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ADIS DRUG Q&A

Guselkumab in psoriatic arthritis: a profile of its use

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Abstract

Guselkumab (TREMFYA®), a fully human immunoglobulin G1λ (IgG1λ) monoclonal antibody that selectively targets interleukin (IL)-23, is an effective and generally well-tolerated treatment option for active psoriatic arthritis. Guselkumab is administered subcutaneously and can be used alone or in combination with methotrexate. In randomized, double-blind, placebo-controlled phase 3 trials in adults with active psoriatic arthritis and an inadequate response to or intolerance of standard treatment, guselkumab was effective in reducing disease activity and structural damage progression. Guselkumab conferred improvements in arthritis, enthesitis, dactylitis, psoriasis, axial symptoms, physical function and health-related quality of life. The clinical benefits of guselkumab for the diverse signs and symptoms of psoriatic arthritis increased or were maintained through two years of treatment, with no new safety signals emerging.

Plain Language Summary

Psoriatic arthritis is an inflammatory joint disease that commonly occurs in patients with psoriasis. While several drugs are now available for the treatment of psoriatic arthritis, patients often need to switch treatments due to inadequate efficacy or tolerability concerns. Guselkumab (TREMFYA®) treats psoriatic arthritis via a novel mechanism of action. In well-designed clinical trials, guselkumab provided durable improvements in the various signs and symptoms of psoriatic arthritis (including arthritis, joint inflammation and structural damage, skin disease and spinal manifestations). Guselkumab recipients reported gains in physical function and health-related quality of life. Guselkumab is an effective option for the treatment of active psoriatic arthritis and is generally well tolerated, with no new safety concerns identified during longer-term use.

Digital Features for this Adis Drug Q&A can be found at https://doi.org/10.6084/m9.figshare.14331431.

Adis evaluation of guselkumab in the management of psoriatic arthritis

First-in-class fully human IgG1λ monoclonal antibody selectively targeting IL-23
Reduces disease activity in patients with active psoriatic arthritis despite standard treatment
Improves diverse signs/symptoms of psoriatic arthritis
Clinical benefits durable over longer-term treatment
Favourable benefit-risk profile

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What is the rationale for developing guselkumab in psoriatic arthritis?

Psoriatic arthritis is a chronic inflammatory joint disease commonly associated with psoriasis [1, 2]; while relatively rare in the general population (with prevalence estimates of < 1% [3]), psoriatic arthritis occurs in ≈ 20–30% of patients affected by psoriasis [4–6]. There is considerable overlap in the pathophysiological features of the two conditions [1, 7]. Aside from psoriasis, clinical manifestations of psoriatic arthritis are diverse and include peripheral arthritis, enthesitis, dactylitis, spinal disease, nail lesions and uveitis [1, 7]. In order to prevent lasting structural damage and disability, early diagnosis and treatment is vital [8]. Treatment aims should include the achievement of disease remission or, alternatively, a state of low disease activity [9].

Historically, the treatment of psoriatic arthritis has been approached in a similar manner to that of rheumatoid arthritis, with the use of conventional synthetic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate [8,

10]. However, evidence for the efficacy of these agents in treating the diverse features of psoriatic arthritis is limited [8, 10]. Increased understanding of the immunopathogenesis of psoriatic arthritis has facilitated the development of treatments that target specific signalling pathways implicated in the disease, and the last decade has seen a proliferation of novel treatment options for psoriatic arthritis, including biologic and targeted synthetic DMARDs [2, 10]. As patients often need to switch treatments due to a lack of efficacy, a loss of efficacy over time or tolerability concerns [11], the availability of effective and well-tolerated agents with distinct mechanisms of action is desirable. The interleukin (IL)-23/IL-17 axis cytokines have been implicated in the pathogenesis of both psoriasis and psoriatic arthritis, and the inhibition of IL-12/23 or IL-17A with monoclonal antibodies has proved an efficacious approach to the treatment of these conditions [7].

Guselkumab (TREMFYA®), a fully human immunoglobulin G1λ (IgG1λ) monoclonal antibody selectively targeting IL-23, was the first in its class to be approved for the treatment of moderate to severe plaque psoriasis in the EU and USA [12]. Use of guselkumab in this indication has been reviewed previously [12]. Guselkumab has since been approved for use in the treatment of psoriatic arthritis in several countries/regions including the EU [13], USA [14] and Japan [15]. Table 1 provides a summary of the prescribing information for guselkumab in the treatment of psoriatic arthritis in the aforementioned regions [13–15]. Consult local prescribing information for further details.

What are the pharmacological properties of guselkumab?

Guselkumab, a fully human IgG1λ monoclonal antibody, binds selectively to the p19 subunit of IL-23 with high affinity [13, 16]. In doing so, it blocks interaction between IL-23 and the cell surface IL-23 receptor, thus inhibiting IL-23-mediated signalling, activation and pro-inflammatory cytokine cascades [13].

Guselkumab reduced levels of acute phase proteins C-reactive protein (CRP) and serum amyloid A (SAA), IL-6, and Th17 effector cytokines (IL-17A, IL-17F and IL-22) as early as 4 weeks after treatment initiation in patients with active psoriatic arthritis in phase 3 clinical trials [17]. At week 24, levels of all aforementioned proteins were significantly ($p < 0.05$) reduced with each guselkumab regimen (100 mg administered subcutaneously at week 0, week 4, and either every 4 or every 8 weeks thereafter) relative to those at week 0. At baseline, patients had significantly ($p < 0.05$) higher levels of CRP, SAA, IL-6, IL-17A and IL-17F than healthy controls [17].

Guselkumab pharmacokinetics in patients with psoriatic arthritis are similar to those in patients with plaque psoriasis (previously reviewed [12]) [13, 14]. In brief, guselkumab exhibited linear pharmacokinetics in patients with moderate to severe psoriasis (subcutaneous dose range 10–300 mg) [18]. In patients with psoriatic arthritis administered subcutaneous guselkumab 100 mg at week 0, week 4 and every 8 weeks thereafter, steady-state trough serum concentrations were generally reached by week 20 [16]. When guselkumab 100 mg was administered in patients with psoriatic arthritis at week 0, week 4 and either every 8 weeks or 4 weeks thereafter, mean steady-state trough serum concentrations were ≈ 1.2 µg/mL and ≈ 3.8 µg/mL with the respective regimens [13]. The absolute bioavailablity of guselkumab after a single subcutaneous 100 mg dose was estimated to be ≈ 49% in healthy volunteers [13, 14]. In a population pharmacokinetic (PPK) analysis in patients with plaque psoriasis, guselkumab had an apparent volume of distribution of 13.5 L and clearance of 0.516 L/day in the final model; the model-derived elimination half-life was 18.1 days [19].

Like endogenous IgG, human IgG monoclonal antibodies such as guselkumab are expected to be eliminated via intracellular catabolism into amino acids and small peptides [13, 14]. Based on this elimination route, neither hepatic impairment nor abnormal kidney function is anticipated to impact guselkumab pharmacokinetics to any clinically meaningful extent [13]. Concomitant medications (e.g. NSAIDs, oral corticosteroids, conventional DMARDs including methotrexate) did not impact guselkumab clearance in PPK analyses [13, 14].

What is the efficacy of guselkumab in psoriatic arthritis?

Guselkumab 100 mg administered subcutaneously every 4 or 8 weeks is effective in treating active psoriatic arthritis in patients with an inadequate response to or intolerance of standard treatment [20–22]. The efficacy of guselkumab was demonstrated in the double-blind, multinational, phase 3 DISCOVER-1 [21] and DISCOVER-2 [20] trials. These trials enrolled adults meeting classification criteria for psoriatic arthritis, with ≥ 3 swollen joints, ≥ 3 tender joints and CRP ≥ 0.3 mg/dL [21] or ≥ 5 swollen joints, ≥ 5 tender joints and CRP ≥ 0.6 mg/dL [20] despite standard therapies. Eligibility criteria included psoriasis or a history thereof and an inadequate response to or intolerance of apremilast (discontinued > 4 weeks before study treatment), non-biologic DMARDs or NSAIDs for psoriatic arthritis [20, 21]. In DISCOVER-1, ≈ 30% of participants had previously received one or two tumour necrosis factor (TNF) inhibitors while the remaining participants were biologic-naïve [21]. All participants in DISCOVER-2

Table 1 Summary of the prescribing information of guselkumab (TREMFYA®) in psoriatic arthritis in the EU [13], USA [14] and Japan [15]

What is the approved indication for guselkumab?	
EU	Alone or in combination with methotrexate for the treatment of active psoriatic arthritis in adult pts who have had an inadequate response or who have been intolerant to a prior DMARD therapy
USA	For the treatment of adult pts with active psoriatic arthritis (alone or in combination with a conventional DMARD such as methotrexate)
Japan	For the treatment of psoriatic arthritis for which existing treatments are inadequate
How is guselkumab available?	
In a single-dose prefilled syringe (EU, USA, Japan) or single-dose prefilled pen/injector (EU, USA) containing guselkumab 100 mg in 1 mL solution for subcutaneous injection	
How should guselkumab be stored?	
Store syringe or pen/injector in refrigerator at 2–8°C (do not freeze); to protect from light, keep in outer carton until time of use	
How should guselkumab be administered?	
Administration schedule	100 mg at weeks 0 and 4, followed by a 100 mg maintenance dose every 8 weeks
	In pts at high risk for joint damage, a 100 mg dose every 4 weeks may be considered (EU)
	Consider discontinuing guselkumab if no response after 16 weeks (Japan) or 24 weeks (EU) of treatment
Injection site	Inject into front of thigh (recommended site; EU, USA), lower abdomen or back of upper arm
	Avoid using areas of skin affected by psoriasis as injection sites
What are the contraindications to the use of guselkumab?	
Serious hypersensitivity to guselkumab or any of the excipients (EU, USA); history of hypersensitivity to the ingredients of the drug (Japan)	
Clinically important active infections (e.g. active tuberculosis) (EU); serious infections or active tuberculosis (Japan)	
How should guselkumab be used in special populations?	
Pts aged ≥ 65 years	No dose adjustment required; data limited in pts aged ≥ 65 years (EU, USA)
	Closely monitor for adverse effects such as infectious diseases (Japan)
Paediatric pts	Safety and efficacy not established
Hepatic impairment	No dose recommendations made (lack of data); not anticipated to impact drug clearance (EU)
Abnormal kidney function	No dose recommendations made (lack of data); not anticipated to meaningfully impact drug clearance (EU)
Pregnant pts	No data on use during pregnancy, although animal studies do not indicate adverse effects
	Preferably avoid administering guselkumab during pregnancy, as a precaution (EU)
	Encourage pts exposed during pregnancy to enrol in pregnancy registry monitoring outcomes (USA)
	Only administer if benefits outweigh risks (Japan)
Breastfeeding pts	No data on presence of guselkumab in human milk
	Consider benefits of breastfeeding alongside benefits of guselkumab for mother (EU, USA, Japan) and any potential adverse effects of guselkumab or underlying maternal condition on breastfed infant (USA)
Pts of childbearing potential	Use effective contraception methods during and for ≥ 12 weeks after treatment (EU)
What clinically relevant drug interactions may potentially occur with guselkumab?	
CYP450 substrates	No dose adjustment required; drug interactions unlikely (EU)
	Consider monitoring CYP450 substrates (especially those with narrow therapeutic indices) for therapeutic effect or concentration when initiating guselkumab and consider adjusting dosage if required (USA)

DMARD disease-modifying antirheumatic drug, *pts* patients

were biologic-naïve [20]. In each trial, patients were randomized to receive subcutaneous guselkumab 100 mg every 4 weeks (referred to hereafter as guselkumab 4-weekly), guselkumab 100 mg at week 0, week 4 and every 8 weeks thereafter (hereafter guselkumab 8-weekly), or placebo, with randomization stratified by baseline non-biologic DMARD use and either previous TNF inhibitor use [21] or CRP concentration [20]. Across trials, ≈ 58% of patients received methotrexate as background therapy [13]. After the 24-week placebo-controlled treatment period, there was an active treatment period up until week 52 [21] or week 100 [20]; at week 24, all placebo recipients commenced treatment with guselkumab 4-weekly [23, 24]. Results from the DISCOVER trials are supported by those from an earlier randomized, double-blind, placebo-controlled, multinational, phase 2a trial, in which a guselkumab 8-weekly regimen ($n = 100$ randomized) significantly improved the signs and symptoms of psoriatic arthritis relative to placebo ($n = 49$) in patients with active psoriatic arthritis despite standard therapy [22, 25].

Guselkumab 4-weekly and guselkumab 8-weekly significantly improved American College of Rheumatology 20% (ACR20) response rates relative to placebo at week 24 (primary endpoint; Table 2) of the DISCOVER trials [20, 21]. With both regimens, ACR20 response gains were consistent across subgroups based on demographic variables, disease characteristics at baseline (including skin disease severity [26]), and previous or baseline medication use (including methotrexate use at baseline and, in DISCOVER-1, previous TNF inhibitor use) [20, 21]. Treatment differences (nominal $p < 0.05$ vs placebo) in ACR20 were evident as early as week 4 (i.e. after a single injection) in DISCOVER-2 [20] and week 8 in DISCOVER-1 [21]. Improvements with the guselkumab regimens versus placebo were demonstrated across all individual ACR components at week 24 [13, 27]. At week 24, higher proportions of guselkumab 8-weekly

Table 2 Efficacy of subcutaneous guselkumab in psoriatic arthritis: results from DISCOVER-1 [21] and DISCOVER-2 [20]

Treatment (no. of randomized and treated pts)	Response rate (% of pts)		LSM change from baseline		
	ACR20[a]	IGA[b,c]	HAQ-DI[c]	SF-36 PCS[c]	SF-36 MCS[c]
Outcomes at week 24					
DISCOVER-1 (in pts who were biologic-naïve or had previously received TNF inhibitors)					
Guselkumab 100 mg Q8W (127)	52***	57***	−0.32***	6.10***	3.20
Guselkumab 100 mg Q4W (128)	59***	75***	−0.40***	6.87***	3.60
Placebo (126)	22	15	−0.07	1.96	2.37
DISCOVER-2 (in pts who were biologic-naïve)					
Guselkumab 100 mg Q8W (248)	64***	70***	−0.37***	7.39*	4.17
Guselkumab 100 mg Q4W (245)	64***	68***	−0.40***	7.04*	4.22
Placebo (246)	33	19	−0.13	3.42	2.14
Outcomes at week 52					
DISCOVER-1 (in pts who were biologic-naïve or had previously received TNF inhibitors)					
Continuing guselkumab 100 mg Q8W (127)	60	63	−0.4	6.6	4.4
Continuing guselkumab 100 mg Q4W (128)	73	82	−0.5	8.6	4.3
Initiating guselkumab 100 mg Q4W[d] (126)	56	68	−0.3	5.5	4.1
DISCOVER-2 (in pts who were biologic-naïve)					
Continuing guselkumab 100 mg Q8W (248)	75	74	−0.5	9.0	4.3
Continuing guselkumab 100 mg Q4W (245)	71	79	−0.5	8.6	4.4
Initiating guselkumab 100 mg Q4W[d] (246)	64	79	−0.4	7.5	4.0

ACR20 American College of Rheumatology 20% improvement, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *IGA* investigator's global assessment (score of 0–4, with higher scores representing more severe psoriasis), *LSM* least squares mean, *MCS* mental component summary score, *PCS* physical component summary score, *pts* patients, *Q4W* administered every 4 weeks, *Q8W* administered week 0, week 4 and every 8 weeks thereafter, *SF-36* Short-Form 36, *TNF* tumour necrosis factor

*$p < 0.05$, ** $p < 0.01$, ***$p < 0.0001$ vs placebo (controlled for multiplicity)

[a]ACR20 at week 24 was the primary endpoint in DISCOVER-1 and DISCOVER-2

[b]IGA skin response (defined as a score of ≤ 1 with an improvement from baseline of ≥ 2 points) was assessed in pts with ≥ 3% body surface area affected by psoriasis and IGA score ≥ 2 at week 0

[c]Major secondary endpoints at week 24 in DISCOVER-1 and DISCOVER-2

[d]Pts initially randomized to placebo switched to guselkumab Q4W at week 24

and 4-weekly recipients than placebo recipients achieved an ACR 50% (ACR50) response in DISCOVER-1 (30% and 36% vs 9%) and DISCOVER-2 (31% and 33% vs 14%) [nominal $p < 0.0001$ for each comparison] [20, 21]. An ACR 70% (ACR70) response was achieved by 12% and 20% of guselkumab 8-weekly and 4-weekly recipients versus 6% of placebo recipients (nominal $p = 0.0005$ for guselkumab 4-weekly vs placebo) in DISCOVER-1 and 19% and 13% versus 4% in DISCOVER-2 (nominal $p \leq 0.0004$ for each comparison) [20, 21].

Guselkumab also reduced disease activity based on rates of minimal disease activity achievement and change in the 28-joint disease activity score with CRP (DAS28-CRP) [20, 21]. Higher proportions of guselkumab 8-weekly and 4-weekly recipients than placebo recipients achieved a state of minimal disease activity in DISCOVER-1 (23% and 30% vs 11%; nominal p-values ≤ 0.012) and DISCOVER-2 (25% and 19% vs 6%; nominal p-values < 0.0001). In each trial, least squares mean (LSM) reductions from baseline to week 24 in DAS28-CRP were greater with each guselkumab regimen than with placebo (nominal p-values < 0.0001 for all comparisons) [20, 21].

With respect to the diverse signs and symptoms of psoriatic arthritis, guselkumab offered the following benefits over placebo at week 24 of the DISCOVER trials:

- *Skin disease* Both guselkumab regimens significantly improved skin disease based on investigator's global assessment response (Table 2) [20, 21]. Similarly, higher proportions of guselkumab 8-weekly and 4-weekly recipients than placebo recipients had psoriasis area and severity index (PASI) 75%, 90% and 100% improvements in each trial (nominal $p \leq 0.0005$ for all) [20, 21].
- *Enthesitis and dactylitis* Resolution of enthesitis was achieved by significantly higher proportions of guselkumab 8-weekly and 4-weekly recipients than placebo recipients (50% and 45% vs 29%; $p < 0.05$ for both comparisons) in a preplanned pooled analysis of DISCOVER-1 and DISCOVER-2 data from patients with enthesitis at baseline ($n = 728$) [20]. Resolution of dactylitis was observed in significantly higher proportions of guselkumab 8-weekly and 4-weekly recipients than placebo recipients (59% and 64% vs 42%; $p < 0.05$ for both comparisons) in a preplanned pooled analysis of data from patients with dactylitis at baseline ($n = 473$). Both guselkumab regimens afforded greater LSM improvement from baseline in Leeds enthesitis index score and dactylitis score relative to placebo (nominal p-values $\leq$ 0.0025) [20].
- *Axial symptoms* Both guselkumab regimens afforded greater LSM improvement from baseline in Bath ankylosing spondylitis disease activity index (BASDAI), spinal pain, and ankylosing spondylitis disease activity score (ASDAS) with CRP relative to placebo (nominal p-values < 0.001) in a pooled analysis of DISCOVER-1 and DISCOVER-2 data from patients who were identified by physicians as having symptoms consistent with spondylitis and had sacroiliitis confirmed via prior radiograph/MRI or screening radiograph ($n = 312$) [28].

Guselkumab inhibited radiographic structural damage progression as assessed using psoriatic arthritis-modified van der Heijde-Sharp (vdHS) scores in DISCOVER-2 [20]. Guselkumab 4-weekly recipients demonstrated significantly less radiographic progression than placebo recipients at week 24 (LSM change from baseline in psoriatic arthritis-modified vdHS score 0.29 vs 0.95; $p = 0.011$), whilst guselkumab 8-weekly recipients demonstrated a non-significant reduction in progression relative to placebo recipients (0.52 vs 0.95) [20].

Both guselkumab regimens significantly improved physical function and health-related quality of life (HR-QOL) as assessed by change from baseline in health assessment questionnaire-disability index (HAQ-DI) and short form-36 (SF-36) physical component summary score at week 24 (Table 2) [20, 21]. Improvements relative to placebo in the change from baseline in SF-36 mental component summary score did not reach statistical significance (Table 2) [20, 21]. At week 24, guselkumab 8-weekly and 4-weekly recipients achieved greater reductions in fatigue (based on functional assessment of chronic illness therapy-fatigue scores) than placebo recipients in both trials (nominal p-values < 0.001) [16, 29].

The clinical benefits of guselkumab were sustained through longer-term treatment in both DISCOVER trials [23, 24]. In each trial, ACR20 response rates at week 52 were numerically higher than those at week 24 in patients randomized to guselkumab 8-weekly or 4-weekly (Table 2). ACR50 response rates increased to 39% and 54% in patients randomized to guselkumab 8-weekly and 4-weekly in DISCOVER-1 and to 48% and 46% in the respective groups in DISCOVER-2, while ACR70 response rates increased to 26% and 29% in DISCOVER-1 and 28% and 26% in DISCOVER-2 [23, 24]. At week 100 of DISCOVER-2, ACR20 response rates were 74% and 76% in patients randomized to guselkumab 8-weekly and 4-weekly [30]. ACR50 response rates were 55% and 56% in the respective groups, while ACR70 rates were 36% and 35% [30].

Guselkumab continued to suppress progression of structural damage seen on plain radiographs during the active treatment period of DISCOVER-2 [30]. In patients randomized to guselkumab 8-weekly and 4-weekly, the observed mean changes in total psoriatic arthritis-modified vdHS scores were 0.99 and 1.06, respectively, during weeks 0–52 and 0.46 and 0.75 during weeks 52–100. In patients randomized to placebo who switched to guselkumab 4-weekly at

week 24, mean changes in total psoriatic arthritis-modified vdHS scores were 1.12, 0.34 and 0.13 during weeks 0–24, 24–52 and 52–100, respectively [30].

Guselkumab provided sustained skin responses, including IGA (Table 2) and PASI 75%, 90% and 100% responses, through one year of treatment in DISCOVER-1 and DISCOVER-2 [23, 24], with robust responses persisting through week 100 of the longer DISCOVER-2 trial [30]. In pooled analyses of DISCOVER-1 and DISCOVER-2 data from patients with enthesitis or dactylitis at baseline, enthesitis and dactylitis resolution rates at week 24 were maintained at week 52, as were improvements in Leeds enthesitis index scores or dactylitis severity [24]. At week 52, enthesitis and dactylitis resolution rates were 58% and ≈ 75% in patients randomized to either guselkumab regimen [24]. Resolution rates were maintained through week 100 of DISCOVER-2 [30]. With respect to axial symptoms in patients who were identified by physicians as having symptoms consistent with spondylitis and had sacroiliitis confirmed via prior radiograph/MRI or screening radiograph, LSM changes in BASDAI, spinal pain and ASDAS were stable from week 24 to week 52 in patients randomized to either guselkumab regimen (pooled DISCOVER-1 and DISCOVER-2 data) [31]. Improvements in physical function and HR-QOL were maintained through one year of treatment with guselkumab in both DISCOVER trials (Table 2) and through week 100 of treatment in DISCOVER-2 [30]. The majority of patients treated in DISCOVER-1 (90%) and DISCOVER-2 (93%) completed one year of treatment [23, 24], while 88% of randomized and treated patients completed week 100 of DISCOVER-2 [30].

What is the tolerability profile of guselkumab?

Guselkumab 100 mg administered subcutaneously 8-weekly or 4-weekly is generally well tolerated in patients with psoriatic arthritis, based on data from the phase 2 and 3 clinical trials [20–22]. The overall safety profile of guselkumab was largely consistent with that established in patients with psoriasis [20–22].

In a pooled analysis of data from the 24-week placebo-controlled periods of the DISCOVER-1 and DISCOVER-2 trials in adults with psoriatic arthritis, the incidence of treatment-emergent adverse events (TEAEs) was similar across treatment arms (48.5% and 48.8% of guselkumab 8-weekly and 4-weekly recipients, compared with 47.3% of placebo recipients) [16, 32]. The most common TEAEs in guselkumab 8-weekly or 4-weekly recipients were nasopharyngitis, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST) and upper respiratory tract infection (Fig. 1). ALT and AST elevations were generally

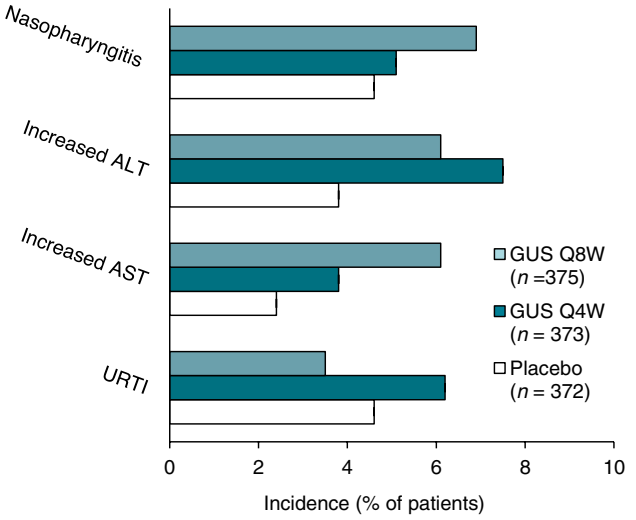

Fig. 1. Most common treatment-emergent adverse events (occurring in ≥ 5% of patients in any treatment arm) with guselkumab in the DISCOVER trials in patients with psoriatic arthritis (through week 24) [16, 32]. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GUS Q4W* guselkumab administered 4-weekly, *GUS Q8W* guselkumab administered at weeks 0, 4 and 8-weekly thereafter, *URTI* upper respiratory tract infection

mild, transient and not accompanied by clinically significant elevations in bilirubin [16, 32]. Serious TEAEs occurred in 1.9% and 2.1% of guselkumab 8-weekly and 4-weekly recipients compared with 3.2% of placebo recipients [16, 32]. TEAEs of severe intensity were infrequent with guselkumab (occurring in 0.8% and 0.5% of guselkumab 8-weekly and 4-weekly recipients vs 1.6% of placebo recipients) [16]. TEAEs seldom led to discontinuation of the study agent, doing so in 1.3% and 2.1% of guselkumab 8-weekly and 4-weekly recipients versus 1.9% of placebo recipients, and injection-site reaction rates were low (1.3% and 1.1% vs 0.3% of placebo patients) [16, 32].

Several warnings and precautions pertain to the use of guselkumab, including a potentially increased risk of infection (Table 3) [13–15]. While decreased neutrophil counts were somewhat more common with guselkumab than placebo in the pooled dataset (grade 1: 5.6% and 5.9% of guselkumab 8-weekly and 4-weekly recipients vs 3.2% of placebo recipients; grade 2: 1.6% and 1.6% vs 0.8%; grade 3–4: 0% and 0.3% vs 0.3%), most of these laboratory results were transient and not associated with infection [16, 32]. The guselkumab 8-weekly and 4-weekly groups were comparable to the placebo group with respect to the proportions of recipients reporting ≥ 1 infection (19.5% and 21.4% vs 20.7%) or serious infection (0.3% and 0.8% vs 0.8%) through week 24 [16, 32]. There were no instances of active tuberculosis during DISCOVER-1 or DISCOVER-2, and no opportunistic infections during placebo-controlled treatment [16, 23, 24].

Table 3 Summary of warnings and precautions in the prescribing information of guselkumab in the EU [13], USA [14] and Japan [15]

Infections	May ↑ risk of infection
	Do not initiate in pts with any clinically important active infection until it has resolved or been adequately treated (EU, USA); consider risks and benefits before initiating in pts with a chronic infection or past recurrent infection (USA)
	Instruct recipients to seek medical advice if they experience signs/symptoms of a clinically important infection (chronic or acute); closely monitor any pt who develops a serious or clinically important infection (or is not responding to standard therapy) and discontinue guselkumab until infection resolves (EU, USA)
Pre-treatment evaluation for TB	Evaluate pts for TB infection before initiating guselkumab
	Commence treatment of latent TB before administering guselkumab (USA); consider anti-TB therapy in pts with a history of TB (latent or active) if no adequate treatment can be confirmed (EU, USA)
	Monitor pts for signs/symptoms of active TB during (EU, USA, Japan) and after (EU, USA) treatment; do not use guselkumab in pts with active TB infections
Hypersensitivity	Serious hypersensitivity reactions, including anaphylaxis, have been reported with guselkumab (EU, USA)
	Immediately discontinue guselkumab administration if a serious hypersensitivity reaction occurs (EU, USA)
Immunisations	Complete appropriate immunisations before initiating guselkumab (EU, USA)
	Do not use live vaccines in pts receiving guselkumab; withhold guselkumab for ≥ 12 weeks (from last dose) before giving a live viral or bacterial vaccination and do not resume guselkumab until ≥ 2 weeks after vaccination (EU)
Hepatic transaminase elevations (EU)	↑ incidence of liver enzyme elevations with 4-weekly guselkumab (vs 8-weekly guselkumab or placebo) in pts with psoriatic arthritis in clinical trials; in pts with psoriatic arthritis, evaluate liver enzymes prior to initiating 4-weekly guselkumab and as appropriate thereafter
	In pts with ALT or AST elevations and suspected drug-induced liver injury, temporarily interrupt treatment with guselkumab until this diagnosis is ruled out
Malignancies (Japan)	Skin and non-skin malignancies have been reported in clinical trials of guselkumab, although a causal relationship has not been established

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *pt(s)* patient(s), *TB* tuberculosis, ↑ increase(d)

The longer-term tolerability of guselkumab was comparable to that observed during placebo-controlled treatment, with no new safety signals identified through week 60 of DISCOVER-1 (total 365 patient-years of follow-up) [23] or week 112 of DISCOVER-2 (total 1392 patient-years of follow-up) [30]. Guselkumab treatment through week 60 of DISCOVER-1 or week 112 of DISCOVER-2 did not increase the time-adjusted incidences of infections, adverse events leading to treatment discontinuation, or serious adverse events relative to placebo treatment through week 24 of the respective trial [23, 30]. The incidence of serious infections with guselkumab was 1.1 events per 100 patient-years in DISCOVER-1 and 1.9 events per 100 patient-years in DISCOVER-2 (vs 3.5 and 0.9 events per 100 patient-years with placebo through week 24). Opportunistic infections were reported in three guselkumab recipients through week 112 of DISCOVER-2 (fungal esophagitis and disseminated herpes zoster in guselkumab 8-weekly recipients and listeria meningitis in a patient who switched from placebo to guselkumab 4-weekly), while there were no opportunistic infections reported during DISCOVER-1. One patient who switched from placebo to guselkumab 4-weekly in DISCOVER-2 died in a road traffic accident; no other deaths occurred in guselkumab recipients [23, 30].

In the DISCOVER trials, 2% of guselkumab recipients (n = 15) developed anti-drug antibodies during up to 24 weeks of treatment [13]. Of these patients, one had neutralizing antibodies and none developed injection-site reactions [13].

What is the current clinical position of guselkumab in psoriatic arthritis?

The therapeutic landscape for psoriatic arthritis has rapidly evolved over recent years and guselkumab represents an effective and generally well-tolerated treatment option that expands the range of available pharmaceuticals. In adults with active psoriatic arthritis, treatment with subcutaneous guselkumab reduces disease activity [irrespective of dosing interval (8-weekly or 4-weekly), background methotrexate use or previous use of TNF inhibitors] and inhibits the progression of structural joint damage [20, 21]. Psoriatic arthritis is a clinically heterogeneous condition and guselkumab 8-weekly and 4-weekly regimens offer benefits for arthritis symptoms, psoriasis, enthesitis and dactylitis, as well as

axial manifestations of the disease. Importantly, guselkumab also improves physical function and physical components of HR-QOL in patients with psoriatic arthritis [20, 21]. Patients with psoriatic arthritis typically report reduced HR-QOL relative to the general population [33], with contributing factors including the psychosocial burden, impaired physical function and comorbidities associated with the condition [34]. Guselkumab provides durable clinical benefits based on results through two years of treatment in clinical trials [23, 30].

Guselkumab is currently the only selective IL-23 inhibitor approved for use in patients with psoriatic arthritis [35]. In patients with psoriasis, the selective blockade of IL-23 appears to be more effective than combined blockade of IL-12/23, with fewer risks [35]. Like that of many other therapies approved for use in psoriatic arthritis, the efficacy of guselkumab in this indication was established in placebo-controlled trials and head-to-head comparisons with active treatments are currently lacking. Systemic reviews and network meta-analyses suggest that guselkumab is generally comparable to most other targeted treatments for psoriatic arthritis with respect to improvements in arthritis, soft tissue damage and physical function, as well as with respect to safety outcomes [36, 37]. Guselkumab may provide greater improvements in psoriasis than some targeted psoriatic arthritis treatments [36, 37], although the results of such indirect comparisons must be interpreted with caution. The 2019 EULAR recommendations for the management of psoriatic arthritis precede the approval of guselkumab, but suggest that a biologic DMARD should be commenced in patients with peripheral arthritis and an inadequate response to ≥ 1 conventional synthetic DMARD (and be considered in certain settings in patients with unequivocal enthesitis or predominantly axial disease) [9]. In patients who respond inadequately to (or are intolerant of) a biologic DMARD, switching to another biologic DMARD or targeted synthetic DMARD should be considered [9]. Well-designed clinical trials directly comparing the efficacy, tolerability and cost-effectiveness of guselkumab with those of other biologic DMARDs are needed to further elucidate the relative position of guselkumab in the treatment of psoriatic arthritis.

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