weeks through database lock at week 204). Note the durations of exposure were non-contemporaneous across treatment groups (ie, year 1–4 for the guselkumab group, year 1.3–4 [weeks 16–204] for the placebo crossover group, and year 2–4 in the adalimumab→guselkumab group in VOYAGE 1 and variable times to crossover from placebo or adalimumab to guselkumab in VOYAGE 2).

RESULTS

Demographic and disease characteristics of all guselkumab-treated patients (n=1721, including 1221 in the guselkumab group and 500 in the adalimumab→guselkumab group) indicate that patients, on average, were middle-aged (mean age, 43.5 years) and overweight (mean weight, 88.8 kg) and had moderate-to-severe psoriasis based on Investigator's Global Assessment scores ≥ 3 (Table 1). Medical history included conditions typically observed in patients with psoriasis (eg, cardiovascular disease and risk factors, depression, and diabetes). The incidence of pre-existing IBD is unknown, as these specific data were not collected at baseline. Current use of alcohol and tobacco were reported in approximately two-thirds and one-third of patients,

TABLE 1.

Patient Characteristics at Baseline by Treatment Group: All Guselkumab-treated Patients

	Guselkumab ^a (n=1221)	Adalimumab →Guselkumab ^b (n=500)	All Guselkumab (n=1721)
Age, years	43.8 ± 12.45	43.0 ± 12.22	43.5 ± 12.38
Female	359 (29.4)	140 (28.0)	499 (29.0)
White	1000 (81.9)	412 (82.4)	1412 (82.1)
Weight (kg)	88.9 ± 20.97	88.5 ± 21.50	88.8 ± 21.12
% BSA	28.0 ± 16.56	28.3 ± 16.00	28.1 ± 16.40
PASI (0-72)	21.7 ± 8.86	21.7 ± 8.50	21.7 ± 8.76
IGA score (0-4)			
Mild (2)	0	2 (0.4)	2 (0.1)
Moderate (3)	937 (76.7)	379 (75.8)	1316 (76.5)
Severe (4)	284 (23.3)	119 (23.8)	403 (23.4)
Duration of psoriasis, years	17.9 ± 12.05	17.4 ± 11.57	17.8 ± 11.91

Data are presented as n (%) or mean ± standard deviation.

BSA, body surface area; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index.

^aIncludes patients randomized to guselkumab at baseline and those randomized to placebo who crossed over to receive guselkumab at week 16.

^bIncludes patients randomized to adalimumab at baseline who crossed over to receive guselkumab at week 52 in VOYAGE 1 and at or after week 28 in VOYAGE 2.

TABLE 2.**Extent of Exposure to Guselkumab by Treatment Group Through Week 204; All Guselkumab-treated Patients**

	Guselkumab ^a (n=1221)	Adalimumab →Guselkumab ^b (n=500)	All Guselkumab (n=1721)
Duration of exposure to guselkumab			
At least 6 months ^c	1174 (96.2)	488 (97.6)	1662 (96.6)
At least 1 year ^d	1131 (92.6)	481 (96.2)	1612 (93.7)
At least 2 years ^e	1082 (88.6)	463 (92.6)	1545 (89.8)
At least 3 years ^f	1034 (84.7)	420 (84.0)	1454 (84.5)
At least 4 years ^g	661 (54.1)	0	661 (38.4)
Guselkumab injections, average number	21.5	18.7	20.7
Total guselkumab dose (mg)			
Mean ± SD	2152.1 ± 665.02	1873.6 ± 413.58	2071.2 ± 615.88

Data are presented as n (%), unless otherwise indicated. SD, standard deviation. ^aIncludes patients randomized to guselkumab at baseline and those randomized to placebo who crossed over to receive guselkumab at week 16. ^bIncludes patients randomized to adalimumab at baseline who crossed over to receive guselkumab at week 52 in VOYAGE 1 and at or after week 28 in VOYAGE 2. ^cThe duration between the first and last guselkumab administration was at least 16 weeks. ^dThe duration between the first and last guselkumab administration was at least 40 weeks. ^eThe duration between the first and last guselkumab administration was at least 88 weeks. ^fThe duration between the first and last guselkumab administration was at least 136 weeks. ^gThe duration between the first and last guselkumab administration was at least 184 weeks.

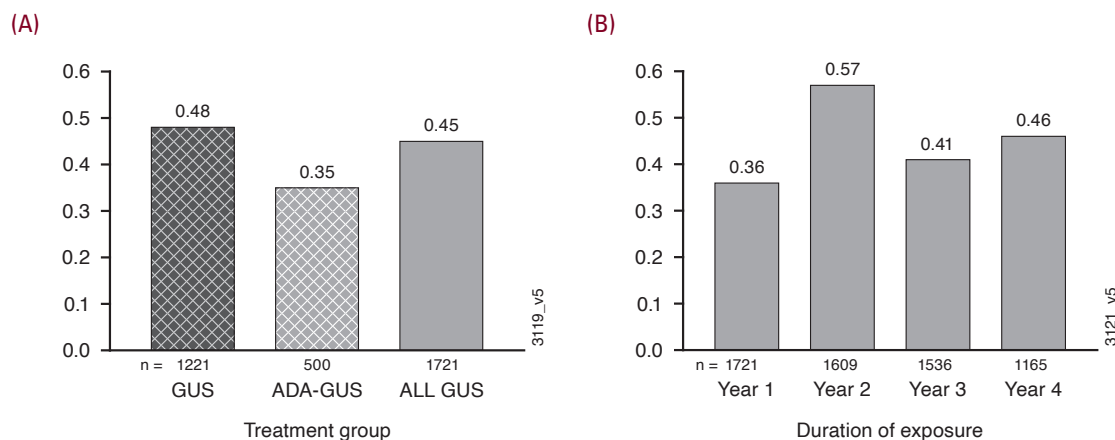
Overall, 1612 patients were exposed to guselkumab for at least 1 year (93.7%), 1545 for at least 2 years (89.8%), 1454 for at least 3 years (84.5%), and 661 for at least 4 years (38.4%) (Table 2). Patients received an average of 20.7 guselkumab injections for a mean total dose of 2071 mg. Note that the follow-up period

for the adalimumab→guselkumab group was shorter compared with the guselkumab group (average duration, 148.0 vs 177.1 weeks; median duration, 2.9 vs 3.9 years; total PYs, 1418 vs 4145).

A total of 1721 patients were treated with guselkumab through 4 years (5564 PY of follow-up) (Table 3). Cumulative rates of GI SAEs through week 204 were 0.45/100PY in all guselkumab-treated patients (n=25 events in 22 patients), with 0.48/100PY in the guselkumab group (n=18) and 0.35/100PY in the adalimumab→guselkumab group (n=4) (Figure 1A). Rates remained stable with longer duration of exposure in all guselkumab-treated patients (range, 0.36–0.57/100PY) (Figure 1B).

No cases of IBD were reported as either an AE or SAE. The most commonly reported GI SAEs were hemorrhoids and inguinal hernia (0.07/100PY [n=4 patients each]) and umbilical hernia (0.05/100PY [n=3]); gastritis, pancreatitis, and acute pancreatitis each occurred at a rate of 0.04/100PY (n=2 each). Abdominal hernia, colitis, duodenal ulcer, enterocutaneous fistula, hemorrhoidal hemorrhage, intestinal strangulation, irritable bowel syndrome, and upper GI hemorrhage were each reported at a rate of 0.02/100PY (n=1 each). The SAE of exacerbated irritable bowel syndrome was reported in a 43-year-old female with a history of irritable bowel syndrome (VOYAGE 2); the diagnosis was not associated with IBD (CD or UC). Of note, an additional SAE of infectious colitis associated with a resolving SAE of infectious appendicitis was reported in a 48-year-old male in VOYAGE 1 (due to the nature of the event, this SAE was reported in the Infections and Infestations SOC). Both patients recovered and continued in their respective study.

FIGURE 1. Number of guselkumab-treated patients/100 patient-years (PY) with gastrointestinal-related serious adverse events through 4 years of follow-up in VOYAGE 1 and VOYAGE 2: (A) by treatment group, (B) by exposure period.^a GUS, guselkumab group (including placebo-to-guselkumab crossover); ADA-GUS, adalimumab-to-guselkumab crossover group; ALL GUS, all guselkumab-treated patients.



^a Total patient-years of follow-up: 1662 (Year 1), 1570 (Year 2), 1464 (Year 3), and 867 (Year 4). Median patient-years of follow-up: 1.0 (Year 1), 1.0 (Year 2), 1.0 (Year 3), and 0.9 (Year 4).

TABLE 3.**Number of Serious Adverse Events per 100 Patient-years in the Gastrointestinal Disorders System Organ Class by Treatment Group Through Week 204; All Guselkumab-treated Patients**

	Guselkumab ^a (n=1221)	Adalimumab →Guselkumab ^b (n=500)	All Guselkumab (n=1721)
Total patient-years of follow-up	4145	1418	5564
Median patient-years of follow-up	3.9	2.9	3.6
Inflammatory bowel disease			
Crohn's disease	0	0	0
Ulcerative colitis	0	0	0
Gastrointestinal Disorders	0.48	0.35	0.45
Hemorrhoids	0.07	0.07	0.07
Inguinal hernia	0.07	0.07	0.07
Umbilical hernia	0.02	0.14	0.05
Gastritis	0.05	0.00	0.04
Pancreatitis	0.05	0.00	0.04
Pancreatitis acute	0.02	0.07	0.04
Abdominal hernia	0.02	0.00	0.02
Colitis	0.02	0.00	0.02
Duodenal ulcer	0.02	0.00	0.02
Enterocutaneous fistula	0.02	0.00	0.02
Hemorrhoidal hemorrhage	0.02	0.00	0.02
Intestinal strangulation	0.02	0.00	0.02
Irritable bowel syndrome	0.02	0.00	0.02
Upper gastrointestinal hemorrhage	0.02	0.00	0.02

Data are presented as number of serious adverse events per 100 patient-years, unless otherwise indicated.

^aIncludes patients randomized to guselkumab at baseline and those randomized to placebo who crossed over to receive guselkumab at week 16.^bIncludes patients randomized to adalimumab at baseline who crossed over to receive guselkumab at week 52 in VOYAGE 1 and at or after week 28 in VOYAGE 2.

DISCUSSION

Approximately 1.3% of the population has ever been diagnosed with IBD in the United States, and rates of 1.0% to 1.6% have been reported among patients with psoriasis worldwide.^{17,18} An extensive review of multiple epidemiological studies found a global prevalence of 0.7% for CD and 0.5% for UC among psoriasis patients.¹⁹ Of note, the prevalence of psoriasis in patients with CD and UC is 11.2% and 5.7%, respectively.²⁰ An association between anti-IL-17 agents and IBD onset/exacerbation has underscored the need to evaluate this potential safety concern in patients treated with IL-23 inhibitors, which indirectly block IL-17, for psoriasis.³⁻⁵ Based on this safety summary from the long-term VOYAGE 1 and VOYAGE 2 studies, no new cases or exacerbations of IBD were reported and GI SAE rates were low through 4 years of treatment with guselkumab in psoriasis patients. In the phase 3 ECLIPSE study that compared the efficacy and safety between an anti-IL-17A inhibitor (secukinumab) and guselkumab through one year, three psoriasis patients in the secukinumab group and none in the guselkumab group

reported an event of CD through year 1.¹⁴ The current analysis provides the first long-term study of GI safety for an anti-IL-23 biologic in psoriasis, although a similar analysis of another IL-23 blocker (tildrakizumab) reported a similar conclusion following a shorter one-year treatment period.¹¹

Both psoriasis and IBD are immune-mediated inflammatory diseases, and the IL-23/IL-17A axis is central to both pathogenesis; IL-23 acts on Th17 cells upstream of IL-17A, which serves as the key mediator of inflammation.^{1,21} In the gut, IL-17A provides a protective/anti-inflammatory effect on the epithelial barrier of the intestinal mucosa, which may be related to the CD onset/exacerbation observed with biologics that interfere with IL-17A function.^{6,7,22} The pooled safety data from clinical trials of IL-17A inhibitors indicate that IBD occurs rarely;²³ however, secukinumab and ixekizumab should be used with caution in patients with psoriasis and a concurrent diagnosis of IBD, and brodalumab is contraindicated in patients with CD.^{3,4,24}

Conversely, the safety results reported for another anti-IL-23 agent (risankizumab) in patients with CD and an IL-12/23 blocker (ustekinumab) with CD or UC further support the hypothesis that it is the downstream inhibition of IL-17A, and not IL-23, that is possibly associated with induction or exacerbation of IBD.⁸⁻¹⁰ Specifically, IL-17 blockers appear to eliminate the positive effects on the epithelial integrity of the gut while IL-23 inhibition may allow residual protection of the intestinal mucosa.²⁵ As such, guselkumab is currently being studied for the treatment of IBD.

Limitations of these analyses should be noted. Specific data regarding diagnosis or history suggestive of IBD were not collected at baseline. Additionally, although comparisons between treatment groups were adjusted for duration of follow-up, treatment periods in the guselkumab vs adalimumab crossover groups were non-contemporaneous. Nevertheless, this summary of GI SAEs of a large dataset from two long-term phase 3 studies through 4 years indicate that IBD is not a concern when patients with moderate-to-severe psoriasis are treated with guselkumab.

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