Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2360

guselkumab 100mg solution for injection in pre-filled pen or syringe (Tremfya®)

Janssen-Cilag Ltd

09 July 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

guselkumab (Tremfya®) is accepted for restricted use within NHSScotland.

Indication under review: alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

SMC restriction: (i) patients whose disease has not responded adequately or who have been intolerant to two previous conventional disease-modifying antirheumatic drug (DMARD) therapies but have not received biologic DMARD therapy (biologic-naïve population); (ii) patients whose disease has not responded adequately to conventional DMARDs and one or more tumour necrosis factor (TNF) inhibitors (biologic-experienced population); and (iii) patients in whom TNF inhibitors are contraindicated or not tolerated.

Three phase III studies demonstrated superiority of guselkumab when compared with placebo in reducing signs and symptoms of psoriatic arthritis in patients who had not previously received a tumour necrosis factor (TNF) inhibitor medication and in those with an inadequate response or intolerance to TNF inhibitors.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

Alone or in combination with methotrexate (MTX), for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.[1]

Dosing Information

The recommended dose of guselkumab is 100mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered.

Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.

Guselkumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriatic arthritis. See Summary of Product Characteristics (SPC) for more details.[1]

Product availability date

20 November 2020

Summary of evidence on comparative efficacy

Guselkumab is a human monoclonal antibody that binds selectively to the interleukin 23 (IL-23) protein with high specificity and affinity. Guselkumab exerts clinical effects in plaque psoriasis and psoriatic arthritis through blockade of the IL-23 cytokine pathway.[1]

The submitting company has proposed that guselkumab be considered in the following three subpopulations of patients with psoriatic arthritis:

- patients whose disease has not responded adequately or who have been intolerant to two previous conventional disease-modifying antirheumatic drug (DMARD) therapies but have not received biologic DMARD therapy (biologic-naïve population).
- patients whose disease has not responded adequately to conventional DMARDs and one or more tumour necrosis factor (TNF) inhibitors (biologic-experienced population).
- patients in whom TNF inhibitors are contraindicated or not tolerated.

DISCOVER-1 and DISCOVER-2 are multicentre, randomised, double-blind, phase III studies which evaluated the efficacy and safety of guselkumab compared with placebo in 1,122 patients with active psoriatic arthritis. Adult patients with active psoriatic arthritis were required to have had inadequate response to standard therapies (for example conventional DMARDs, apremilast or non-steroidal anti-inflammatory drugs [NSAIDs]). Up to 30% of DISCOVER-1 were permitted to have been previously exposed to up to 2 TNF inhibitors whilst patients in DISCOVER-2 were biologic naïve. Other key inclusion criteria included diagnosis with psoriatic arthritis for at least 6

months prior to the study, classification criteria for psoriatic arthritis at screening, ≥3 tender and ≥3 swollen joints (≥5 tender and ≥5 swollen joints in DISCOVER-2) at both screening and baseline, c-reactive protein (CRP) level ≥0.3mg/dL (DISCOVER-1) or CRP ≥0.6mg/dL (DISCOVER-2) at screening, at least 1 of the psoriatic arthritis subsets: distal interphalangeal (DIP) joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis, and either active plaque psoriasis or documented history of plaque psoriasis.[2, 3]

Patients were randomised equally to receive guselkumab 100mg subcutaneously (SC) every 4 weeks (DISCOVER-1 n= 128; DISCOVER-2 n= 245), guselkumab SC 100mg at week 0, week 4, and then every 8 weeks (DISCOVER-1 n= 128; DISCOVER-2 n= 248), or placebo (DISCOVER-1 n= 126; DISCOVER-2 n= 246). Double-blind treatment continued from week 0 to week 24, followed by an active treatment period from week 24 to week 52 in DISCOVER-1 and until week 100 in DISCOVER-2 where placebo patients crossed over to receive guselkumab. Patients were allowed to continue stable doses of methotrexate, low-dose oral corticosteroid, or NSAIDs and other analgesics during the study.[2-4]

The primary outcome was the proportion of patients with an American College of Rheumatology 20% improvement (ACR20) response at week 24. The ACR joint count documents the number of joints with joint-line tenderness, stress pain, and/or swelling. Efficacy analyses up to week 24 included all randomly assigned patients who received at least one dose of study drug, analysed by assigned treatment group (Full Analysis Set). Key secondary outcomes for both studies were controlled for multiplicity via a hierarchical testing strategy.[2, 3]

Both DISCOVER-1 and 2 met their primary outcome: significantly greater proportions of patients achieved an ACR20 response at week 24 in the guselkumab every 4 weeks group and guselkumab every 8 weeks group compared with placebo. Secondary outcomes measuring improvement in signs and symptoms of psoriatic arthritis, improvements in skin disease, and improvement in physical function were also supportive (Table 1). Efficacy with guselkumab (both doses) was maintained up to week 52 for outcomes such as ACR20/50/70 and Health Assessment Questionnaire-Disability Index (HAQ-DI).[5, 6]

Table 1. Primary and selected key secondary results at week 24 for DISCOVER-1 and DISCOVER-2 (Full Analysis Set).[4]

	DISCOVER-1			DISCOVER-2		
	Guselkumab 100mg every 4 weeks (n=128)	**Guselkumab 100mg every 8 weeks (n=127)**	**Placebo (n=126)**	**Guselkumab 100mg every 4 weeks (n=245)**	**Guselkumab 100mg every 8 weeks (n=248)**	**Placebo (n=246)**
Improvement in signs and symptoms of psoriatic arthritis						
ACR20	59%[a]	52%[a]	22%	64%[a]	64%[a]	33%
ACR50	60%[b]	30%[b]	8.7%	33%	32%	14%
ACR70	20%[b]	12%	5.6%	13%	18%	4.1%

DAS28-CRP (mean change from baseline)	-1.61[b]	-1.43[b]	-0.70	-1.62	-1.59[b]	-0.97[b]
PsARC	73%	60%	31%	69%	73%	45%
Improvement in skin disease						
	n=89*	n=82*	n=78*	n=184*	n=176*	n=183*
IGA	75%[b]	57%[b]	15%	68%	70%[b]	19%[b]
PASI75	86%	76%	14%	78%	79%	23%
Improvement in physical function						
HAQ-DI (mean change from baseline)	-0.37	-0.32	-0.09	-0.41	-0.39	-0.16
Impact on Structural Damage						
Total modified vdH-S Score (mean change from baseline)	-	-	-	0.29	0.52	0.95

[a] p<0.001 (primary outcome)

[b] p<0.001 (multiplicity-controlled secondary outcome)

*Full Analysis Set but in patients with ≥3% Body Surface Area (BSA) of psoriatic involvement and an IGA score ≥2 (mild) at baseline. ACR20 = American College of Rheumatology 20% improvement response; ACR50 = American College of Rheumatology 50% improvement response; ACR70 = American College of Rheumatology 70% improvement response; DAS28-CRP= 28 joint Disease Activity Score using CRP; HAQ-DI= Health Assessment Questionnaire-Disability Index; IGA= Investigator's Global Assessment of Psoriasis response, defined as IGA score of 0 (cleared) or 1 (minimal), and ≥ 2 grade reduction from baseline; PASI75= at least a 75% improvement in Psoriasis Area and Severity Index (PASI).

Subgroup analyses were conducted to assess efficacy of guselkumab by prior and baseline medication use for the primary outcome, ACR20 at week 24. The subgroups that most closely reflect the proposed positioning (prior TNF inhibitor: yes or no and number of prior conventional DMARDs: 2 or ≥3 [DISCOVER-2]) were consistent with the primary findings. Prior TNF inhibitor exposure did not appear to affect ACR20 response with guselkumab. Secondary outcomes such as ACR50/70 and PASI75/90 were also evaluated post-hoc in the same subgroups and were supportive of treatment with guselkumab over placebo.[4]

Health Related Quality of Life (HRQoL) was assessed using the 36-Item Short Form Health Survey and the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) questionnaire. HAQ-DI results have been reported above in Table 1. For SF-36 PCS and FACIT Fatigue, results favoured both guselkumab regimens over placebo at week 24. EuroQol-five dimension (EQ-5D) was also assessed in DISCOVER-2 and results were supportive of guselkumab over placebo.[4, 6]

COSMOS is a phase IIIb, multicentre, randomised, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of guselkumab 100mg 8-weekly in a subpopulation of patients with psoriatic arthritis who are inadequate responders to TNF inhibitor. Patients were required to have ≥3 tender and ≥3 swollen joints and an inadequate response or intolerance to TNF inhibitor therapy, defined as the presence of active psoriatic arthritis (as assessed by the investigator) despite previous treatment with either 1 or 2 TNF inhibitors.[7]

Patients were randomly assigned in a 2:1 ratio to guselkumab SC 100mg administered at weeks 0 and 4 and then every 8 weeks (Weeks 12, 20, 28, 36) through Week 44, or placebo. The primary outcome was the proportion of participants who achieve an ACR20 response at week 24. Key secondary outcomes were assessed within the following hierarchical order: change from baseline in HAQ-DI score at week 24, proportion of patients who achieved an ACR50 response at week 24, change from baseline in SF-36 PCS score at week 24, proportion of patients who achieve PASI100 response at week 24 among participants with ≥3% body surface area psoriatic involvement and an IGA score of ≥2 (mild) at baseline.[7]

A significantly greater proportion of patients achieved an ACR20 response at week 24 in the guselkumab every 8 weeks group compared with placebo. All four key secondary outcomes evaluated at week 24 achieved statistical significance.[7] Results are presented in Table 2.

Table 2. Primary and selected secondary outcome results for COSMOS at week 24 (Full Analysis Set).[7]

	Guselkumab 100mg 8-weekly (n=189)	Placebo (n=96)
ACR20	44%[a]	20%
ACR50	20%[b]	5.2%
PASI100	31%[b]	3.8%
HAQ-DI score (LS mean change from baseline)	-0.178[b]	-0.009
Enthesitis resolution	40%	19%
Dactylitis resolution	45%	25%
SF-36 PCS (LS mean change from baseline)	3.51[b]	-0.39

[a] p<0.001 (primary outcome)

[b] p<0.01 (multiplicity-controlled secondary outcome)

ACR = American College of Rheumatology; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS mean = least squares mean; MDA = minimal disease activity; PASI = psoriasis area and severity index; PsARC = psoriatic arthritis response criteria.

The submitting company presented three Bayesian Network Meta-analyses (NMAs) of 26 studies that compared the efficacy and safety of guselkumab, via best supportive care (BSC) as the common comparator, with TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab; interleukin inhibitors: ixekizumab, secukinumab, ustekinumab; the phosphodiesterase-4 inhibitor (PDE4i) apremilast and the Janus kinase (JAK) inhibitor tofacitinib in adult patients with active psoriatic arthritis. The outcomes assessed included ACR 20/50/70 response, PASI 50/75/90/100 response, PsARC response, HAQ-DI, HAQ conditional on PsARC

(reported by both PsARC response and PsARC non-response), adverse events (AE), and serious adverse events (SAEs). The NMAs were conducted separately for each of the three subpopulations outlined by the submitting company: biologic-naïve population, biologic-experienced population, and TNF inhibitor-contraindicated population.

In the biologic-naïve NMA, both doses of guselkumab were superior to apremilast and placebo and had similar efficacy to remaining comparators for ACR20. For PASI75/90/100 outcomes, both doses of guselkumab were superior to all comparators with the exception of ixekizumab (both regimens) and secukinumab 300mg, in which no differences were identified. For PsARC response, guselkumab 4-weekly was superior to adalimumab, ustekinumab 45mg, tofacitinib, apremilast and placebo and no differences were identified with remaining treatments. Similar results were noted for guselkumab 8-weekly for PsARC response, however, unlike guselkumab 4-weekly, was not superior to adalimumab. For AEs, both doses of guselkumab were lower than golimumab, certolizumab pegol and placebo. No differences in AEs were identifed against remaining comparators. The TNF inhibitor-contraindicated population were a subgroup of the biologic-naïve population and results were broadly similar, however, fewer comparators were included in this analysis.

In the biologic-experienced NMA, both doses of guselkumab were superior to placebo and had similar efficacy to remaining comparators for ACR20. For PASI75/90/100, guselkumab 4-weekly was superior to ustekinumab, certolizumab pegol, apremilast, tofacitinib and placebo whilst guselkumab 8-weekly was only superior to apremilast, tofacitinib and placebo. No differences in efficacy were noted for guselkumab against all the remaining treatments. For PsARC response, guselkumab 4-weekly was superior to apremilast and placebo and no differences were identified between guselkumab 8-weekly and all treatments (only superior to placebo). For AEs, no differences were found between guselkumab 4-weekly and all other comparators; guselkumab 8-weekly had a lower incidence of AEs than apremilast and had similar AEs as the remaining comparators.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

Between DISCOVER-1 and 2, 1,100 patients were exposed to guselkumab; 89% had been treated for at least 6 months and 47% had been treated for at least 1 year. Through week 24 in the pooled analysis of both studies, in the guselkumab 4-weekly (n=373), 8-weekly (n=375), and placebo (n=372) groups respectively, at least one adverse event (AE) was reported by 49%, 48% and 47%; serious AE 2.1%, 1.9% and 3.2%; AEs leading to discontinuation 2.1%, 1.3% and 1.9%.[4]

The most frequently reported AEs in patients treated with guselkumab 4-weekly, 8-weekly, and placebo were increase in alanine aminotransferase (ALT) (7.5%, 6.1% and 3.8%), nasopharyngitis (5.1%, 6.9% and 4.6%), increase in aspartate aminotransferase (AST) (3.8%, 6.1% and 2.4%), and upper respiratory tract infection (URTI) (6.2%, 3.5% and 4.6%).[4]

Overall, the EMA concluded that the safety profile of guselkumab in the psoriatic arthritis population was generally comparable to what has previously been observed in the psoriasis population and can be considered well-tolerated. The number of AEs in the guselkumab groups and placebo groups were similar at week 24 and up to one year. Longer-term data will be submitted when available. Respiratory tract infection (very common), transaminases increased (common), and neutrophil count decreased (uncommon) were identified as a new adverse drug reactions for guselkumab and added to the SPC.[4]

Summary of clinical effectiveness issues

Psoriatic arthritis is a chronic inflammatory arthropathy of the peripheral and axial joints associated with psoriasis, which can result in functional disability and impaired quality of life. Treatment for psoriatic arthritis includes NSAIDs (for short-term symptom relief), DMARDs and intra-articular corticosteroid injections, depending on the pattern and severity of the arthritis. Initially, conventional DMARDs such as methotrexate, sulfasalazine and leflunomide are recommended. Biologic DMARDs adalimumab, etanercept, infliximab, golimumab, certolizumab pegol (TNF inhibitors), secukinumab (interleukin [IL]-17a inhibitor), apremilast (phosphodiesterase-4 inhibitor), and tofacitinib (Janus Kinase inhibitor) are recommended for use in patients with psoriatic arthritis in NHSScotland following inadequate response with at least two prior conventional DMARD therapies. The following medicines are accepted for use in NHSScotland in patients with psoriatic arthritis who had an inadequate response to, or are unsuitable for, treatment with a TNF inhibitor: certolizumab pegol, secukinumab, tofacitinib, ustekinumab (biologic DMARD: IL-12/IL-23 inhibitor) and ixekizumab (biologic DMARD: IL-17 inhibitor). Typically patients are offered a TNF inhibitor as the first-line biologic DMARD option, however, when there is relevant skin involvement an IL-17 inhibitor may be preferred. Following failure of a biologic DMARD, switching to an alternative can be considered, including one switch within a class.[4, 8, 9]

The submitting company has requested that SMC considers guselkumab when positioned for use in three patient populations: those whose disease has not responded adequately or who have been intolerant to two previous conventional DMARD therapies but have not received biologic DMARD therapy; those whose disease has not responded adequately to conventional DMARDs and one or more TNF inhibitors; or those in whom TNF inhibitors are contraindicated or not tolerated.

Across three large placebo-controlled phase 3 studies, guselkumab 100mg given either 4-weekly or 8-weekly was associated with significant and clinically meaningful benefits compared with placebo. In all three studies, superiority of guselkumab over placebo was demonstrated for the primary outcome, ACR20 response. In COSMOS (patients with inadequate response to TNF inhibitors) efficacy was less pronounced. Secondary outcomes measuring improvement in signs and symptoms of psoriatic arthritis, improvements in skin disease, improvement in physical function, and quality of life were supportive.

There were some limitations with the evidence presented that should be considered. The double-blind treatment period of DISCOVER-1 and 2 and COSMOS was 24 weeks, a limitation given that psoriatic arthritis is a lifelong condition requiring chronic treatment. Data up to one year suggest maintenance of treatment effect and a tolerable safety profile for guselkumab. Longer-term data are awaited.[2, 3]

The patient population in DISCOVER-1 and 2 may not fully reflect the proposed positioning, due to the relatively small proportion of patients who had previously received two conventional DMARDs. Subgroup analyses of DISCOVER-1 by prior use of TNF inhibitor were based on small groups that may not be representative to patients who have failed TNF due to lack of effect and should be interpreted with caution. Data from COSMOS can be considered more robust and more reflective of the biologic-experienced subpopulation described by the submitting company above. Inclusion criteria of DISCOVER-1 and 2 might reduce the generalisability of findings to individuals presenting with milder systemic inflammation and less active disease. In addition, there are very limited data in the use of guselkumab in patients aged 65 years of age or older.[1-4]

There are no direct data comparing guselkumab with relevant comparators. To address this issue, the submitting company conducted numerous NMAs in different subpopulations. These were associated with the following limitations: there was considerable variation in placebo response for efficacy outcomes across studies; data from mixed populations were included in the biologic-naïve and biologic-experienced outcome networks due to the lack of availability of subgroup data; in the biologic-experienced NMA, data from the phase III COSMOS study which recruited patients who had an inadequate response to TNF inhibitors were excluded; in the biologic-naïve NMA, there was generally no information about the number of previous conventional DMARDs except for three studies; there was heterogeneity with respect to baseline characteristics; confidence intervals for comparisons were in general wide, particularly for the biologic-experienced NMAs, suggesting uncertainty in the results; the NMAs did not assess resolution of enthesitis and dactylitis, as well as long-term outcomes such as effect on joint damage. Due to these limitations, the company's conclusions are uncertain. However, despite the limitations of the NMA, overall it could be concluded that guselkumab is likely to have similar efficacy to comparators.

Clinical experts consulted by SMC felt that the introduction of guselkumab would provide patients with another effective treatment option with a novel mechanism of action relative to other biologic DMARDs currently available. They felt guselkumab would most likely be used following treatment with other biologic DMARDs.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The company submitted cost-utility analyses for the comparison of guselkumab with a range of biologic DMARDs and best supportive care for the treatment of active psoriatic arthritis in three sub-populations of adult patients in the licensed indication. The list of comparators included adalimumab, secukinumab, etanercept, infliximab, golimumab, certolizumab, apremilast and tofacitinib in the biologic-naïve population, secukinumab, certolizumab, tofacitinib, ustekinumab and ixekizumab in the biologic-experienced population and secukinumab, tofacitinib and ustekinumab in the TNF-inhibitor contraindicated population. However, the company presented adalimumab and secukinumab as the most relevant comparators.

Three semi-Markov models were presented, with several health states: treatment-specific trial period, maintenance for responders, up to three subsequent lines of active therapy for non-responders and a final stage of best supportive care for non-responders. Patients could transition to the all-absorbing dead state from any other health state after the end of the trial period. The models incorporated monthly cycles and a 40-year time horizon.

Clinical efficacy data for PsARC response rates, change from baseline in HAQ-DI score and distribution of PASI scores came from a Bayesian NMA in biologic-naïve and biologic-experienced populations but were incorporated as absolute probabilities in the economic model. Equivalent efficacy was assumed in the biologic-naïve and TNF-inhibitor contraindicated populations. All patients received guselkumab or a comparator at the licensed dose for the duration of the treatment-specific trial period of 12 to 24 weeks. Treatment responders entered a maintenance stage and were assumed to discontinue at annual treatment-specific discontinuation rates as observed in the relevant studies included in the NMA.

At baseline, patients were assigned a HAQ-DI and PASI score as observed in the two guselkumab studies (DISCOVER 1 and DISCOVER 2).[2,3] Improvement for responders in both scores was assumed to occur instantaneously and remain constant. Non-responders were assigned the change in HAQ-DI score associated with the next subsequent line of treatment or the score returned to baseline if best supportive care, followed by a constant annual deterioration rate of 0.072 as observed in the Norfolk Arthritis Registry.[10] Patients were assigned the response-dependent and treatment-specific distribution of PASI scores while on treatment or scores reverted to baseline and remained constant if on best supportive care.

In the biologic-naïve and TNF-inhibitor contraindicated populations, one line of active subsequent treatment (ustekinumab) was assumed, whereas only best supportive care was included in the biologic-experienced population following first treatment discontinuation.

Health-related quality of life in the model was incorporated as a function of HAQ-DI and PASI scores consistent with a previously used York algorithm,[11] adjusted for age and sex using standard methodology. Baseline utilities were calculated using the baseline HAQ-DI and PASI scores for each

sub-group based on severity level as observed in DISCOVER 1 and DISCOVER 2. No utility decrements associated with adverse events were included.

Apart from medicine acquisition and administration costs, other costs in the model included fixed costs for resource use associated with routine patient monitoring, including physician visits and laboratory tests. An assumption was made that £207.63 will be spent on resources for the first year of treatment and £15.56 for subsequent years of maintenance. Disease-related costs were included in the model to capture the impact of both arthritis and psoriasis severity on healthcare costs. As such, they were based on absolute HAQ-DI scores and the proportion of patients achieving a PASI 75 response.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a confidential discount was offered on the list price. A PAS discount is also in place for secukinumab, golimumab, certolizumab, apremilast, tofacitinib, ustekinumab and ixekizumab and these were included in the results used for decision-making.

The base case results versus the key comparators are shown in Table 3. The results presented do not take account of the PAS for the comparator medicines or the PAS for guselkumab but these were considered in the results used for decision making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for the comparator medicines due to commercial confidentiality and competition law issues.

Table 3: Base case results: pairwise comparisons vs guselkumab (main comparators): list price for all medicines

Treatment	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
All bio-naïve (TNFi-contraindicated vs secukinumab only)					
Guselkumab Q8W	£182,514	8.402			
Adalimumab	£123,513	7.395	£59,001	1.006	£58,636
Secukinumab	£138,149	7.730	£44,365	0.671	£66,082
All bio-experienced					
Guselkumab Q8W	£161,629	6.734			
Secukinumab 300 mg	£136,184	5.801	£25,445	0.929	£27,389
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years, Q8W, every 8 weeks;					

Base case results were primarily sensitive to assumptions around treatment discontinuation rates and less sensitive to source of utility data, assumptions around HAQ-DI and PASI and using ACR20 for assessment of response as shown in Table 4 below.

Table 4: Selected scenario analyses: pairwise comparisons vs guselkumab (main comparators): list price for all medicines

	Scenario	Comparator	ICER-Bio-naive	ICER – Bio-experienced	ICER – TNFi-contraindicated
1	Equivalent annual treatment discontinuation rate – 16.5% consistent with MTA 445	Adalimumab	£206,639	-	-
		Secukinumab	£1,373,562	£20,610	£1,373,562
2	Using utility data from DISCOVER 2	Adalimumab	£71,695	-	-
		Secukinumab	£80,964	£33,963	£80,964
3	Using ACR20 as response criteria (primary outcome in clinical trials)	Adalimumab	£52,583	-	-
		Secukinumab	£61,332	£29,235	£61,332
4	HAQ-DI and PASI improvement at the end of trial/revering to baseline adjusted for BSC response	Adalimumab	£63,632	-	-
		Secukinumab	£71,575	£29,571	£71,575
5	Secukinumab 150 mg only in bio-naïve/TNFi-contraindicated	Adalimumab	-	-	-
		Secukinumab	£75,794	-	£75,794

A cost-minimisation analysis was also considered by SMC, which assumed equivalent efficacy of guselkumab and comparators in the biologic-experienced population. The results of this analysis with PAS applied indicated guselkumab was a cost-effective treatment option.

Key limitations with the analyses were:

- There is a lack of direct comparative data for guselkumab and any biologic DMARD in the licensed indication. The efficacy data in the economic evaluation came from a Bayesian NMA associated with many uncertainties as discussed in the clinical effectiveness section. A cost-minimization analysis against all comparators where no difference in efficacy (PsARC, change in HAQ-DI and PASI) were found, was requested at clarification stage and was noted as the preferred analysis in the biologic-experienced population by NDC. In this analysis, the efficacy outcomes for comparators were assumed to be equivalent to those for guselkumab.
- There are uncertainties around the long-term treatment duration for guselkumab and other biologic DMARDs. The model incorporated treatment-specific annual discontinuation rates as observed in the relevant studies with guselkumab having the lowest discontinuation rate. This approach is inconsistent with previous appraisals where a treatment agnostic annual discontinuation rate of 16.5% was used, based on European registry data. The assumption of a lower discontinuation rate for guselkumab leads to a QALY gain due to the assumption of maintained HAQ-DI and PASI improvement while on treatment. When this QALY gain is removed by the introduction of equal discontinuation rate for all treatments, the ICER substantially increases (especially vs secukinumab in the bio-naïve population). SMC heard from clinical experts who generally considered the assumption of treatment-specific discontinuation rates not supported by current evidence.
- There are uncertainties regarding the most relevant comparator(s) in the biologic-experienced population. The company presented secukinumab as the most relevant comparator. Clinical experts consulted by SMC generally indicated that TNF inhibitors (mainly adalimumab) or secukinumab are primarily used as first line biologic, followed by secukinumab (if not already used) and ixekizumab and other biologics in no particular order. The experts generally agreed

that guselkumab was expected to be used after a few biologics have failed, indicating that the analyses in the biologic-experienced population were most relevant.

- There are uncertainties associated with the approach to estimating utilities as a function of HAQ-DI and PASI scores using the previously derived York algorithm Using EQ-5D data from DISCOVER 2 leads to an increase in the ICER, primarily due to a lower constant and HAQ-DI coefficient.

Despite these weaknesses, the economic case was demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and The Psoriasis Association. PAPAA is a registered charity and The Psoriasis Association is charitable incorporated organisation.

- PAPAA has not received any pharmaceutical company funding in the past two years. The Psoriasis Association has received 3.9% pharmaceutical company funding in the past two years, including from the submitting company.

- Psoriatic arthritis is a destructive form of arthritis and often affects people in young or mid adulthood. Although the condition affects people differently, as severity increases it can impact on every aspect of people's lives. Symptoms including swollen and painful joints, fatigue, nail psoriasis and an itchy, dry scaly skin, can be painful and disabling and also cause dexterity and mobility issues. Owing to the age of onset of the condition, its effects on the joints, and the unpredictable nature of flare-ups, the impact on work, social life and relationships can be marked. The psychological effect is also an issue.

- There are currently a number of effective therapies for psoriatic arthritis, but given the long-term nature and potential adverse events or treatments beginning to fail, alternate therapies are needed in order to provide patients with options and choice.

- Guselkumab has a novel mechanism of action to current treatments for psoriatic arthritis. This presents opportunities for improved disease control and to give a further treatment option. Guselkumab is given every 8 weeks, allowing for travel and the ability to not be tied to a timetable of therapy. Having a self-administration device that is easy to use is also of great value.

Additional information: guidelines and protocols

The 2010 SIGN guideline for the diagnosis and management of psoriasis and psoriatic arthritis in adults states that treatment for psoriatic arthritis may include NSAIDs (for short-term symptom

relief), DMARDs and intra-articular corticosteroid injections, depending on the pattern and severity of the arthritis. Initially, conventional DMARDs such as methotrexate, sulfasalazine and leflunomide are recommended. The biologic DMARDs adalimumab, etanercept or infliximab are recommended for treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two disease-modifying therapies.[12]

The European League against Rheumatism (EULAR) published updated recommendations in 2019. These comprise five overarching principles and ten recommendations, covering pharmacological therapies for psoriatic arthritis. The overarching principles address the need for shared decision making and treatment objectives, that is, treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy. The recommendations indicate that initially in patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. Conventional DMARDs are recommended as an initial therapy after failure of NSAIDs and local therapy for active disease, followed, if necessary, by a biologic DMARD or a targeted synthetic DMARD. The first biologic DMARD would usually be a TNF inhibitor, however when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred. Biologic DMARDs targeting interleukin (IL)-12/23 (ustekinumab) or IL-17 pathways (secukinumab) may be used in patients for whom TNF inhibitors are inappropriate and a targeted synthetic DMARD such as apremilast, a phosphodiesterase 4- inhibitor, if biologic DMARDs are inappropriate. If the first biologic DMARD strategy fails, any other biologic DMARD or targeted synthetic DMARD may be used.[8]

The 2012 British Society for Rheumatology guidelines are currently under review.

Additional information: comparators

Adalimumab, etanercept, infliximab, golimumab, apremilast, certolizumab pegol, secukinumab, tofacitinib, ustekinumab, and ixekizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year
Guselkumab	**100mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks** **or** **100mg by subcutaneous injection every 4 weeks**	**First year: £18,000** **Subsequent years: £15,750** **£29,250**

Costs from BNF online on 02 May 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 1,420 patients eligible for treatment with guselkumab in year 1 and 2,414 patients in year 5. In addition, it was estimated that there would be 798 bio-experienced patients eligible for treatment in year 1 and 1,358 in year 5. Confidential estimates of treatment uptake were applied to these figures.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

These estimates do not take account of any patient access schemes applied to displaced medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 June 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.