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ORIGINAL RESEARCH ARTICLE

# Long-Term Safety of Guselkumab in Patients with Psoriatic Disease: An Integrated Analysis of Eleven Phase II/III Clinical Studies in Psoriasis and Psoriatic Arthritis

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## Abstract

**Introduction** The benefit/risk profiles of biologics can be affected by comorbidities, certain demographic characteristics, and concomitant medications; therefore, it is important to evaluate the long-term safety profiles of biologics across broad patient populations. Guselkumab was well tolerated and efficacious across individual pivotal clinical studies in adults with moderate-to-severe psoriasis and/or active psoriatic arthritis (PsA).

**Objectives** The objective of the current analysis was to evaluate guselkumab safety in a large population of patients with psoriatic disease by pooling adverse event (AE) data from 11 phase II/III studies (seven in psoriasis; four in PsA).

**Methods** Guselkumab was generally administered as 100 mg subcutaneous injections at Week 0, Week 4, then every 8 weeks (Q8W) in psoriasis studies and at Week 0, Week 4, then every 4 weeks (Q4W) or Q8W in PsA studies. Safety data were summarized for the placebo-controlled period (Weeks 0–16 in psoriasis; Weeks 0–24 in PsA) and through the end of the reporting period (up to 5 years in psoriasis; up to 2 years in PsA). Using the integrated data, incidence rates of key AEs were determined post hoc, adjusted for duration of follow-up, and reported per 100 patient-years (PYs). AE rates were also determined in subgroups of patients defined by sex, age, body mass index (BMI), and prior biologic use.

**Results** During the placebo-controlled period, 1061 patients received placebo (395 PYs) and 2257 received guselkumab (856 PYs). Through the end of the reporting period, 4399 guselkumab-treated patients contributed 10,787 PYs of follow-up. During the placebo-controlled period, in the guselkumab and placebo groups, respectively, rates of AEs were 281 versus 272/100 PYs, and infections were 76.0 versus 72.2/100 PYs. Rates of serious AEs (5.6 vs. 7.8/100 PYs), AEs leading to discontinuation (4.9 vs. 6.6/100 PYs), serious infections (1.0 vs. 2.3/100 PYs), malignancy (0.59 vs. 0.25 patients/100 PYs), and major adverse cardiovascular events (MACE; 0.35 vs. 0.25/100 PYs) were low and comparable between guselkumab and placebo. Among guselkumab-treated patients, safety event rates through the end of the reporting period were numerically lower than or comparable with rates observed during the placebo-controlled period: AEs, 164/100 PYs; infections, 61.2/100 PYs; serious AEs, 5.4/100 PYs; AEs leading to discontinuation, 1.8/100 PYs; serious infections, 1.0/100 PYs; malignancy, 0.6/100 PYs; and MACE, 0.3/100 PYs. No AEs of Crohn's disease, ulcerative colitis, or active tuberculosis were reported among guselkumab-treated patients. In the psoriasis studies, no opportunistic infections were reported among guselkumab-treated patients. Three AEs of opportunistic infections were reported in guselkumab-treated patients with PsA (0.14/100 PYs; all after Week 52 in DISCOVER-2). AE rates were largely consistent across subgroups of guselkumab-treated patients defined by sex, age, BMI, and prior biologic use.

**Conclusions** In this analysis of 4399 guselkumab-treated patients with psoriatic disease followed for 10,787 PYs, guselkumab had a favorable AE profile. AE rates were similar between guselkumab- and placebo-treated patients and were consistent throughout long-term guselkumab treatment and across broad subgroups of patients with psoriatic disease.

**Clinical Trials Registrations** Clinicaltrials.gov identifiers: NCT01483599, NCT02207231, NCT02207244, NCT02203032, NCT02905331, NCT03090100, NCT02325219, NCT02319759, NCT03162796, NCT03158285, and NCT03796858.

Extended author information available on the last page of the article

## Graphical Abstract

# Long-Term Safety of Guselkumab in Patients With Psoriatic Disease: An Integrated Analysis of Eleven Phase 2/3 Clinical Studies in Psoriasis and Psoriatic Arthritis

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## Why was this research needed?

Psoriasis (PsO) and psoriatic arthritis (PsA) can cause itchy and painful skin plaques and/or joint damage. Patients with these chronic diseases usually need life-long treatment with safe and effective medicines.

Guselkumab is a biologic therapy that improved signs and symptoms of both diseases and showed similar side effects vs. placebo in clinical trials of patients with PsO and patients with PsA.

To better understand the long-term safety (up to 5 years) of guselkumab in a large and diverse group of patients with psoriatic disease, we combined data from clinical trials of adults with PsO or PsA.

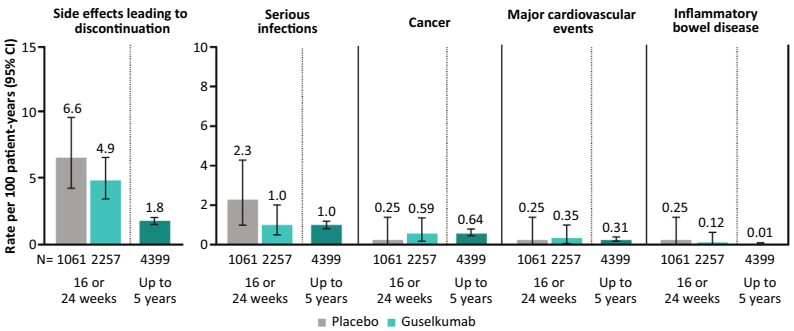
## How was this research done?

7 PsO trials + 4 PsA trials ≈ 11,000 patient-years of follow-up (# patients x length of follow-up)

**Rates of side effects:**

- Compared between patients treated with guselkumab vs. placebo
- Determined among patients who received guselkumab for up to 2 (PsA) or 5 (PsO) years
- Assessed in subgroups of patients with characteristics that are relevant to drug safety (sex, age, weight, prior biologic experience)

## What did this research tell us?




16 - 24 weeks: Types and rates of side effects were similar between patients receiving guselkumab and those receiving placebo.

Up to 5 years: Rates of important side effects remained low and stable in patients treated with guselkumab for up to 5 years.

Rates of side effects were similar between patients receiving guselkumab and placebo, and stable over time, regardless if they were:

- Male or female
- Normal weight or obese
- Younger or older (<65 or ≥65 years)
- Biologic naive or biologic experienced

In ~4400 adults with psoriatic disease who were treated for up to 5 years (~11,000 patient-years), guselkumab had a favorable long-term safety profile.

Findings support guselkumab as a safe treatment for a wide range of adults with psoriatic disease.

**Additional Information:** This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

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**Key Points**

Guselkumab safety was evaluated in a broad cohort of patients with psoriatic disease (11 trials; 10,787 patient-years).

Exposure-adjusted adverse event rates were similar in guselkumab- and placebo-treated patients, stable over time, and consistent across baseline patient subgroups.

## 1 Introduction

Psoriatic disease is a chronic, systemic, inflammatory disorder that includes psoriasis, psoriatic arthritis (PsA), and associated metabolic, cardiovascular, and psychosocial comorbidities [1–3]. Uncontrolled psoriatic disease can substantially reduce patients' quality of life as a result of impaired physical and emotional function, pain, fatigue, negative body image, reduced work productivity, and negative effects on personal relationships [1, 4].

Moderate-to-severe psoriasis and active PsA often require long-term continuous treatment with biologics or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) to achieve sustained resolution of skin and joint symptoms and improved quality of life [5–7]. When choosing a biologic therapy, patients report both the expectation for rapid and sustained efficacy and the fear of adverse effects as important factors influencing their treatment decisions [8–10]. The benefit/risk profiles of available biologics are influenced by comorbidities and associated conditions (e.g., obesity, diabetes, cardiovascular disease, metabolic syndrome, infections, malignancy, inflammatory bowel disease [IBD]), certain demographic characteristics (e.g., age, sex, psoriatic disease duration, body mass index [BMI]), concomitant medications (e.g., methotrexate, phototherapy, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids), and inadequate response or intolerance to prior biologics, which can increase risk for certain adverse events (AEs) [11, 12]. Therefore, it is important to evaluate the long-term safety profile of biologics across a broad range of patient populations.

Guselkumab, a fully human monoclonal antibody that selectively binds and inhibits the p19 subunit of interleukin (IL)-23, is approved for the treatment of adults with moderate-to-severe plaque psoriasis and active PsA. In randomized controlled trials, guselkumab had durable efficacy and a favorable safety profile for up to 5 years in psoriasis [13–15] and up to 2 years in PsA [16, 17].

The objective of this analysis was to evaluate the cumulative safety experience with guselkumab in patients with psoriatic disease using pooled data from seven phase II/III studies in patients with moderate-to-severe psoriasis [18–24] and four phase II/III studies in patients with active PsA [25–28]. Together, the 11 studies evaluated 4399 patients exposed to guselkumab for 10,787 patient-years (PYs). Results are presented for the overall pooled population and for subgroups defined by age, sex, BMI, and prior biologic use.

## 2 Patients and Methods

### 2.1 Study Designs

The seven psoriasis studies included in this analysis are the phase II dose-ranging X-PLORE study (NCT01483599) and the phase III VOYAGE 1 (NCT02207231), VOYAGE 2 (NCT02207244), NAVIGATE (NCT02203032), ORION (NCT02905331), ECLIPSE (NCT03090100), and Japan registration (NCT02325219) studies [18–24]. The guselkumab dosing schedules in these studies are shown in Fig. 1. Two psoriasis studies were placebo-controlled (ORION and Japan registration), three were placebo- and active-controlled (X-PLORE, VOYAGE 1, and VOYAGE 2), and two were active-controlled (NAVIGATE and ECLIPSE). The placebo-controlled periods in the X-PLORE, VOYAGE 1, VOYAGE 2, Japan registration, and ORION studies were from Weeks 0–16.

The four PsA studies included in this analysis are the phase II study (NCT02319759), the phase III DISCOVER-1 (NCT03162796) and DISCOVER-2 (NCT03158285) studies, and the phase IIIb COSMOS (NCT03796858) study [25–28]. As shown in Fig. 1, patients in DISCOVER-1 and DISCOVER-2 were randomized to guselkumab every 4 weeks (Q4W); guselkumab at Week 0, Week 4, then every 8 weeks (Q8W); or placebo with crossover to guselkumab Q4W at Week 24; patients in the phase II and COSMOS studies were randomized to guselkumab at Week 0, Week 4, then Q8W, or placebo with crossover to guselkumab Q8W at Week 24.

### 2.2 Patients

Detailed eligibility criteria for all studies have been reported previously [18–28]. Patients in the psoriasis studies had moderate-to-severe plaque-type psoriasis for ≥ 6 months and were candidates for systemic therapy or phototherapy. Moderate-to-severe psoriasis was defined as Psoriasis Area and Severity Index [29] ≥ 12, Investigator's Global Assessment [30] score ≥ 3, and body surface area of psoriasis ≥ 10%. Prior exposure to biologic agents was allowed in all studies (predominantly tumor necrosis factor [TNF] inhibitors, and also brodalumab, ixekizumab, secukinumab, and ustekinumab in some studies). Previous exposure to guselkumab was prohibited, as was any

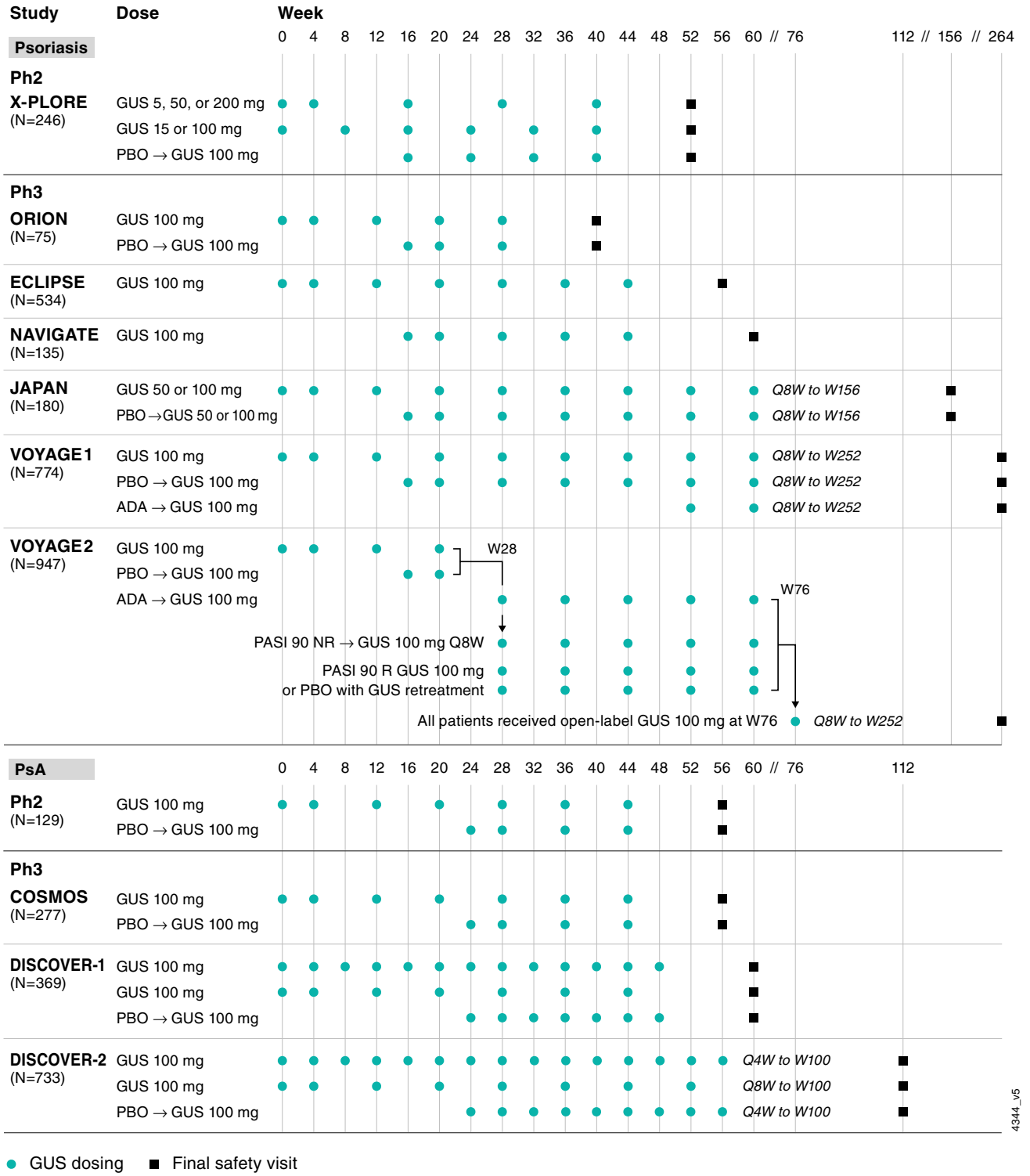


**Fig. 1** Study designs. *ADA* adalimumab, *GUS* guselkumab, *N* total number of patients exposed to GUS in each study, *NR* nonresponders, *PASI* Psoriasis Area and Severity Index, *PBO* placebo, *Ph* phase, *PsA* psoriatic arthritis, *Q4/8W* every 4/8 weeks, *R* responders, *W* week

previous exposure to the active comparator (adalimumab, secukinumab, or ustekinumab) in active-controlled studies [18–21, 23]. In general, concomitant psoriasis therapies, including topical therapies, phototherapy, conventional systemic therapies (e.g., methotrexate, cyclosporine, acitretin), steroids, and biologics, were prohibited during

study participation, with the exception of topical moisturizers and non-prescription medicated shampoos. In studies with open-label extensions [19, 20, 24], topical therapies, excluding ultra-high potency corticosteroids, could be used during the open-label periods.

Patients in the PsA studies had active PsA for ≥ 6 months, current or documented history of psoriasis, and inadequate response to, or intolerance of, standard therapies [25–28]. Patients were required to meet the Classification Criteria for Psoriatic Arthritis (CASPAR) [31] and to have either ≥ 3 tender and ≥ 3 swollen joints (phase II, DISCOVER-1, COSMOS) or ≥ 5 tender and ≥ 5 swollen joints (DISCOVER-2) at baseline. The phase II and DISCOVER-1 studies included both TNF inhibitor-naïve and -experienced patients; the TNF inhibitor-experienced groups were limited to 20% and 30% of patients in the phase II and DISCOVER-1 studies, respectively. DISCOVER-2 included only TNF inhibitor-naïve patients, and COSMOS enrolled only patients with inadequate response to prior TNF inhibitor therapy, defined as lack of efficacy or intolerance. With the exception of prior use of TNF inhibitors by all patients in the COSMOS study and some patients in the phase II and DISCOVER-1 studies, previous exposure to biologics and Janus kinase (JAK) inhibitors was prohibited. Stable use of concomitant methotrexate and corticosteroids was permitted in all four studies.

In all psoriasis and PsA studies, patients were eligible to participate if they had a history of malignancy > 5 years prior to enrollment. In the psoriasis studies, patients were also eligible if they had a history of treated nonmelanoma skin cancer (NMSC) or cervical cancer *in situ* without evidence of recurrence for ≥ 3 months. In all studies, patients with active tuberculosis (TB) were excluded. Patients with latent TB infection identified during screening were eligible if active TB was ruled out and appropriate latent TB treatment was initiated prior to or simultaneously with the first administration of study agent. In all studies, women of childbearing potential were required to have a negative urine pregnancy test at enrollment and to practice a highly effective method of birth control.

### 2.3 Safety Assessments

Short-term safety was evaluated using integrated data from all patients randomized and treated with placebo or guselkumab through the placebo-controlled period, defined as Weeks 0–16 in the psoriasis studies [18–20, 22, 24] and Weeks 0–24 in the PsA studies [25–28]. Long-term safety was evaluated using integrated data from all patients who received one or more administrations of guselkumab. In the psoriasis studies, this included patients randomized to placebo, guselkumab, or adalimumab (VOYAGE 1 and 2 only) at baseline who crossed over to guselkumab [18–20, 22–24] and patients randomized to guselkumab after receiving open-label ustekinumab (NAVIGATE) [21]. In the PsA studies, this included patients randomized to placebo who crossed over to guselkumab at Week 24 [25–28].

AEs were classified according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. AEs, AEs leading to study drug discontinuation, serious AEs (SAEs), infections, and AEs of interest were evaluated. AEs of interest included serious infections, opportunistic infections including TB, *Candida* (MedDRA high-level term of *Candida* infections), non-pathogen-specific fungal infections suspicious for *Candida* (determined by diagnosis and location; MedDRA terms included fungal balanitis, genital fungal infection, vulvovaginal mycotic infection, oral fungal infection, tongue fungal infection, fungal oropharyngitis, and fungal esophagitis), malignancy (including NMSC and malignancies other than NMSC), major adverse cardiovascular events (MACE; defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; identified based on clinical review), IBD (including preferred terms of Crohn's disease, ulcerative colitis, and IBD), uveitis (including preferred terms of uveitis, iridocyclitis, and iritis), and injection site reactions (ISRs).

### 2.4 Statistical Analyses

Using the integrated safety dataset, incidence rates of key AEs were determined post hoc, adjusted for duration of follow-up, and reported per 100 PYs. An exact method was used to calculate 95% confidence intervals (CIs) surrounding each exposure-adjusted incidence rate (EAIR), assuming the observed number of events followed a Poisson distribution. Event-level analyses were performed for AEs, SAEs, AEs leading to study drug discontinuation, infections, serious infections, MACE, and IBD. Patient-level analyses were performed to evaluate malignancies, uveitis, and ISRs. Incidence rates of AEs, AEs leading to discontinuation, SAEs, infections, and serious infections were determined for patient subgroups based on baseline characteristics of sex (male, female), age (< 65, ≥ 65 years), BMI (underweight/normal [< 25 kg/m$^2$], overweight [25.0–29.9 kg/m$^2$], obese [≥ 30 kg/m$^2$]), and prior biologic use (yes, no).

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute collects cancer incidence data (excluding NMSC, cervical cancer *in situ*, and other neoplasms of low malignancy potential) from population-based registries encompassing approximately 48% of the United States (US) population [32]. Standardized incidence ratios (SIRs) adjusted for age, sex, and race were calculated as the number of malignancies other than NMSC and cervical cancer *in situ* reported in guselkumab-treated patients divided

by the expected number of malignancies in the general US population according to the SEER database (2000–2017) [32]. Only patients with race identified as White, Black or African American, Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander were included for consistency with the race categories in the SEER database. Data from COSMOS were excluded from SIR calculations versus SEER because race was not documented in this study.

The ratio of basal cell carcinoma (BCC) to squamous cell carcinoma (SCC) was calculated as the number of BCC events for every one SCC event in patients with NMSC. This ratio has been used as a potential signal for immunosuppression; ratios < 1 (i.e., more SCC than BCC) have been observed in organ transplant recipients receiving immunosuppressive drugs [33, 34], and ratios ranging from approximately 1:1 to as high as 4:1 have been reported in general populations [35–37].

## 3 Results

### 3.1 Patients

In total, 3708 patients were randomized in the psoriasis studies and 1554 were randomized in the PsA studies. In this pooled psoriatic disease population, the short-term safety analysis dataset included 1061 patients who received placebo (395 PYs) and 2257 who received guselkumab (856 PYs). The long-term safety analysis dataset included 4399 patients who received one or more administrations of guselkumab (2891 in psoriasis studies and 1508 in PsA studies), for a total of 10,787 PYs of follow-up. The median duration of guselkumab exposure was 1.7 years in the pooled population (3.5 years in psoriasis studies and 1.2 years in PsA studies). Detailed patient disposition data have been reported for each study [18–28]. In the psoriasis studies, treatment was completed by 84–95% of guselkumab-treated patients in the five studies with a duration of ≤ 3 years and by 78% of patients in the 5-year VOYAGE 1 and 2 studies [14, 18, 21–24]. In the pooled PsA studies, nearly 90% of guselkumab-treated patients completed treatment in the 1- or 2-year studies [17].

Overall, across the psoriasis and PsA studies, patients were predominantly White, < 65 years of age, overweight or obese, and biologic-naïve (Table 1). Baseline characteristics were generally similar for guselkumab-treated patients in the psoriasis and PsA studies, although higher proportions of patients in the psoriasis studies were male (71% vs. 52%) and had no prior methotrexate exposure (63% vs. 42%) (Table 1). Importantly, concomitant medication use also differed between the psoriasis and PsA study populations, with approximately 56% of patients in the PsA studies receiving concomitant methotrexate, 18% receiving oral corticosteroids, and 63% receiving NSAIDs, while in the psoriasis studies, concomitant use of these medications was prohibited for the treatment of psoriasis or PsA. As expected based on study enrollment criteria, patients in the psoriasis studies generally had more extensive skin disease at baseline than in the PsA studies. Approximately 18% of patients in the psoriasis studies had self-reported PsA (Online Resource Tables 1 and 2).

### 3.2 Safety

In the pooled psoriatic disease population, EAIRs of overall AEs were similar between guselkumab- and placebo-treated patients during the placebo-controlled period (281 vs. 272/100 PYs) (Table 2) and did not increase in the guselkumab group through the end of study follow-up (164/100 PYs) (Table 3). EAIRs of AEs leading to study drug discontinuation were low and similar for guselkumab and placebo through the placebo-controlled period (4.9 vs. 6.6/100 PYs) (Table 2) and remained low with guselkumab treatment for up to 5 years (1.8/100 PYs) (Table 3). Within each of the sex, age, BMI, and prior biologic use subgroups, EAIRs of AEs and AEs leading to discontinuation during the placebo-controlled period were generally similar for guselkumab- and placebo-treated patients and did not increase through the long-term follow-up period in guselkumab-treated patients (Online Resource Fig. 1).

In the overall pooled population, EAIRs of SAEs were numerically lower with guselkumab [5.6 (4.1–7.4)] than with placebo [7.8 (5.3–11.2)], although the 95% CIs overlap (Table 2). SAE EAIRs remained low in guselkumab-treated patients through the long-term reporting period (5.4/100 PYs) (Table 3). Within each of the sex, age, BMI, and prior biologic use subgroups, EAIRs of SAEs were low and comparable in guselkumab- and placebo-treated patients during the placebo-controlled period and remained low and stable through the end of the reporting period for guselkumab-treated patients (Fig. 2).

#### 3.2.1 Infections

Infections (commonly, nasopharyngitis and upper respiratory tract infection) were the most frequently reported type of AE across treatment groups, with EAIRs of 76.0/100 PYs in the guselkumab group and 72.2/100 PYs in the placebo group during the placebo-controlled period (Table 2), and 61.2/100 PYs in the guselkumab group through the end of the reporting period (Table 3).

EAIRs of serious infections were low with guselkumab (1.0/100 PYs) and placebo (2.3/100 PYs) through the placebo-controlled period and remained low with guselkumab through the end of the reporting period (1.0/100 PYs). Through the end of the reporting period, serious infections

**Table 1** Baseline demographic characteristics

| Characteristic | Pooled PsO | Pooled PsA | Pooled PsO + PsA | | |
|---|---|---|---|---|---|
| | All guselkumab-treated patients [$n = 2891$] | All guselkumab-treated patients [$n = 1508$] | Patients included in the placebo-controlled period[a] analysis | | Patients included in the analysis through end of the reporting period (up to 5 years) |
| | | | Placebo [$n = 1061$] | Guselkumab [$n = 2257$] | Guselkumab [$n = 4399$] |
| Age, years | | | | | |
| Mean ± SD | 44.5 ± 12.8 | 47.1 ± 11.9 | 45.9 ± 12.2 | 45.6 ± 12.3 | 45.4 ± 12.5 |
| < 65 | 2708 (93.7) | 1407 (93.3) | 1003 (94.5) | 2115 (93.7) | 4115 (93.5) |
| ≥ 65 | 183 (6.3) | 101 (6.7) | 58 (5.5) | 142 (6.3) | 284 (6.5) |
| Sex | | | | | |
| Male | 2042 (70.6) | 777 (51.5) | 640 (60.3) | 1412 (62.6) | 2819 (64.1) |
| Female | 849 (29.4) | 731 (48.5) | 421 (39.7) | 845 (37.4) | 1580 (35.9) |
| Race | | | | | |
| White | 2313 (80.0) | 1185 (78.6) | 806 (76.0) | 1732 (76.7) | 3498 (79.5) |
| Asian | 480 (16.6) | 41 (2.7) | 134 (12.6) | 294 (13.0) | 521 (11.8) |
| Black/African American | 47 (1.6) | 0 | 13 (1.2) | 16 (0.7) | 47 (1.1) |
| Native Hawaiian/other Pacific Islander | 7 (0.2) | 1 (0.1) | 2 (0.2) | 5 (0.2) | 8 (0.2) |
| American Indian/Alaska Native | 6 (0.2) | 0 | 1 (0.1) | 3 (0.1) | 6 (0.1) |
| Other | 27 (0.9) | 0 | 5 (0.5) | 13 (0.6) | 27 (0.6) |
| Multiple | 11 (0.4) | 0 | 2 (0.2) | 5 (0.2) | 11 (0.3) |
| Not collected/reported[b] | 0 | 281 (18.6) | 98 (9.2) | 189 (8.4) | 281 (6.4) |
| BMI, kg/m$^2$ [c] | | | | | |
| Mean ± SD | 29.5 ± 6.6 | 29.3 ± 6.2 | 29.3 ± 6.5 | 29.3 ± 6.3 | 29.4 ± 6.5 |
| < 25 | 747 (25.9) | 380 (25.2) | 280 (26.4) | 581 (25.7) | 1130 (25.7) |
| 25 to < 30 [overweight] | 993 (34.4) | 516 (34.2) | 369 (34.8) | 773 (34.2) | 1509 (34.3) |
| ≥ 30 [obese] | 1148 (39.8) | 612 (40.6) | 410 (38.7) | 903 (40.0) | 1760 (40.0) |
| Prior biologic treatment | | | | | |
| Yes | 712 (24.6) | 401 (26.6) | 260 (24.5) | 596 (26.4) | 1113 (25.3) |
| No | 2179 (75.4) | 1107 (73.4) | 801 (75.5) | 1661 (73.6) | 3286 (74.7) |
| Prior methotrexate treatment | | | | | |
| Yes | 1073 (37.1) | 841 (55.8) | 469 (44.2) | 1041 (46.1) | 1926 (43.8) |
| No | 1818 (62.9) | 638 (42.3) | 592 (55.8) | 1216 (53.9) | 2289 (52.0) |

Data are expressed as *n* (%) unless otherwise specified

*BMI* body mass index, *PsA* psoriatic arthritis, *PsO* psoriasis, *SD* standard deviation

[a]Weeks 0–16 in psoriasis studies; Weeks 0–24 in PsA studies

[b]Race data were not collected in the COSMOS study and were not reported for two patients in DISCOVER-1

[c]Pooled PsA, $n = 1507$; placebo, $n = 1059$; guselkumab through end of the reporting period, $n = 4395$

reported in more than one patient in the guselkumab group included pneumonia ($n = 15$; 0.14/100 PYs), cellulitis ($n = 12$; 0.11/100 PYs), appendicitis ($n = 10$; 0.09/100 PYs), diverticulitis ($n = 5$; 0.05/100 PYs), erysipelas ($n = 4$; 0.04/100 PYs), pyelonephritis ($n = 3$; 0.03/100 PYs), and two patients each with bronchitis, influenza, ovarian abscess, cystitis, urosepsis, and limb abscess (0.02/100 PYs).

Within each of the baseline patient subgroups, EAIRs of infections were comparable. EAIRs of serious infections were low and comparable in the guselkumab and placebo groups during the placebo-controlled period and remained

**Table 2** Exposure-adjusted incidence rates of events per 100 PYs of follow-up (95% CI) during the placebo-controlled period[a]

| | PsO (Weeks 0–16) | | PsA (Weeks 0–24) | | | Pooled PsO and PsA | |
|---|---|---|---|---|---|---|---|
| | PBO[b] [*n* = 544] | GUS Q8W[c] [*n* = 1220] | PBO[b] [*n* = 517] | GUS Q8W [*n* = 664] | GUS Q4W [*n* = 373] | PBO[b] [*n* = 1061] | All GUS [*n* = 2257] |
| Total (median) PYs | 165 (0.3) | 378 (0.3) | 230 (0.5) | 305 (0.5) | 172 (0.5) | 395 (0.3) | 856 (0.3) |
| No. of events/100 PYs (95% CI) | | | | | | | |
| AEs | 341 (314, 370) | 346 (327, 365) | 223 (204, 243) | 233 (216, 250) | 223 (201, 246) | 272 (256, 289) | 281 (269, 292) |
| SAEs | 6.7 (3.3, 11.9) | 6.3 (4.1, 9.4) | 8.7 (5.3, 13.4) | 4.9 (2.8, 8.1) | 5.2 (2.4, 9.9) | 7.8 (5.3, 11.2) | 5.6 (4.1, 7.4) |
| AEs leading to study agent discontinuation | 9.7 (5.5, 15.7) | 5.0 (3.0, 7.8) | 4.4 (2.1, 8.0) | 3.6 (1.8, 6.4) | 7.0 (3.6, 12.2) | 6.6 (4.3, 9.6) | 4.9 (3.5, 6.6) |
| Infections | 83.6 (70.2, 98.8) | 95.9 (86.3, 106.3) | 64.0 (54.1, 75.2) | 59.0 (50.7, 68.2) | 62.6 (51.4, 75.6) | 72.2 (64.1, 81.1) | 76.0 (70.3, 82.1) |
| Serious infections | 1.2 (0.2, 4.4) | 1.1 (0.3, 2.7) | 3.0 (1.2, 6.3) | 0.7 (0.08, 2.4) | 1.7 (0.4, 5.1) | 2.3 (1.0, 4.3) | 1.0 (0.5, 2.0) |
| Opportunistic infections[d] | 0 (0, 1.82) | 0 (0, 0.79) | 0 (0, 1.30) | 0 (0, 0.98) | 0 (0, 1.74) | 0 (0, 0.76) | 0 (0, 0.35) |
| *Candida* infections | 1.82 (0.37, 5.31) | 0.53 (0.06, 1.91) | 0 (0, 1.30) | 0 (0, 0.98) | 0 (0, 1.74) | 0.76 (0.16, 2.22) | 0.23 (0.03, 0.84) |
| Non-specific fungal infections suspicious for *Candida* | 0 (0, 1.82) | 0.53 (0.06, 1.91) | 0 (0, 1.30) | 0.33 (0.01, 1.83) | 0 (0, 1.74) | 0 (0, 0.76) | 0.35 (0.07, 1.02) |
| Malignancy[e] | 0 (0, 1.82) | 0.53 (0.06, 1.91) | 0.44 (0.01, 2.43) | 0.99 (0.20, 2.88) | 0 (0, 1.74) | 0.25 (0.01, 1.41) | 0.59 (0.19, 1.37) |
| NMSC | 0 (0, 1.82) | 0.26 (0.01, 1.47) | 0 (0, 1.30) | 0 (0, 0.98) | 0 (0, 1.74) | 0 (0, 0.76) | 0.12 (0, 0.65) |
| Other malignancies | 0 (0, 1.82) | 0.26 (0.01, 1.47) | 0.44 (0.01, 2.43) | 0.99 (0.20, 2.88) | 0 (0, 1.74) | 0.25 (0.01, 1.41) | 0.47 (0.13, 1.20) |
| MACE[f] | 0 (0, 1.82) | 0.26 (0.01, 1.47) | 0.44 (0.01, 2.43) | 0.33 (0.01, 1.83) | 0.58 (0.01, 3.23) | 0.25 (0.01, 1.41) | 0.35 (0.07, 1.02) |
| IBD | 0 (0, 1.82) | 0 (0, 0.79) | 0.44 (0.01, 2.43) | 0.33 (0.01, 1.83) | 0 (0, 1.74) | 0.25 (0.01, 1.41) | 0.12 (0, 0.65) |
| Crohn's disease/ulcerative colitis | 0 (0, 1.82) | 0 (0, 0.79) | 0 (0, 1.30) | 0 (0, 0.98) | 0 (0, 1.74) | 0 (0, 0.76) | 0 (0, 0.35) |
| Uveitis[e] | 0 (0, 1.82) | 0 (0, 0.79) | 0.44 (0.01, 2.43) | 0 (0, 0.98) | 0 (0, 1.74) | 0.25 (0.01, 1.41) | 0 (0, 0.35) |

*AEs* adverse events, *CI* confidence interval, *GUS* guselkumab, *IBD* inflammatory bowel disease, *MACE* major adverse cardiovascular event, *NMSC* nonmelanoma skin cancer, *PBO* placebo, *PsA* psoriatic arthritis, *PsO* psoriasis, *PYs* patient-years, *Q4/8/12W* every 4/8/12 weeks, *SAEs* serious adverse events

[a]Includes patients in all treatment groups who discontinued study treatment early, with the last study treatment (PBO or GUS) administered prior to Week 16/24 and who did not receive any study agent (PBO or GUS) at or after Week 16/24; all data including the final safety follow-up visit collected through up to 2 years were included in this period

[b]Includes data prior to GUS exposure in PBO-treated patients who switched from PBO to GUS

[c]All patients received GUS 100 mg Q8W, except in X-PLORE (*n* = 250 randomized to GUS 5 mg at Week 0, Week 4, then Q12W; 15 mg Q8W; 50 mg at Week 0, Week 4, then Q12W; 100 mg Q8W; or 200 mg at Week 0, Week 4, then Q12W; or PBO with crossover to GUS 100 mg Q8W at Week 16); and the Japan registration study (*n* = 65 randomized to GUS 50 mg Q8W and *n* = 26 randomized to PBO with crossover to GUS 50 mg Q8W)

[d]Identified based on clinical review

[e]Patient-level analysis

[f]MACE was predefined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, and was identified based on clinical review

**Table 3** Exposure-adjusted incidence rates of events per 100 PYs of follow-up (95% CI) through the end of the reporting period

| | PsO | PsA | | | Pooled PsO and PsA |
|---|---|---|---|---|---|
| | All GUS Q8W[a,b] [$n = 2891$] | All GUS Q8W [$n = 783$] | All GUS Q4W [$n = 725$] | Combined GUS Q4W+Q8W[c] [$n = 1508$] | All GUS [$n = 4399$] |
| Total (median) PYs | 8662 (3.5) | 1019 (1.1) | 1106 (1.7) | 2125 (1.2) | 10,787 (1.7) |
| No. of events/100 PYs (95% CI) | | | | | |
| AEs | 169 (166, 172) | 160 (152, 168) | 133 (126, 140) | 146 (141, 151) | 164 (162, 167) |
| SAEs | 5.3 (4.8, 5.8) | 6.3 (4.8, 8.0) | 5.2 (3.9, 6.7) | 5.7 (4.7, 6.8) | 5.4 (4.9, 5.8) |
| AEs leading to study agent discontinuation | 1.6 (1.3, 1.9) | 2.4 (1.5, 3.5) | 3.1 (2.1, 4.3) | 2.7 (2.1, 3.5) | 1.8 (1.6, 2.1) |
| Infections | 65.9 (64.2, 67.6) | 43.5 (39.5, 47.7) | 40.6 (36.9, 44.5) | 42.0 (39.3, 44.8) | 61.2 (59.7, 62.7) |
| Serious infections | 0.88 (0.69, 1.10) | 1.67 (0.97, 2.67) | 1.54 (0.90, 2.46) | 1.60 (1.11, 2.24) | 1.02 (0.84, 1.23) |
| Opportunistic infections[d] | 0 (0, 0.03) | 0.20 (0.02, 0.71) | 0.09 (0, 0.50) | 0.14 (0.03, 0.41) | 0.03 (0.01, 0.08) |
| *Candida* infections | 0.60 (0.45, 0.79) | 0 (0, 0.29) | 0.18 (0.02, 0.65) | 0.09 (0.01, 0.34) | 0.50 (0.38, 0.65) |
| Non-specific fungal infections suspicious for *Candida* | 0.10 (0.05, 0.20) | 0.39 (0.11, 1.01) | 0 (0, 0.27) | 0.19 (0.05, 0.48) | 0.12 (0.06, 0.21) |
| Malignancy[e] | 0.74 (0.57, 0.95) | 0.39 (0.11, 1.01) | 0.09 (0, 0.50) | 0.24 (0.08, 0.55) | 0.64 (0.50, 0.81) |
| NMSC | 0.35 (0.23, 0.50) | 0.10 (0, 0.55) | 0.09 (0, 0.50) | 0.09 (0.01, 0.34) | 0.30 (0.20, 0.42) |
| Other malignancies | 0.43 (0.30, 0.59) | 0.29 (0.06, 0.86) | 0.09 (0, 0.50) | 0.19 (0.05, 0.48) | 0.38 (0.27, 0.52) |
| MACE[f] | 0.33 (0.22, 0.48) | 0.20 (0.02, 0.71) | 0.27 (0.06, 0.79) | 0.24 (0.08, 0.55) | 0.31 (0.21, 0.43) |
| IBD | 0 (0, 0.03) | 0.10 (0, 0.55) | 0 (0, 0.27) | 0.05 (0, 0.26) | 0.01 (0, 0.05) |
| Crohn's disease/ulcerative colitis | 0 (0, 0.03) | 0 (0, 0.29) | 0 (0, 0.27) | 0 (0, 0.14) | 0 (0, 0.03) |
| Uveitis[e] | 0.05 (0.01, 0.12) | 0.10 (0, 0.55) | 0 (0, 0.27) | 0.05 (0, 0.26) | 0.05 (0.02, 0.11) |

*AEs* adverse events, *CI* confidence interval, *GUS* guselkumab, *IBD* inflammatory bowel disease, *MACE* major adverse cardiovascular event, *NMSC* nonmelanoma skin cancer, *PsA* psoriatic arthritis, *PsO* psoriasis, *PYs* patient-years, *Q4/8/12W* every 4/8/12 weeks, *SAEs* serious adverse events, *W* week

[a]Includes PsO patients originally randomized to placebo or adalimumab at baseline who crossed over and were treated with GUS

[b]All patients received GUS 100 mg Q8W, except in X-PLORE ($n = 250$ randomized to GUS 5 mg at Week 0, Week 4, then Q12W; 15 mg Q8W; 50 mg at Week 0, Week 4, then Q12W; 100 mg Q8W; or 200 mg at Week 0, Week 4, then Q12W; or PBO with crossover to GUS 100 mg Q8W at Week 16); and the Japan registration study ($n = 65$ randomized to GUS 50 mg Q8W and $n = 26$ randomized to PBO with crossover to GUS 50 mg Q8W)

[c]Includes PsA patients randomized to PBO who crossed over to GUS at W24

[d]Identified based on clinical review

[e]Patient-level analysis

[f]MACE was predefined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, and was identified based on clinical review

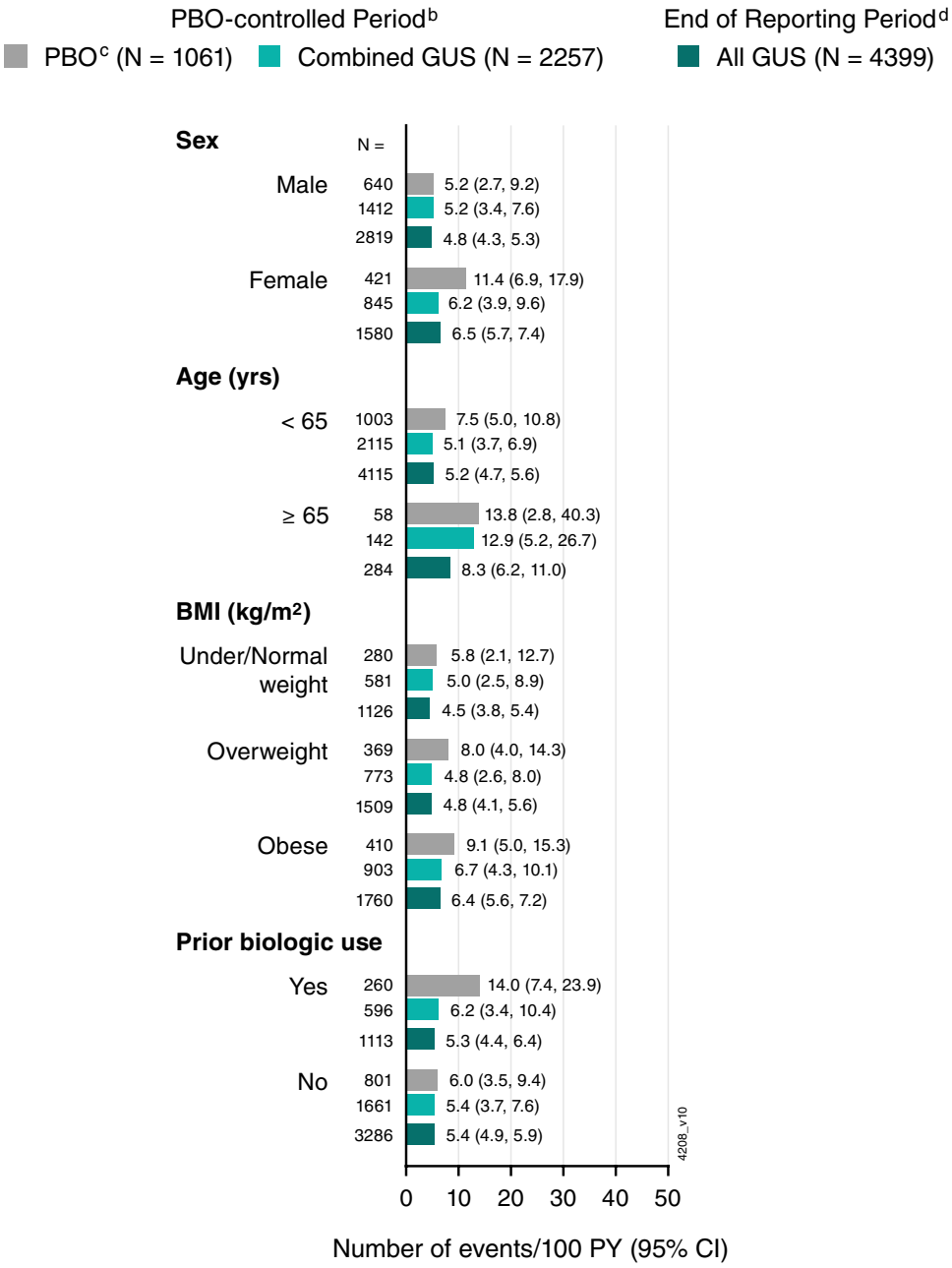


**Fig. 2** Rates of SAEs stratified by baseline characteristics [events/100 PYs (95% CI)] in the pooled psoriasis + PsA population[a]. [a]CIs based on an exact method assuming that the observed number of events follows a Poisson distribution. Events are counted only once if events were started from the same date with the same derived term. [b]Includes patients who discontinued study treatment early, with the last study treatment (PBO or GUS) administered prior to W16/24, and who did not receive any study agent (PBO or GUS) at or after W16/24; all data including the final safety follow-up visit collected through up to 2 years were included in this period. [c]Only includes data prior to administration of GUS in PBO patients who switched from PBO to GUS. [d]Only includes data after administration of GUS in PBO patients who switched from PBO to GUS. *BMI* body mass index (under/normal weight: < 18.5–24.9 kg/m$^2$; overweight: 25.0–29.9 kg/m$^2$; obese: 30.0–34.9 kg/m$^2$), *CI* confidence interval, *GUS* guselkumab, *PsA* psoriatic arthritis, *PBO* placebo, *PYs* patient-years, *SAEs* serious adverse events, *W* week

low and stable through the end of the reporting period in guselkumab-treated patients (Fig. 3).

*Candida* infections were infrequent during the placebo-controlled period, reported for three patients in the placebo group (EAIR = 0.76/100 PYs; two events of vulvovaginal candidiasis, one event of oral candidiasis) and two patients in the guselkumab group (EAIR = 0.23/100 PYs; one event of vulvovaginal candidiasis, one event of cutaneous candidiasis); all events occurred in psoriasis studies. Through the end of the reporting period, *Candida* infections in guselkumab-treated patients remained low (0.50/100 PYs) and were reported with the MedDRA preferred terms of vulvovaginal candidiasis ($n = 23$; 0.21/100 PYs), cutaneous candidiasis ($n = 16$; 0.15/100 PYs), oral candidiasis ($n = 10$; 0.09/100 PYs), *Candida* infection ($n = 2$; 0.02/100 PYs), genital candidiasis ($n = 2$; 0.02/100 PYs), and *Candida* balanitis ($n = 1$; 0.009/100 PYs). All events occurred in the psoriasis studies except for one case of oral thrush in DISCOVER-1 and one case of cutaneous candidiasis in DISCOVER-2 (EAIR of *Candida* infections in the pooled PsA studies through 2 years = 0.09/100 PYs).

In the pooled psoriasis and PsA population, rates of non-pathogen-specific fungal infections suspicious for *Candida* were low (0.12/100 PYs) in guselkumab-treated patients

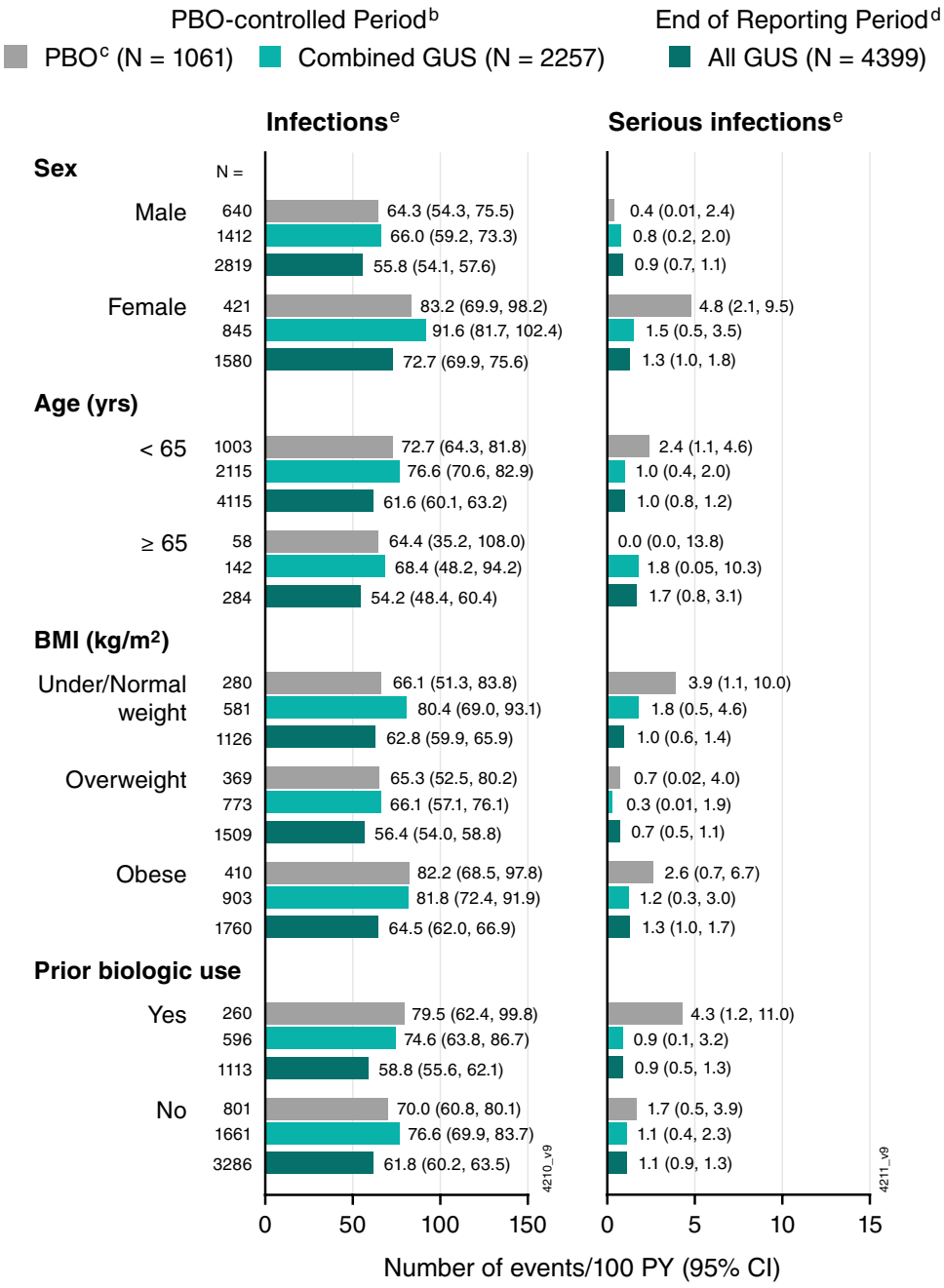


**Fig. 3** Rates of infections and serious infections stratified by baseline characteristics [events/100 PYs (95% CI)] in the pooled psoriasis + PsA population[a]. [a]CIs based on an exact method assuming that the observed number of events follows a Poisson distribution. Events are counted only once if events were started from the same date with the same derived term.. [b]Includes patients who discontinued study treatment early, with the last study treatment (PBO or GUS) administered prior to W16/24, and who did not receive any study agent (PBO or GUS) at or after W16/24; all data including the final safety follow-up visit collected through up to 2 years were included in this period. [c]Only includes data prior to administration of GUS in PBO patients who switched from PBO to GUS. [d]Only includes data after administration of GUS in PBO patients who switched from PBO to GUS. [e]Infections were defined by clinician review in COSMOS and by infection flag in all other studies. *BMI* body mass index (under/normal weight: <18.5–24.9 kg/m$^2$; overweight: 25.0–29.9 kg/m$^2$; obese: 30.0–34.9 kg/m$^2$), *CI* confidence interval, *GUS* guselkumab, *PsA* psoriatic arthritis, *PBO* placebo, *PYs* patient-years, *W* week

through the end of the reporting period and included vulvovaginal mycotic infection ($n = 9$; 0.08/100 PYs), oral fungal infection ($n = 2$; 0.02/100 PYs), fungal esophagitis ($n = 1$; 0.009/100 PYs), and genital fungal infection ($n = 1$; 0.009/100 PYs).

In the pooled psoriasis studies, no opportunistic infections occurred in guselkumab-treated patients. In the pooled PsA studies, three opportunistic infections were reported in guselkumab-treated patients (EAIR = 0.14/100 PYs) (Table 3). Each case occurred after Week 52 in the DISCOVER-2 study and included fungal esophagitis in a patient receiving concomitant methotrexate with a long-standing history of gastroesophageal reflux disease and a recent course of antibiotics, disseminated herpes zoster in a 62-year-old patient with a history of diabetes mellitus and no shingles vaccination, and *Listeria* meningitis in a patient receiving concomitant methotrexate. Across all studies, no cases of active TB were reported in guselkumab-treated patients.

#### 3.2.2 Malignancies

Malignancy EAIRs were low during the placebo-controlled period, with reports for one patient in the placebo group (renal clear cell carcinoma; EAIR = 0.25/100 PYs) and five guselkumab-treated patients (EAIR = 0.59/100 PYs). Malignancies in the guselkumab group included one patient with NMSC (0.12/100 PYs; BCC) and four patients with malignancies other than NMSC (0.47/100 PYs; rectal adenocarcinoma, prostate cancer, plasma cell myeloma, and melanoma *in situ*) (Table 2). The rectal adenocarcinoma was not diagnosed prior to enrollment but was considered by the investigator to have likely been present before administration of study drug.

During long-term treatment, malignancy EAIRs remained low in the guselkumab group. Thirty-two patients (0.30/100 PYs) had a total of 41 NMSC events (Table 3), including 27 BCCs and 14 SCCs, resulting in a BCC:SCC ratio across studies of 1.9:1, suggesting no signal for SCC-related immunosuppression in patients treated with guselkumab for up to 5 years. Forty-one patients had a malignancy other than NMSC (0.38/100 PYs) (Table 3). Malignancies other than NMSC reported in more than one patient included breast ($n = 7$), colorectal ($n = 7$), melanoma ($n = 6$ [including three cases of melanoma *in situ*]), prostate ($n = 5$), head and neck ($n = 4$), bladder ($n = 2$), and lymphoma ($n = 2$).

Of note, the VOYAGE 1 and VOYAGE 2 psoriasis studies included 18 guselkumab-treated patients with a history of malignancy (excluding NMSC) > 5 years prior to enrollment. Of these 18 patients, one patient had a recurrence of lung cancer and three patients developed new malignancies (breast cancer, melanoma, and sebaceous carcinoma). All patients with new or recurrent malignancies had underlying risk factors. These cases are described in detail in a separate publication [38].

The number of malignancies other than NMSC and cervical cancer *in situ* in guselkumab-treated patients through the end of the reporting period ($n = 40$; excluding COSMOS data) was consistent with the number (adjusted for age, sex, and race) expected in the general US population based on SEER data ($n = 51.4$). The SIR (95% CI) for the guselkumab group versus SEER was 0.78 (0.56–1.06).

#### 3.2.3 Major Adverse Cardiovascular Events

MACE EAIRs were low and similar in the placebo (0.25/100 PYs; one event of cardiovascular death) and guselkumab (0.35/100 PYs; two nonfatal myocardial infarctions and one nonfatal stroke) groups during the pooled placebo-controlled period (Table 2). MACE EAIRs remained low through the long-term reporting period. There were 34 events (0.31/100 PYs) reported among 33 guselkumab-treated patients, including 22 nonfatal myocardial infarctions (0.20/100 PYs), nine nonfatal strokes (0.08/100 PYs; one patient [Japan registration study] had two nonfatal strokes), and three cardiovascular deaths (0.03/100 PYs) (Table 3). Most patients with MACE, including the three patients with cardiovascular deaths, had three or more cardiovascular risk factors at baseline. Among patients with nonfatal strokes, three of eight had previous stroke history, including the patient with two strokes in the Japan registration study.

#### 3.2.4 Inflammatory Bowel Disease

During the placebo-controlled period, one case of suspected IBD (EAIR = 0.25/100 PYs) was reported in a PsA patient who received placebo, and one case of suspected IBD (EAIR = 0.12/100 PYs) was reported in a PsA patient who received three doses of guselkumab Q8W (Table 2). The guselkumab-treated patient was also suspected of having celiac disease; neither the IBD nor the celiac diagnosis was confirmed, and the patient was lost to follow-up. Through the end of the reporting period, no cases of Crohn's disease or ulcerative colitis were reported in guselkumab-treated patients (Table 3).

#### 3.2.5 Uveitis

During the placebo-controlled period, one patient in the placebo group experienced iridocyclitis in both eyes (0.25/100 PYs), and no AEs of uveitis occurred in guselkumab-treated patients (Table 2). Through the end of the reporting period, five guselkumab-treated patients experienced AEs of uveitis (0.05/100 PYs) (Table 3), including four patients in the psoriasis studies (0.05/100 PYs; three patients had uveitis, one patient had iritis) and one patient in the PsA studies (0.05/100 PYs; iridocyclitis).

#### 3.2.6 Injection Site Reactions

In the pooled psoriasis studies, ISRs occurred in 153 (5.3%) of 2891 guselkumab-treated patients (464 [0.8%] of 57,063 guselkumab injections were associated with ISRs; most were mild). In the pooled PsA studies, ISRs occurred in 30 (2.0%) of 1508 guselkumab-treated patients (75 [0.4%] of 19,303 guselkumab injections were associated with ISRs; most were mild). Across all studies and time periods, no events of serum sickness-like or anaphylactic reactions related to guselkumab were reported.

## 4 Discussion

The overall safety profile of guselkumab in this analysis was favorable and supports results from the individual studies and in separate pooled psoriasis [15] and pooled PsA [17]

analyses. Rates of SAEs and AEs of interest were low and similar to placebo during short-term treatment and remained low with long-term treatment. The favorable safety profile of guselkumab was consistent across a broad population of patients, irrespective of sex, age, BMI, and prior biologic use.

For many patients with psoriatic disease, drug safety is the most important factor when selecting a long-term treatment [39, 40]. In a cross-sectional analysis of 200 patients' preferences for the treatment of moderate-to-severe psoriasis with biologics, avoiding severe AEs was the treatment attribute that received the highest relative importance score, followed by achieving 90% improvement in skin disease and avoiding mild AEs [39]. Results of the present analysis confirming the reassuring long-term safety profile of guselkumab across both psoriasis and PsA can inform shared decision-making conversations between patients and healthcare providers, with the goal of maximizing patients' treatment satisfaction, adherence, and clinical outcomes.

As patients and providers consider the long-term safety of available biologics for the treatment of psoriatic disease, comorbidities and associated conditions, including cardiovascular disease, obesity, metabolic syndrome, chronic infections, malignancy, and IBD, are recognized as factors that can impact the safety profile of different therapies [12, 41]. For example, current Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines recommend against using IL-17 inhibitors in patients with ulcerative colitis or Crohn's disease because these therapies may exacerbate symptoms in patients with IBD [12]. In contrast, the IL-12/23 p40 subunit inhibitor ustekinumab and several IL-23, TNF, and JAK inhibitors have been approved, or are in late-stage clinical development, for the treatment of moderately to severely active Crohn's disease and ulcerative colitis [42]; these therapies are recommended for patients with psoriatic disease and associated IBD [12]. Results of the current analysis support the gastrointestinal safety of guselkumab in psoriatic disease, as no cases of Crohn's disease or ulcerative colitis were reported in guselkumab-treated patients through the end of the long-term reporting period.

Results from several studies suggest psoriatic disease may be associated with increased risk for certain cancers [43, 44] and this risk may be associated with long-term use of certain treatments, including phototherapy, conventional immunosuppressants, TNF inhibitors, and JAK inhibitors [45–49]. Results of the current analysis identified no signal for malignancy in patients treated with guselkumab for up to 5 years. The observed BCC:SCC ratio of 1.9:1 in this analysis is consistent with ratios reported in general populations [35, 36, 50] and does not reflect the reverse (i.e., more SCC than BCC), which has been reported in immunosuppressed patients after organ transplantation [33, 34].

GRAPPA guidelines recommend all biologics and tsDMARDs be used with caution in patients with a history of recent malignancy [12]. Data on the safety of biologics in patients with a history of malignancy are limited because these patients are typically excluded from clinical trials [51]. The VOYAGE 1 and VOYAGE 2 studies of guselkumab in psoriasis are among the first clinical trials of biologics to include patients with a history of malignancy > 5 years before enrollment. Although a small number of guselkumab-treated patients ($n = 18$) had a history of malignancy (excluding NMSC) in these studies, no concerning patterns were identified in the observed incidence of new or recurrent malignancies, suggesting this patient population may be safely treated with guselkumab [38].

Patients with uncontrolled psoriatic disease may be at increased risk for MACE and cardiovascular mortality [52–56]. Cardiovascular risk surveillance studies in psoriatic disease and rheumatology have yielded different outcomes. In rheumatoid arthritis, PsA, and psoriasis safety surveillance studies, potential increased cardiovascular risks have been observed for some JAK inhibitors, especially in high-risk patients [57–59]. Additional long-term safety studies are being conducted to further evaluate the cardiovascular safety of this class of agents [60]. Treatment with other systemic therapies, including biologics and methotrexate, has been associated with reduced risks of cardiovascular events and mortality in patients with psoriasis [61–63]. In the Psoriasis Longitudinal Assessment and Registry (PSOLAR), systemic treatment with a biologic or methotrexate within the preceding 3 months was protective against overall and cardiovascular mortality compared with no treatment exposure [61]. The reduced mortality risk in patients with moderate-to-severe psoriasis (including some patients with self-reported PsA) was observed in patients treated with biologics regardless of treatment duration. In patients treated with methotrexate, reduced mortality risk was only observed in patients treated for 1 year or longer [61]. Given the inherent elevated risks for cardiometabolic comorbidities in patients with psoriatic disease, it is reassuring that the current analysis in patients treated with guselkumab for up to 5 years identified no signal for increased MACE risk.

Risks of new-onset and reactivated acute and chronic infections are also elevated in patients with psoriatic disease as a result of altered adaptive and innate immune function and reduced skin barrier integrity [64]. The immunomodulatory effects of psoriatic disease treatments may also affect patients' susceptibility to infection, with different classes of therapies having unique safety profiles [6]. For example, recent studies have reported increased risk of TB in patients receiving TNF inhibitors, *Candida* infection with IL-17 inhibitor therapy, and herpes zoster infections with JAK inhibitor treatment

[64–68]. In guselkumab-treated patients, the overall rate of serious infections was low (1.02/100 PYs), with no observed cases of TB, and three observed opportunistic infections (0.03/100 PYs) in > 10,700 PYs of follow-up. The observed rate of *Candida* infections (0.50/100 PYs) is lower than rates reported in pooled safety analyses of IL-17 inhibitors (bimekizumab, 14.2/100 PYs in > 3000 PYs in psoriasis patients; secukinumab, 2.9/100 PYs in > 15,000 PYs in psoriasis, PsA, and ankylosing spondylitis patients; ixekizumab, 1.9/100 PYs in > 17,000 PYs in psoriasis patients) [69–71]. The studies included in this analysis were completed before or very shortly after the onset of the coronavirus disease 2019 (COVID-19) pandemic, when testing was not widely available. As such, very few confirmed COVID cases were reported, and formal analyses of COVID infections were not performed.

Patients with psoriatic disease are also at increased risk for uveitis compared with general populations [72–75]. The uveitis EAIR of 0.05/100 PYs observed in guselkumab-treated patients through the end of the long-term reporting period is consistent with uveitis incidence rates reported in general populations (0.02–0.09/100 PYs) and in patients with psoriatic disease (0.04–0.16/100 PYs) [72, 73].

Results of the current analysis are generally consistent with real-world observations of favorable safety of guselkumab and other IL-23 inhibitors [76–82]. In two small observational 1-year studies of guselkumab in patients with moderate-to-severe psoriasis ($n = 52$) [76] and early PsA ($n = 24$) [77], respectively, guselkumab was generally well tolerated. In the psoriasis cohort, no patients discontinued due to AEs, and in the PsA cohort, no drug-related AEs were reported [76, 77]. A literature review of real-world studies published through 1 April 2022 that evaluated guselkumab, risankizumab, and tildrakizumab efficacy and safety found all three selective IL-23 inhibitors were well tolerated in routine dermatology practice, with no SAEs reported. Several of these real-world studies included older patients with more comorbidities (including COVID-19) than typically seen in clinical trial populations, supporting the safety of IL-23 inhibitors in patient populations at higher risk for AEs [78]. As additional real-world context, EAIRs of serious infections, malignancy, and MACE in guselkumab-treated patients with psoriatic disease in this analysis are similar to rates reported in PSOLAR [15, 79, 80] among > 12,000 patients with psoriasis who were eligible for, or receiving, conventional systemic and biologic treatments [79].

### 4.1 Strengths and Limitations

Pooling data across the spectrum of psoriatic disease provided a population of approximately 4400 patients with > 10,700 PYs of guselkumab exposure. The majority of these patients completed their respective studies (78% of patients completed the 5-year VOYAGE studies, and 85–95% of patients completed the nine shorter psoriasis and PsA studies) [14, 16, 18, 21–25, 28, 83], indicating guselkumab has a consistent long-term safety profile, as evident from the trial dispositions. Although differences in patient characteristics, guselkumab dosing frequency (Q8W in psoriasis studies vs. Q4W or Q8W in PsA studies), and the use of concomitant immunosuppressive medications in the PsA studies may limit interpretation of results from these pooled analyses, most demographic characteristics were similar across studies (Online Resource Tables 1 and 2), and previous analyses of pooled safety across the four PsA studies showed rates of AEs were generally similar in the guselkumab Q4W and Q8W groups [17].

An important limitation of the available safety data for biologics in psoriatic disease is that the clinical trial patient populations are not necessarily representative of the demographics (e.g., age and race) of the general populations in the regions where the studies were conducted. The inclusion/exclusion criteria of the studies may have introduced selection bias, limiting the generalizability of the results. For example, in these guselkumab studies, patients with malignancy within the last 5 years, or active infection, were excluded. Furthermore, this long-term safety assessment was constrained by the relatively short (16 weeks in psoriasis and 24 weeks in PsA studies) placebo-controlled periods. Since most of the studies included in this pooled analysis were ≤2 years in duration, year-to-year safety analyses were not performed. However, pooled data from the 5-year VOYAGE 1 and VOYAGE 2 studies showed that while there was some year-to-year variability in AE rates over time, no increasing trend was observed [14]. Pooled immunogenicity analyses were not performed because guselkumab antidrug antibody levels were not measured in the PsA COSMOS study. However, in the studies that included immunogenicity assessments, small proportions of patients tested positive for antibodies, and antibody titer levels were consistently low [14, 16, 18, 21, 22, 24]. Furthermore, pooled results from the VOYAGE 1 and 2 studies showed development of guselkumab antidrug antibodies was not clinically relevant [84].

## 5 Conclusions

In this analysis of guselkumab safety evaluating approximately 4400 patients with psoriatic disease (10,787 PYs of exposure), guselkumab had a favorable safety profile. During the placebo-controlled periods, safety event rates were similar in guselkumab- and placebo-treated patients, and event rates

remained stable throughout long-term follow-up for up to 5 years. Safety event rates were generally similar in guselkumab-treated patients with psoriasis and PsA and across baseline subgroups based on sex, age, BMI, and prior biologic use.

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## Declarations

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**Conflicts of Interest** Bruce Strober has served as a consultant (honoraria) and/or speaker and/or investigator for AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Cara, Connect Biopharma, CorEvitas Psoriasis Registry, Dermavant, Dermira, Eli Lilly, EPI Health, Evelo Biosciences, Immunic Therapeutics, Incyte, Janssen, LEO Pharma, Maruho, Meiji Seika Pharma, Mindera Health, Novartis, Ono, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma, UCB Pharma, Union Therapeutics, Ventyxbio, and vTv Therapeutics; and served as Co-Scientific Director (consulting fee) of CorEvitas (formerly Corrona) Psoriasis Registry and Editor-in-Chief (honorarium) of the Journal of Psoriasis and Psoriatic Arthritis. Laura C. Coates has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, MoonLake, Novartis, Pfizer, and UCB; and has been paid as a speaker for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Medac, Novartis, Pfizer, and UCB. Dr. Coates is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and are not necessarily those of the NHS, the NIHR, or the Department of Health. Mark G. Lebwohl is an employee of Mount Sinai and receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, Inc., and is a consultant for Almirall, AltruBio Inc., AnaptysBio, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Brickell Biotech, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, CorEvitas, Dermavant Sciences, EPI, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica. Atul Deodhar has received consulting fees for participation in advisory boards from AbbVie, Amgen, Aurinia, Bristol Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, MoonLake, Novartis, Pfizer, and UCB; research grant funding from AbbVie, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and UCB; and speaker fees from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB. Evan Leibowitz, Katelyn Rowland, Soumya D. Chakravarty, and Daphne Chan are employees of Janssen Scientific Affairs, LLC (a subsidiary of Johnson & Johnson); employees may own Johnson & Johnson stock/stock options. Alexa P. Kollmeier, Megan Miller, Yanli Wang, Shu Li, and May Shawi are employees of Janssen Research & Development, LLC (a subsidiary of Johnson & Johnson); employees may own Johnson & Johnson stock/stock options. Ya-Wen Yang is an employee of Janssen Pharmaceutical Companies of Johnson & Johnson; employees may own Johnson & Johnson stock/stock options. Diamant Thaçi has received honoraria for participation on advisory boards, as a speaker, and for consultancy from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Galderma, Janssen, Kyowa Hakko Kirin, La Roche-Posay, LEO Pharma, Merck Sharp & Dohme, Morphosys, New Bridge, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz-Hexal, Sanofi, Sun Pharma, and UCB, and has received research grants from LEO Pharma and Novartis. Proton Rahman discloses consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, and UCB; travel support from Janssen; and grant/research support from Janssen and Novartis.

**Ethics Approval** All studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice. For all studies, the protocol was approved by an Institutional Review Board (IRB) or independent Ethics Committee at each site. Sterling IRB was a central US IRB for several studies (VOYAGE 1, 4809C; VOYAGE 2, 4810C; NAVIGATE, 4808C; ORION, 5600C; ECLIPSE, 5789C; DISCOVER-1, 5959C; DISCOVER-2, 5910C). A full listing of IRBs and Ethics Committees for all studies is provided in Online Resource Table 3. Additional details are available upon request.

**Consent to Participate** All participants provided written informed consent to participate.

**Consent for Publication** All participants provided consent acknowledging that the results of the studies may be published in a medical book or journal, or presented at meetings for educational purposes.

**Availability Of Data And Materials** 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 the Yale Open Data Access Project site at http://yoda.yale.edu.

**Code Availability** Not applicable.

**Author Contributions** All authors were involved in drafting the article or revising it critically for important intellectual content, and approved the final version to be published. All authors contributed to study conception and design. BS, LCC, MGL, AD, DT, and PR contributed to the acquisition of data, and all authors contributed to the analysis and interpretation of data.

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