Single Technology Appraisal

Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs [ID4013]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs [ID4013]

This is a rapid review of published guidance TA711 and is for the consideration of a new patient access scheme proposal only.

Contents:

The following documents are made available to consultees and commentators:

1. **Final guidance TA711 - Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs.**

2. **Company rapid review submission** from Janssen

3. **Clarification questions and company responses**

NICE National Institute for Health and Care Excellence

NICE guidance

Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs

Technology appraisal guidance

Published: TBC

www.nice.org.uk/guidance/ta711

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Guselkumab, alone or with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults whose disease has not responded well enough to disease-modifying antirheumatic drugs (DMARDs) or who cannot tolerate them, only if they have:

- peripheral arthritis with 3 or more tender joints and 3 or more swollen joints
- moderate to severe psoriasis (a body surface area of at least 3% affected by plaque psoriasis and a Psoriasis Area and Severity Index [PASI] score greater than 10)
- had 2 conventional DMARDs and at least 1 biological DMARD.

Guselkumab is recommended only if the company provides it according to the commercial arrangement.

1.2 Assess the response to guselkumab from 16 weeks. Stop guselkumab at 24 weeks if psoriatic arthritis has not responded adequately using the Psoriatic Arthritis Response Criteria (PsARC; an adequate response is an improvement in at least 2 of the 4 criteria, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria). If PsARC response does not justify continuing treatment but there is a PASI 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response.

1.3 Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the PsARC, and make any appropriate adjustments.

1.4 Take into account how skin colour could affect the PASI score, and make any appropriate adjustments.

1.5 These recommendations are not intended to affect treatment with guselkumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Guselkumab is a biological DMARD. People with psoriatic arthritis that is not controlled well enough with 2 conventional DMARDs are usually offered biological DMARDs. Many of these are already recommended by NICE for treating psoriatic arthritis.

Clinical evidence shows that guselkumab is effective for active psoriatic arthritis compared with placebo. Guselkumab has not been compared directly with other biological DMARDs for psoriatic arthritis. But the results of an indirect comparison suggest that guselkumab is as effective as the biological DMARDs secukinumab and ixekizumab for the outcomes included in the comparison, and particularly for skin symptoms.

Guselkumab's cost-effectiveness estimates are within what NICE normally considers acceptable for some people with psoriatic arthritis. That is, people who have had 2 conventional DMARDs and at least 1 biological DMARD, and with moderate to severe psoriasis. So guselkumab is recommended for this group.

2 Information about guselkumab

Marketing authorisation indication

2.1 Guselkumab (Tremfya, Janssen), 'alone or in combination with methotrexate, is indicated 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The cost of a 100-mg pre-filled disposable injection of guselkumab is £2,250.00 (excluding VAT; BNF online, accessed February 2021). The company has a commercial arrangement. This makes guselkumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The cost of an hour of nurse time is included in the economic model as a one-off cost when a person begins treatment.
- All monitoring costs should be the same regardless of how the drug is administered and should be consistent with costs used in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab.
- Kobelt et al. (2002) is the preferred source for arthritis-related costs.
- Adverse events should be excluded from the cost-effectiveness model.
- The placebo response-unadjusted network meta-analysis results, in addition to the placebo response-adjusted results, should be considered.

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed issues 3.1 to 3.4, 3.6, 4.1 and 4.2 from the technical report, which were outstanding after the technical engagement stage. The committee also discussed 2 new issues, identified after technical engagement:

- Whether it is reasonable to exclude etanercept from the economic analysis.
- Including a more frequent dose (every 4 weeks) for people identified as being at high risk of joint damage.

Clinical need

Psoriatic arthritis substantially affects health-related quality of life

3.1 The patient and clinical experts explained that active psoriatic arthritis (defined

as 3 or more tender joints and 3 or more swollen joints) is a lifelong condition that seriously affects people's quality of life. It can develop at a young age, and affects a person's education, career, relationships and family life. The patient experts explained that symptoms such as fatigue, pain and associated comorbidities such as inflammatory bowel disorders, cardiovascular disease and diabetes, can have a substantial physical and psychological effect. The clinical and patient experts explained that psoriatic arthritis symptoms range from mild, non-destructive disease to erosive and deforming arthritis that substantially affects daily life. Symptoms can include swollen fingers and toes, inflammation of larger joints such as elbows, knees, and back, and tendonitis. Skin and nail psoriasis also affect quality of life. The committee concluded that active psoriatic arthritis substantially affects health-related quality of life.

Clinical management

Clinicians and people with psoriatic arthritis would welcome additional biological treatments that target different inflammation pathways

3.2 The clinical experts explained that treatment for active psoriatic arthritis aims to control joint and connective tissue inflammation. This prevents joint damage progressing and the associated pain and disability. People will usually have treatment with non-steroidal anti-inflammatory drugs, corticosteroids and conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate. In line with NICE's technology appraisal guidance on etanercept, infliximab and adalimumab, people are eligible for biological or small molecule treatments if their disease is poorly controlled after 2 conventional DMARDs. Biological or small molecule treatments include:

- tumour necrosis factor inhibitors such as etanercept and adalimumab
- interleukin (IL) inhibitor treatments such as secukinumab and ixekizumab (IL-17A inhibitors) and ustekinumab (IL-12 and IL-23 inhibitor)
- tofacitinib

- apremilast.

The clinical experts explained that psoriatic arthritis is unpredictable and can flare and change over time. Sometimes it responds to the first conventional DMARD, or to a second or third, or it may not respond at all. The clinical experts highlighted that because flares and periods of disease remission are common, the treatment pathway varies. After conventional DMARDs, people often switch among the different tumour necrosis factor inhibitors, or to different interleukin inhibitors (ustekinumab, secukinumab and ixekizumab) or to tofacitinib. People with psoriatic arthritis would benefit from an additional class of treatment targeting a different inflammatory mediator if:

- their disease has not responded (or has stopped responding) to DMARDs and other biologicals or small molecules **or**
- they need to stop their previous treatment because of side effects.

Guselkumab is the first monoclonal antibody specifically targeting IL-23 to be considered by NICE for use in psoriatic arthritis. The committee concluded that people with psoriatic arthritis and clinicians would welcome a further treatment option.

Clinical evidence

Guselkumab is clinically effective compared with placebo

3.3 The efficacy and safety evidence for guselkumab in psoriatic arthritis comes from 2 pivotal trials, DISCOVER-1 and DISCOVER-2. These trials randomised people to have 100 mg guselkumab every 8 weeks or every 4 weeks, or to have placebo. The guselkumab trial arms both showed statistically significant and clinically important benefits compared with placebo on disease activity, joint and skin symptoms, functional capacity and health-related quality of life. Guselkumab met the primary endpoint; a higher proportion of people had an American College of Rheumatology (ACR) 20 response compared with placebo at 24 weeks in both trials. The committee noted that the 4-weekly dose of guselkumab was potentially relevant for a subgroup considered to be at high risk of joint damage (see section 3.15). But both doses were assessed in the full trial populations. The committee concluded that both doses of guselkumab were clinically effective compared with placebo across a range of clinically important outcomes.

The populations in the clinical trials are broadly generalisable to NHS clinical practice and are appropriate for decision making

3.4 In its submission, the company assumed that the baseline characteristics of people in the DISCOVER trials reflected those of people seen in NHS clinical practice. The ERG explained that the DISCOVER trials did not include people from the UK. The trials recruited mainly from eastern Europe, where local health systems may have different treatment provision for psoriatic arthritis. The ERG had concerns about the generalisability of the results of the trials because of key differences in the populations compared with populations in the NHS. The company submission identified 4 subgroups and included analyses for:

- people whose disease is not adequately controlled by 2 conventional DMARDs but who have not had a biological DMARD
- people whose disease is not adequately controlled by 2 conventional DMARDs or by at least 1 biological DMARD

- people whose disease is not adequately controlled by 2 conventional DMARDs, and tumour necrosis factor inhibitors (class of biological DMARD) are contraindicated.

The clinical experts confirmed the ERG's view that guselkumab was unlikely to be used as the first-line biological treatment in the NHS. So, in clinical practice a high proportion of people would have had another biological treatment before starting guselkumab. The proportion of people in the trials who had previously had a biological treatment (31% in DISCOVER-1, 0% in DISCOVER-2) did not therefore reflect NHS clinical practice. The ERG further explained that in the trials less than a third of people had 2 or more conventional DMARDs before. Also, just under 10% of people had no conventional DMARD before. Because NICE recommends that biological DMARDs are offered after 2 conventional DMARDs have been tried (see section 3.2), this further limits the applicability of the trials to the NHS. Another generalisability concern was the baseline Psoriasis Area and Severity Index (PASI) scores of people in the trials. The clinical experts agreed with the ERG that these were high and it was rare to see people with psoriatic arthritis with PASI scores above 5 in the NHS. Because less than a third of people had 2 conventional DMARDs before starting the DISCOVER trials, it was reasonable to expect that the level of disease at baseline was higher. The committee recalled that in previous NICE psoriatic arthritis technology appraisals, clinical experts considered that trial PASI scores were higher than would be seen in clinical practice. The clinical experts confirmed that the populations in the trials and in the NHS were different in terms of prior treatments and disease severity at baseline. But they advised that because psoriatic arthritis is unpredictable and the available treatments do not cure it, both populations represented people with active disease. The committee agreed that:

- there were differences between the trial populations and people with psoriatic arthritis seen in NHS clinical practice
- the trial populations were broadly similar to those in comparator trials in the network meta-analyses, and to those in previous NICE psoriatic arthritis technology appraisals.

The committee concluded that although there were differences between the populations in the trials and in the NHS, the evidence from the DISCOVER trials was broadly appropriate for decision making.

The low discontinuation rates in DISCOVER-1 and DISCOVER-2 are not likely to be seen in the NHS

3.5 Discontinuation rates for the 4-weekly dose in the pivotal trials were between 2.3% (DISCOVER-1) and 3.7% (DISCOVER-2). In its submission, the company said these low rates were evidence of guselkumab's sustained efficacy, safety and tolerability. The committee recalled the ERG's and clinical experts' opinion about the differences between the trial populations and the people who would have treatment in NHS clinical practice (see section 3.4). The baseline characteristics suggested that people in the countries participating in the trials, mostly eastern Europe, had limited access to the range of treatments available in the NHS. The clinical experts explained that the low discontinuation rates in the trials, including in the placebo groups, might reflect this overall lack of access to other treatments. They added that trial discontinuation rates often do not translate into the actual rates seen in clinical practice. In the UK, people whose disease is not controlled would be expected to move quickly to another active treatment. The ERG considered that the company's justification for guselkumab's very low discontinuation rates was not robust. The ERG felt that the company had not shown an underlying biological mechanism for these low rates. The ERG rejected the company's claim that the low discontinuation rates for guselkumab (and ustekinumab) may partly be because of better skin response with these biological treatments. This was because people with psoriatic arthritis mainly have biological DMARDs to control joint disease rather than psoriasis, which tends to be less severe. Also, most studies used to inform the treatment-specific discontinuation rates for guselkumab and the comparators did not report treatment stopping rules in the maintenance period. So, it was possible that people in these trials continued treatment beyond the loss of sustained response. This would therefore not reflect the rate seen in clinical practice, where stopping rules would ensure that people did not remain on treatments that were not adequately controlling their disease. The committee agreed with the clinical experts and ERG that the trial populations and the NHS population were not similar. It also agreed about the uncertainties in the evidence base supporting the use of treatment-specific discontinuation rates. The committee concluded that the low discontinuation rates for guselkumab in DISCOVER-1 and DISCOVER-2 were not likely to be the same in the NHS.

Early escape in the guselkumab trials results in bias

3.6 'Early escape' to another treatment is common in clinical trials and stops people staying on a treatment if they have uncontrolled disease. The clinical experts explained that it is important for ensuring people remain in trials, which improves the generalisability of the data. The company had opted to treat early escape as non-response (that is, no change from baseline) in the final analysis at 24 weeks. The ERG explained that early escape, as with treatment switching, always results in the potential for bias. Treating early escape as non-response potentially overestimates the benefit of active treatments because most early escape is expected to be in the placebo arm of trials. Early escape was only allowed after 16 weeks in the DISCOVER trials. The ERG explained that the trial investigators did not have to tell people that they had qualified for early escape. Of those who were eligible, most were in the placebo arms, and less than 50% escaped to another treatment, but the reasons for this were unclear. The ERG explained that it did not agree with the company's method of dealing with early escape in the trials and suggested an assessment time of 16 weeks. This would mean that the data would be free of bias caused by early escape. The company reanalysed the network meta-analyses using guselkumab outcomes assessed at 16 weeks in response to the ERG's request. Also, the ERG did an exploratory analysis to assess the effect on treatment cost at first line of treatment for a 16-week stopping rule. The ERG preferred an alternative approach, to include the full observed response of people who escaped early to another treatment. This would also introduce bias by assigning the benefits of an active treatment to placebo. In contrast to the company's preferred approach, this approach would potentially underestimate guselkumab's benefit and would therefore be a more conservative analysis. The company did not consider that either of the ERG's approaches were appropriate. The company claimed that guselkumab's mechanism of action meant that it continued to be effective, particularly in measures of skin response such as PASI scores, between 16 and 24 weeks. To limit analysis to 16 weeks would therefore not represent guselkumab's full benefits. Also, the company claimed that assigning guselkumab's benefits to people in the placebo arm by using the full observed response data from people who escaped early would be clinically implausible. The committee agreed with the ERG that the arguments supporting guselkumab's unique mechanism of action were not convincing and more robust evidence would be needed. The committee agreed that early escape would introduce bias for the 24-week analysis, whether it was treated as non-response or the full observed response

was used. The committee noted that analysing the DISCOVER trials at 16 weeks only and including the outcome data for early escape at 24 weeks reduced guselkumab's effectiveness relative to placebo. However, the company's preferred approach may have overestimated guselkumab's benefit. The committee concluded that early escape resulted in bias, and it would consider all approaches in its decision making.

The assessment time of 24 weeks is appropriate, but clinicians would value the option of assessing response at 16 weeks

3.7 Guselkumab's summary of product characteristics states that consideration should be given to stopping treatment when disease has not responded after 24 weeks of treatment. The patient experts explained that they welcomed the prospect of a new biological treatment that works on an additional inflammation pathway. But they also explained that people with psoriatic arthritis are frequently frustrated by having ineffective treatments, and that irreversible joint damage can occur very quickly. Many people would therefore find it difficult to accept waiting for 24 weeks to have clinical benefit assessed. The clinical experts commented that a 24-week assessment time for guselkumab was much longer than the 12- to 16-week assessment times for other biological DMARDs. They noted that continued response beyond 12 to 16 weeks had also been seen for other biological DMARDs and small molecules. The clinical experts would welcome the option to assess response at 16 weeks, to help decide whether to switch treatment or intervene with salvage treatment. The ERG explained that it was not convinced that the evidence for guselkumab's unique mechanism of action would justify waiting until 24 weeks to assess response. It noted that the maximum Psoriatic Arthritis Response Criteria (PsARC), Health Assessment Questionnaire-Disability Index (HAQ-DI) and ACR 50 responses were recorded at week 20 in the DISCOVER trials. The ERG further explained that the company's economic model could misrepresent the quality-adjusted life-year (QALY) gains associated with an improved PASI response from 16 to 24 weeks. Therefore, the model was not suitable to explore the full effect on outcomes of using a 16-week stopping rule for guselkumab. Also, the ERG explained that it was uncertain whether an improved PASI response from 16 to 24 weeks on guselkumab was confounded by the bias potentially introduced by allowing early escape in the DISCOVER trials. The committee noted that the assessment time for skin response was 16 weeks, in line with guselkumab's marketing authorisation for moderate to severe

psoriasis. The committee agreed with the ERG that the evidence for further improvement in joint disease between 16 and 24 weeks was limited. But it noted that 24 weeks was the assessment time in the summary of product characteristics. The committee concluded, however, that clinicians would value the option of assessing response at 16 weeks.

Clinicians would value the option to continue treatment based on a PASI 75 response

3.8 Continuing guselkumab treatment depends on whether a person has a PsARC response. The ERG explored the possibility of continuing treatment when the PsARC response does not justify continuing but there is a PASI 75 response. The ERG explained that this was particularly relevant for guselkumab, which is likely to produce a comparable PsARC response to other biological DMARDs, but has the highest PASI 75 response. The clinical experts explained that if a person with psoriatic arthritis and mild psoriasis did not have an adequate PsARC response, it would not be appropriate to continue guselkumab only because of a 75% reduction in their mild psoriasis. But the decision could be different for people with moderate to severe psoriasis, which can severely affect quality of life. The committee recalled the patient expert statement that for some people with psoriatic arthritis, psoriasis symptoms in skin and nails can be hugely debilitating (see section 3.1). The patient experts also explained that the person's needs must be considered. For some people, skin and nail psoriasis symptoms can have a greater effect on quality of life than joint symptoms. The clinical experts explained that if there is only a partial PsARC response, but the person has a PASI 75 response for psoriasis that has affected their quality of life, then it may be appropriate to continue treatment while that clinical benefit lasts. Some people in this situation will continue to have slow incremental improvement in their joints over time. Clinical judgement is therefore important in deciding when to continue treatment without a full PsARC response. The clinical experts explained that about 10% to 15% of people with psoriatic arthritis present with moderate to severe psoriasis so this only affects a minority who would have guselkumab. The committee concluded that, when improvement in psoriasis symptoms benefits quality of life but there is only a partial PsARC response, clinicians would value the option to continue treatment based on a PASI 75 response.

Network meta-analyses

The results of the network meta-analyses are uncertain

3.9 To evaluate guselkumab's effectiveness compared with comparator treatments, the company did network meta-analyses for all main outcomes, for:

- people who have not had a biological DMARD

- people who have had a biological DMARD.

  The analysis for people for whom tumour necrosis factor inhibitors were contraindicated was handled by removing these treatments from the analyses for people who have not had a biological DMARD before. The committee noted that all included trials were mainly comparisons with placebo, with few head-to-head comparisons of active treatments. Also, most treatments were examined either in a single trial, or a set of closely related trials from the company making the drug. For the population who have not had a biological DMARD before, guselkumab was likely the best treatment for skin symptoms, based on PASI score. But it had more modest results for other outcomes and was generally ranked inferior to tumour necrosis factor inhibitors, and similar to secukinumab or ixekizumab. For the population who have had a biological DMARD before, guselkumab generally ranked better in these analyses, because tumour necrosis factor inhibitors were excluded. But the limited data meant that few comparisons (except with placebo) were conclusive. For the people for whom tumour necrosis factor inhibitors were contraindicated, guselkumab was the best treatment for PASI outcomes, but not clearly better than secukinumab or ixekizumab. The ERG explained that its main concern with the company's network meta-analyses was that they combined outcomes measured at different times. Comparing outcomes assessed at 24 weeks for guselkumab with outcomes assessed at 16 weeks (or earlier) for other treatments may unfairly bias results in favour of guselkumab. The ERG explained that because of the limited data, most differences in effectiveness across treatments were not conclusive. Also, the network meta-analyses results should be taken as evidence of how guselkumab broadly compares with other treatments, rather than as a robust ranking of treatments. The committee agreed with the ERG that guselkumab appeared to be very similar in effectiveness to other interleukin inhibitors (secukinumab and ixekizumab) for the endpoints included in the indirect comparison. All 3 interleukin inhibitors were ranked higher than tumour necrosis factor inhibitors for PASI outcomes, but lower on ACR and PsARC outcomes. The committee concluded that the results of the network meta-analyses showed treatment class effects, but the specific treatment rankings were uncertain.

Economic model

The model does not reflect NHS clinical practice but is appropriate for decision making

3.10 The committee noted that the company's model was based on that used in

NICE's technology appraisal guidance on certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Using a Markov structure to capture all costs and outcomes associated with guselkumab and the comparators, the model included up to 3 lines of active treatment before best supportive care. The company stated that this structure was intended to reflect current treatment, where multiple lines of targeted treatment are common. The ERG confirmed that this structure was consistent with previous models used in NICE technology appraisals for psoriatic arthritis. But, using a limited number of active treatment lines does not represent NHS clinical practice. The clinical experts agreed with the ERG that because of the range of treatments and because the disease is varied and unpredictable, there is no standard treatment sequence in the NHS. People will almost always start treatment with conventional DMARDs such as methotrexate, and then move onto biological DMARDs if their disease is not adequately controlled. But the exact sequence of treatments is determined by the course of the disease for each person. The committee recalled that people often switch between different biological treatments (see section 3.2). The clinical experts explained that the sequencing of biological treatments is often a mix of clinical and economic considerations. Also, there is no pathway of treatments that would suit everyone. The committee concluded that the model was limited in how much it represents clinical practice. But the committee agreed that it was consistent with previous NICE technology appraisals for psoriatic arthritis and was therefore suitable for decision making.

A 16.5% discontinuation rate should be used for all biological treatments in the economic model

3.11 The committee recalled the low discontinuation rates in DISCOVER-1 and DISCOVER-2, and the ERG and clinical experts' reasons why these may not be seen in NHS clinical practice (see section 3.5). It noted that in psoriatic arthritis appraisals since NICE's technology appraisal guidance on etanercept, infliximab and adalimumab, a 16.5% treatment discontinuation rate had been used for all biological treatments. The ERG explained that the treatment-specific discontinuation rates used in the company's base case were the largest driver of cost effectiveness. The ERG reiterated that the evidence supporting these different treatment-specific discontinuation rates was not robust. But it noted that even if it were, it was not appropriate to use these rates in the economic model. The ERG explained that the company's economic model allowed up to

3 lines of active treatment before people moved to best supportive care (see section 3.10). It noted that this had implications for using treatment-specific discontinuation rates. The clinical experts agreed with the ERG that people often switched between different tumour necrosis factor inhibitors, and to different interleukin inhibitors (ustekinumab, secukinumab and ixekizumab) or to tofacitinib. They also agreed that 16.5% was an appropriate discontinuation rate to use in the model to ensure consistency with other psoriatic arthritis technology appraisals. The ERG explained that in the company's model, people remained on treatment with best supportive care for an implausibly long time. Therefore considerable costs accrue and people's health-related quality of life declines, as their condition deteriorates. Treatment-specific discontinuation rates should only be used when the appropriate range of treatment sequences reflecting the full duration of disease are modelled. Because this was not possible in the company's model, using treatment-specific discontinuation rates introduced bias by inaccurately characterising total costs and QALYs for treatments associated with further lines of active treatment. In its response to technical engagement, the company disagreed with the ERG that treatment-specific discontinuation rates in the model could potentially bias in favour of longer-acting treatments like guselkumab. The company maintained that the additional time spent on guselkumab relative to other treatments before moving to best supportive care represented a real clinical benefit of guselkumab. The ERG further explained that by restricting the number of lines of treatment, the company's model was overly optimistic in quantifying the benefits of 'displacing' best supportive care. This was because it assumed that this occurred earlier than expected in clinical practice. It also assumed that the displaced strategy would be best supportive care rather than another more cost-effective active treatment. The committee agreed that because the model could not accurately portray the range of treatment sequences used in clinical practice, using a 16.5% discontinuation rate for all treatments would offset the risk of bias in the economic model. It would also ensure consistency with other psoriatic arthritis technology appraisals. The committee therefore concluded that a 16.5% discontinuation rate should be used for all treatments in the economic model.

The cost-effectiveness results are considered by psoriasis severity

3.12 The baseline PASI scores for people in the DISCOVER trials were high compared

with those in people having NHS treatment (see section 3.4). The clinical experts explained that only a small proportion of people (10% to 15% of people with psoriatic arthritis; see section 3.8) present with moderate to severe psoriasis symptoms. The committee was aware that in previous psoriatic arthritis appraisals, results were presented by psoriasis subgroup. The ERG considered that this approach was appropriate. It did cost-effectiveness analyses by psoriasis severity using data from the DISCOVER trials. Because guselkumab and the comparators have commercial arrangements, the exact incremental cost-effectiveness ratios (ICERs) are confidential and cannot be reported. However, the committee concluded that the cost-effectiveness results were sensitive to psoriasis severity and would be considered on this basis.

Pairwise analysis comparing guselkumab with best supportive care and net health benefit are considered

3.13 At consultation, the company noted that fully incremental analyses are uncertain when incremental costs and QALYs are small. Therefore it suggested that the committee should also consider pairwise analysis comparing guselkumab with best supportive care, which would be consistent with previous psoriatic arthritis appraisals. The ERG explained that a fully incremental analysis provides the most meaningful comparison when multiple alternative treatments are being evaluated. But pairwise comparisons assume that there are no other treatments available in the health system. A pairwise comparison of guselkumab with best supportive care would also be inconsistent with the modelled treatment options for:

- people who have not had biologicals before **and**

- people for whom tumour necrosis factor inhibitors are contraindicated.

This is when a second line of treatment is considered after guselkumab and before people move to best supportive care. The ERG suggested that calculating net health benefit of the alternative treatments would be a more appropriate way to deal with concerns about uncertainty in the fully incremental analyses. The committee agreed with the ERG that a fully incremental analysis was the most meaningful comparison. It noted that the differences in incremental costs and QALYs were not as small as in previous appraisals where pairwise analyses had been considered. Nevertheless, in addition to the preferred fully incremental analyses, the committee agreed to consider net health benefit and the pairwise comparisons of guselkumab with best supportive care.

Results of the comparison with etanercept should be included in the fully incremental analysis

3.14 Etanercept was included as a comparator in the scope because NICE recommends it for psoriatic arthritis, and it is commonly used in UK clinical practice (see section 3.2). After technical engagement, the company asked whether etanercept should be excluded as a comparator in the cost-effectiveness analysis because its market share was small. Also, in NICE's technology appraisal guidance on tofacitinib for treating active psoriatic arthritis, the committee decided that comparisons with best supportive care were more reliable than the fully incremental analysis. The ERG explained that both pairwise and fully incremental analyses were included in that appraisal, but pairwise comparisons with best supportive care were considered appropriate. This was because the fully incremental analyses were very sensitive to small differences in the estimates of costs and QALYs, given that total costs and QALYs were similar across all active treatments. The ERG explained that the company also raised several concerns about the clinical data supporting etanercept's effectiveness, but did not provide clear evidence of bias in favour of etanercept. The committee noted that etanercept was a comparator in previous psoriatic arthritis appraisals and agreed that there was no case to support excluding it from the comparison. The committee concluded that the results of the comparison with etanercept should be included in the fully incremental analysis.

It is unclear if there are additional benefits from the 4-weekly

dose compared with the 8-weekly dose

3.15 The committee recalled that guselkumab's 2 pivotal trials in psoriatic arthritis, DISCOVER-1 and DISCOVER-2, randomised people to 100 mg guselkumab every 8 weeks or every 4 weeks or to placebo (see section 3.3). The company's submission considered the clinical effectiveness of both the 4-weekly and 8-weekly dose but focused on the 8-weekly dose, which reflected the anticipated marketing authorisation. After technical engagement, the company told NICE that the marketing authorisation would also include a 4-weekly dose for people at high risk of joint damage. The ERG explained that this was difficult to evaluate for several reasons. Firstly, as the company had explained, there was no standard definition among clinicians of 'high risk of joint damage'. Clinical experts had advised the company that any definition was likely to focus on diagnostic criteria such as C-reactive protein (CRP) level and the number of joint erosions at baseline. But they noted that there was currently no agreed definition. The company cited a publication in which the cut-off for a population considered at high risk of joint damage was a CRP level of 2.87 milligrams per decilitre (mg/dL) or more. The ERG considered that this seemed reasonable but agreed with the company that a precise definition was probably not possible, given the accepted variation in clinical judgement. It was not possible to evaluate the cost effectiveness of guselkumab in this high-risk population without knowing its clinical effectiveness for the same group. But the clinical effectiveness of the 4-weekly dose provided by the company was based on its effectiveness in the full trial population, not in a high-risk population. The ERG explained that there was no evidence that effectiveness was different between the 8-weekly and 4-weekly doses after 16 weeks. It therefore considered it reasonable to assume that both doses would also have the same effectiveness for people at high risk of joint damage. The company provided estimates of the proportion of the population at high risk of joint damage who would be expected to be seen in NHS clinical practice. These estimates are commercial in confidence and cannot be reported. The committee agreed with the ERG that this estimated proportion was highly uncertain. At consultation, the company noted that the DISCOVER data showed no statistically significant differences in ACR 20 outcomes between people with CRP less than 2 mg/dL and CRP more than 2 mg/dL. It explained that this was evidence supporting the 4-weekly dose in people with high risk of joint damage. But the ERG noted that in the subgroup who might be at the highest risk of joint damage (people with a CRP of 2 mg/dL or more), there was no evidence that the 4-weekly dose was more effective than

the 8-weekly dose. The committee agreed that it could not reliably evaluate guselkumab's cost effectiveness for people at high risk of joint damage because of the uncertainty in defining the group and in the clinical evidence. However, it concluded that, because any additional clinical benefit was uncertain, the doubled cost of 4-weekly dosing compared with 8-weekly dosing reduced guselkumab's cost effectiveness.

Cost-effectiveness estimates

Guselkumab is cost effective for 1 subgroup

3.16 Because guselkumab and the comparators have commercial arrangements, the exact ICERs are confidential and cannot be reported. The committee's preferred assumptions produced a range of ICERs for guselkumab that were higher than £30,000 per QALY gained in almost all psoriasis severity subgroups for:

- people whose disease is not adequately controlled by 2 conventional DMARDs but who have not had a biological DMARD
- people whose disease is not adequately controlled by 2 conventional DMARDs or by at least 1 biological DMARD

- people whose disease is not adequately controlled by 2 conventional DMARDs and tumour necrosis factor inhibitors are contraindicated.

  Moderate to severe psoriasis is defined as a body surface area of at least 3% affected by plaque psoriasis and a PASI score greater than 10. For people with moderate to severe psoriasis who have had 2 conventional DMARDs and at least 1 biological DMARD, the fully incremental ICER was more than £20,000 per QALY gained but within the range NICE normally considers cost effective. The committee recalled that fully incremental ICERs higher than £20,000 per QALY gained but within the acceptable cost-effectiveness range had been accepted in previous psoriatic arthritis appraisals. The committee also noted that in some previous psoriatic arthritis appraisals, the ICERs were in the south-west quadrant of the cost-effectiveness plane. This meant that the technology was less effective and less costly than its comparator and the usual rule of accepting ICERs below a given threshold was reversed. So, the higher the ICER, the more cost effective a treatment becomes. The committee recalled that when some of these appraisals were done, the only biological treatments available were tumour necrosis factor inhibitors. So, there was a pressing clinical need for treatments with different mechanisms of action at that time. The committee considered these past appraisals, the results of the pairwise analysis with best supportive care and the net health-benefit analysis (see section 3.13) in its decision making. It concluded that guselkumab could be considered cost effective for people who have had 2 conventional DMARDs and at least 1 biological DMARD and have moderate to severe psoriasis.

Conclusion

Guselkumab is recommended for people who have had at least 1 biological DMARD and have moderate to severe psoriasis

3.17 The committee acknowledged the need for further biological treatment options for people with active psoriatic arthritis. It agreed that the ERG's preferred base case by psoriasis severity was suitable for decision making. It took into account all commercial discounts for guselkumab and for other treatments in the pathway. It concluded that the most plausible ICERs were within what NICE normally considers a cost-effective use of NHS resources for 1 subgroup. Therefore, guselkumab was recommended only for people with psoriatic arthritis who have had 2 conventional DMARDs and at least 1 biological DMARD and have moderate to severe psoriasis.

Other factors

Clinicians should take into account factors that may affect PsARC and PASI and make any clinical adjustments needed

3.18 The committee considered that the recommendation to stop treatment based on an inadequate PsARC response (in NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis) was also appropriate for guselkumab. It noted that some people may have physical, sensory or learning disabilities or communication difficulties that could affect their responses to components of the PsARC, and concluded that this should be taken into account when using the PsARC. The committee was also aware that the PASI might underestimate disease severity in people with darker skin. The committee concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score and make the clinical adjustments they consider appropriate.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has active psoriatic arthritis and the doctor responsible for their care thinks that guselkumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Luke Cowie
Technical lead

Caron Jones
Technical adviser

Kate Moore
Project manager

ISBN: 978-1-4731-4164-3

Accreditation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

TA711 - Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs

Rapid Review

Company evidence submission

05/2022

File name	Version	Contains confidential information	Date
TA711 RR Company evidence submission		**Yes**	**05/2022**

Contents

Tables and figures

List of tables

List of figures

Executive Summary

History of NICE appraisal of guselkumab

- Psoriatic arthritis (PsA) is a chronic, progressive inflammatory joint disease which is associated with prior psoriasis in 60–70% of cases (1-3). PsA has an unpredictable clinical course ranging from mild and non-destructive disease to erosive and deforming arthritis (4, 5). The diverse clinical manifestations of PsA require treatments with a range of different mechanisms of action.
- Guselkumab is a novel IL-23 inhibitor licensed for the treatment of patients with PsA who had an inadequate response or contraindicated to cDMARD therapy.
- In June 2021, NICE has issued a positive but optimised recommendation for guselkumab to treat a subpopulation of biologic experienced patients with moderate-to-severe comorbid skin psoriasis (TA711, (6)).
- The Committee identified that the key reason for the restricted recommendation was that "the committee's preferred assumptions produced a range of ICERs for guselkumab that were higher than £30,000 per QALY gained in almost all psoriasis severity subgroups" except the moderate-to-severe (6).

A revised Patient Access Scheme is the main element of this rapid review document

- Janssen proposes two major changes in the existing commercial arrangement, which combined make guselkumab cost-effective in all subpopulations of biologic experienced patients and likely cost-effective in TNFi contraindicated patients:
    - An increase in the simple patient access scheme (PAS) is proposed from [redacted] to [redacted]. Detail on the impact this has on cost-effectiveness is given in Sections B.3.7 and B.3.8.
    - We propose a complex PAS to provide the q4w regimen at the same cost as a q8w regimen by making every other q4w dose available free of charge to the NHS. This makes the q4w dose available for patients at high risk for joint damage according to clinical judgement and improves patients' and clinician's choice at no additional cost to the NHS. Detail on the impact this has is given in Section B.3.9.

New evidence / information may affect the Committee's judgement

- We would like to highlight additional safety risks and restrictions regarding the use of JAK inhibitors that emerged during and after the original appraisal, which the Committee may not have been aware of at the time of guidance publication. These additional safety risks resulted in:
    - MHRA has issued a safety warning for tofacitinib (7)
    - EMA requesting a special warning to restrict tofacitinib wider use and starting a comprehensive benefit-risk assessment of all JAK inhibitors (8, 9)
    - FDA to issue a safety communication on the same topics (10).

  We request that the committee consider that tofacitinib has unknown (but presumably higher) cost and QALY burden than was contained in the original submission. Further, since tofacitinib cannot now be

taken by a significant number of patients (older patients, current and former smokers, or those with cardiovascular or malignancy risk), so it is only a relevant comparator for a minority of patients, compared to guselkumab and other treatments that don't have such restrictions. By including it as a comparator and not giving additional consideration to these issues, the Committee risk using an out of date standard-of-care landscape to assess the cost-effectiveness of guselkumab.

- We would also like to draw NICE and committee's attention to feedback from clinicians that the wording of the NICE Guidance in TA 711 creates an equalities issue. The final guidance requires clinicians to assess the severity of the skin symptoms, which implies the administration of the PASI instrument. However, the leading speciality managing PsA patients in England is the rheumatologist, who does not routinely assess skin conditions, as per the BSR Clinical Guidelines (11). Consequently, the PASI criterion is a barrier for patients diagnosed with PsA and with comorbid skin psoriasis, who could be eligible for treatment but are primarily managed by a rheumatologist. This is in contrast to patients with plaque psoriasis and who have comorbid PsA as diagnosed by a dermatologist that will have access to guselkumab if eligible as per the NICE recommendation (TA521, (12)). Janssen asks the committee to broaden the recommendation beyond strict assessment of skin severity subgroup to ensure equality in recommendation between TA 711 and TA 521.
- In addition, the FAD was ambiguous on whether it applied to just the 8-weekly dose (q8w, the main dose of guselkumab) or extended also to the 4-weekly dose (q4w, the optional dose-escalation regimen). We include new calculations in Section B.3.9 (alongside the revised PAS) to address this ambiguity.

Conclusions

- Janssen is committed to ensuring that patients have appropriate access to innovative treatments such as guselkumab, so a new PAS is proposed in this Rapid Review to further improve the cost effectiveness of guselkumab from the original appraisal and expand the recommendation of guselkumab.
- Despite the relatively large number of available treatment options, there remains a substantial burden of unmet clinical need amongst the PsA patient population. The committee acknowledges this in the FAD, stating "people with psoriatic arthritis and clinicians would welcome a further treatment option."
- Guselkumab is particularly suitable for treating PsA in the biologic experienced and TNFi contraindicated population, as they are likely to have experienced treatment discontinuation due to adverse events or lack/loss of effect of TNFi (22, 23), and therefore may be seeking a treatment with safe, durable control of symptoms. Biologic experienced patients also experience a loss of effectiveness over time and experience the same unmet need for more effective holistic control of symptoms. Janssen ask the committee to consider whether, with the availability of the revised PAS and complex PAS, a recommendation in the full bio-experienced and TNF contraindication populations can be made to support the unmet need in PsA and also address the equality issue that is highlighted by clinicians above.

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Guselkumab received positive NICE recommendation in a subpopulation of biologic experienced patients with moderate-to-severe comorbid skin psoriasis (TA711, (6)). The Committee identified that the key reason for this recommendation was that "the committee's preferred assumptions produced a range of ICERs for guselkumab that were higher than £30,000 per QALY gained in almost all psoriasis severity subgroups" except this subgroup (6). Reading further details of the Committee's opinion suggests that this is principally due to two factors:

- The cost of guselkumab is high relative to other interleukin modulators, and the original proposed confidential discount offered by the manufacturer is insufficient to overcome this issue.
- In all populations where guselkumab could be used, an oral JAK inhibitor, tofacitinib, is also available. Since the Committee believed that tofacitinib was a reasonable alternative to guselkumab, this raised the incremental cost-effectiveness ratio (ICER) for guselkumab above levels where it would conventionally be considered cost-effective.

In addition, the FAD was ambiguous on whether it applied to just the 8-weekly dose (q8w, the main dose of guselkumab) or extended also to the 4-weekly dose (q4w, the optional dose-escalation dose). The Committee commented that the results of the q4w arm of the DISCOVER trial (where q4w was tested in an all eligible patients) may not be generalisable to the licensed population (which was for patients at high-risk of joint damage). We request the Committee consider making a more explicit recommendation regarding the q4w dose once they have had an opportunity to review our detailed calculations in this document.

Following this detailed recommendation from NICE, Janssen made a number of changes to its approach for subsequent submissions, including the submission to the Scottish Medicines Consortium. As a result, guselkumab has a recommendation for its full marketing authorisation in Scotland, in both the q8w and q4w dose. The intention of this Rapid Review is to address NICE's concerns, and consequently normalise the availability of guselkumab across the UK. We summarise the decision problem in this Rapid Review in Table 1 of Appendix A.

The decision problem is broadly unchanged from the original guselkumab submission, albeit with three material changes to the evidence we would request the Committee consider:

- In order to address the point regarding cost-effectiveness, we propose an increase in the simple patient access scheme from [redacted] to [redacted]. Detail on the impact this has on cost-effectiveness is given in Section B.3.7.
- In order to address the point regarding q8w vs q4w dose and improve patient choice, we propose a straightforward-to-implement complex patient access scheme which makes the q4w dose available at the same price as the q8w dose. Detail on the impact this has is given in Section B.3.8.

In order to address the point regarding tofacitinib being a relevant alternative to guselkumab equally to other interleukin modulators, we make reference to a significant amount of new evidence highlighting risks and restrictions with JAK inhibitors such as tofacitinib, which the Committee would not have been aware of at the time of issuing their initial guidance. Detail on this element of the Rapid Review submission is given in Section B.2.1. This means that tofacitinib is unlikely to be a relevant comparator for a large proportion of patients (those over 65 years age, current or former smokers and those with cardiovascular or malignancy risk). Further, the additional safety issues are not accounted for in the economic modelling. This means that tofacitinib is associated with significant structural and parameter uncertainty and is unlikely to be an appropriate comparator to guselkumab, except in a minority of patients, given the change in the standard-of-care landscape for the general PsA population.

B.1.2 Description of the technology being appraised

A summary of the technology being reviewed is presented in Table 1, including new information since the original submission. Additional information is available in the original submission.

Table 1 - Technology being appraised

UK approved name and brand name	Guselkumab (Tremfya)
Mechanism of action	Interleukin 23 (IL-23) modulation
Marketing authorisation/CE mark status	Marketing authorisation received December 2020. NICE guidance issued June 2021
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• Guselkumab, alone or in combination with methotrexate (MTX), is indicated for the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. • This is in addition to the existing indication for guselkumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. • There are no special restrictions on the supply and use of guselkumab.
Recommendation as described in the NICE guidance	• **1.1 -** Guselkumab, alone or with methotrexate, is recommended as an option o for treating active psoriatic arthritis in adults whose disease has not responded well enough to disease-modifying antirheumatic drugs (DMARDs) or who cannot tolerate them, only if they have: o peripheral arthritis with 3 or more tender joints and 3 or more swollen joints o moderate to severe psoriasis (a body surface area of at least 3% affected by plaque psoriasis and a Psoriasis Area and Severity Index [PASI] score greater than 10) o had 2 conventional DMARDs and at least 1 biological DMARD. Guselkumab is recommended only if the company provides it according to the commercial arrangement (see section 2). • **1.2 -** Assess the response to guselkumab from 16 weeks. Stop guselkumab at 24 weeks if psoriatic arthritis has not responded adequately using the Psoriatic Arthritis Response Criteria (PsARC; an adequate response is an improvement in at least 2 of the 4 criteria, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria). If PsARC response does not justify continuing treatment but there is a PASI 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response. • **1.3 -** Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the PsARC and make any appropriate adjustments.

<table>
<tr><td></td><td>

1.4 - Take into account how skin colour could affect the PASI score and make any appropriate adjustments.
1.5 - These recommendations are not intended to affect treatment with guselkumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop

</td></tr>
<tr><td>Method of administration and dosage</td><td>

The recommended dose of guselkumab is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose of 100 mg every 8 weeks. An alternative dose is available, which is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose of 100 mg every 4 weeks. These regimens are distinguished as ‘q8w’ and ‘q4w’ respectively in this submission.
Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.
Patients may self-inject if a clinician determines that this is appropriate.

</td></tr>
<tr><td>Additional tests or investigations</td><td>No additional tests or investigations are needed. In accordance with routine clinical practice for the use of biologics, patients should be evaluated for tuberculosis infection prior to initiation of therapy.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>

The UK list price of a 100mg pre-filled pen (solution for subcutaneous injection) of guselkumab is £2,250.00.
PsA is a chronic condition, and therefore the total cost of guselkumab depends on how long patients continue to take it. As this is subject to a number of personal factors such as immunogenicity, adverse events and life circumstances, it is difficult to accurately give the cost of an average course of treatment in a meaningful way. Consequently, annual costs are given:

<table>
<tr><td></td><td>Year 1 (requires loading dose)</td><td>Subsequent years (no requirement for loading dose)</td></tr>
<tr><td>q8w dose (main dose)</td><td>8 injections
£18,000</td><td>6.5 injections
£14,625</td></tr>
<tr><td>q4w dose (optional dose escalation)</td><td>14 injections
£31,500</td><td>13 injections
£29,250</td></tr>
</table>
</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>

The list price is subject to a confidential Patient Access Scheme, which takes the form of a simple percentage discount. This discount has been increased since the original submission. The new discount is [redacted], making the cost of one vial [redacted]
In addition, a complex patient access scheme is proposed to equalise the cost of q4w and q8w dose regimens.
The table below accounts for this information.

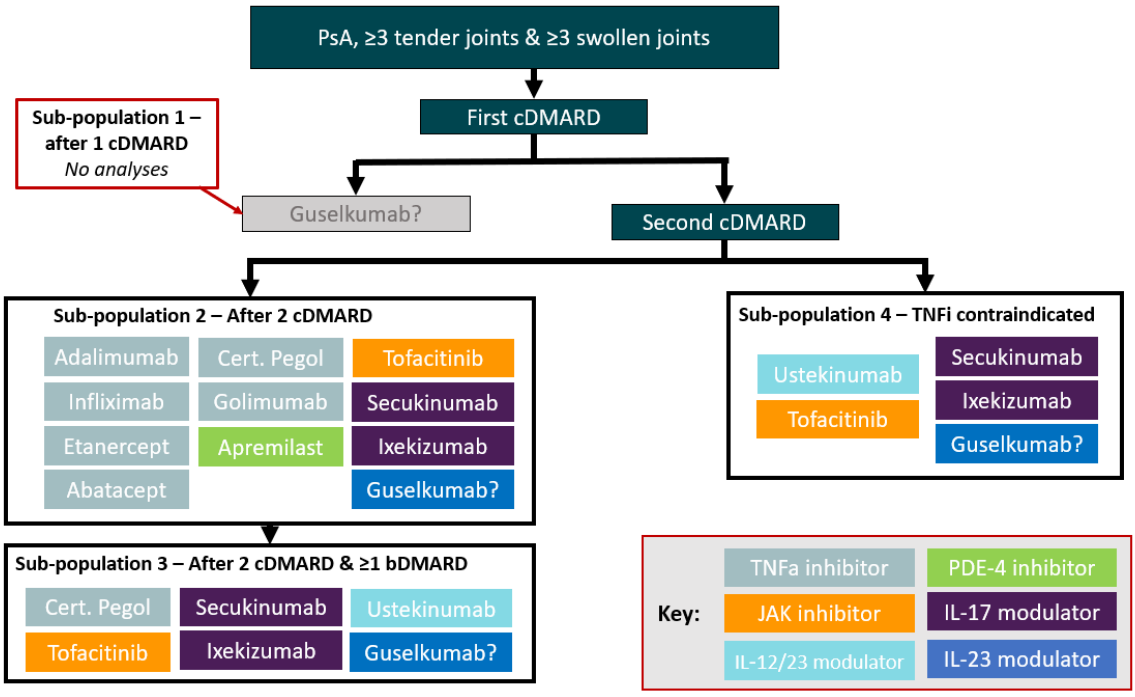
<table>
<tr><td></td><td>Year 1 (requires loading dose)</td><td>Subsequent years (no requirement for loading dose)</td></tr>
<tr><td>q8w dose (main dose)</td><td>8 injections
[redacted]</td><td>6.5 injections
[redacted]</td></tr>
<tr><td>q4w dose</td><td>14 injections</td><td>13 injections</td></tr>
</table>
</td></tr>
</table>

	(optional dose escalation)	[redacted]	[redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

The clinical pathway of care presented in Figure 1 was accepted by the Committee in the FAD as being a reasonable positioning of guselkumab where it might be able to address the highest unmet need. Therefore, no change on the positioning of guselkumab is proposed as part of this Rapid Review.

Figure 1 – Proposed clinical pathway of care



B.1.4 Equality considerations

The NICE recommendation introduces a potential equality concern. Since the guidance requires clinicians to judge between moderate-to-severe comorbid skin symptoms (where guselkumab can be prescribed) and mild-to-moderate comorbid skin symptoms (where it cannot), it requires the prescribing clinician to have high familiarity with the PASI instrument for assessing skin symptom severity. However, the most typical route for a patient to receive a PsA referral would be through a

rheumatologist, who does not routinely assess skin conditions, since BSR Clinical Guidelines suggest that patients with active skin symptoms should be referred to the dermatologist to have an adequate assessment (11). Therefore, the PASI criterion applied to the guselkumab recommendation has resulted in patients who are eligible for and could benefit from guselkumab being unable to access the treatment because of the NICE recommendations.

This compounds an equality concern raised in the original submission, which is that PsA has unique equality considerations with respect to skin psoriasis. The two diseases co-occur extremely frequently, and technologies which treat one condition often treat the other condition too (for example, guselkumab has a licence and NICE recommendation for treating moderate to severe plaque psoriasis in adults (12)). This means that currently a patient who was diagnosed with skin psoriasis with co-morbid PsA may be able to access guselkumab in situations where a patient who was diagnosed with PsA with co-morbid skin psoriasis cannot. Two patients might be identically burdened by both their joints and skin, but the PsA patient may be disadvantaged by the timing or location of their diagnoses.

For these reasons, we believe the ethical case for full access (i.e. unconditioned on skin severity) in at least the biologic experienced and possibly TNFi contraindicated population is extremely strong. The failure to rationalise this recommendation would result in unequal access to treatment depending on whether a dermatologist was working in the local area. Recognising the need for flexibility on Janssen's side to accomplish this, we propose the improved PAS in Section B.3.7. We believe this should ensure that we are cost-effective in this full population and request that the Committee consider that cost-effectiveness should not be the only consideration in light of these equalities concerns; patients who can benefit from guselkumab should be able to access it, and the current recommendations are preventing this in some cases.

These and further equity issues are evidenced with feedback from clinicians, given in Appendix B.

B.2 Clinical effectiveness

Since this Rapid Review mainly concerns an adjustment to the price of guselkumab, the evidence for the clinical effectiveness of guselkumab is the same as for the Original Submission.

B.2.1 Identification and selection of relevant studies

The major new clinical evidence not related to guselkumab which the Committee may wish to consider is an increased awareness of the risks and side-effect profile of tofacitinib and the other JAK inhibitors such as upadacitinib, filgotinib, abrocitinib and baracitinib (9). The Original Submission contains information on a special warning for tofacitinib for patients regarding venous thromboembolism, and information regarding a contraindication for tofacitinib in patients with severe hepatic impairment. However since then clinical consensus has altered following final results from the post-authorisation safety study (13), and further risks of tofacitinib and other JAK inhibitors has being recognised by various Health Authorities:

- In June 2021, EMA issued a variation to product characteristics stating, *"Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available"* (14).
- In July 2021, The Spanish Health Authority (Ministerio de Sanidad) have issued a communication reflecting the EMA warning (15), stating *"Patients over 65 years of age, smokers or ex-smokers, and those with additional cardiovascular risk factors or for the development of neoplasms, should not receive treatment with tofacitinib unless another available therapeutic alternative cannot be used"*
- In October 2021, MHRA have issued a safety warning stating *"Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives."* (7)

- In September 2021, FDA have issued a safety communication covering the entire JAK inhibitor mechanism of action. They write, *"We are requiring revisions to the Boxed Warning, FDA's most prominent warning, for Xeljanz/Xeljanz XR [tofacitinib], Olumiant [baricitinib], and Rinvoq [upadacitinib] to include information about the risks of serious heart-related events, cancer, blood clots, and death.".* Although the post-marketing safety study has investigated only tofacitinib compared to TNF inhibitors, the FDA decided to expand the warning to upadacitinib and baricinitib, since the agency consider these medicines may have a similar risk of tofacitinib as they share the same mechanism of action. (10)

- In February 2022, EMA has started a new procedure to review the benefit-risk profile of all JAK inhibitors approved: tofacitinib, upadacitinib, filgotinib, abrocitinib and baracitinib. The Pharmacovigilance Risk Assessment Committee (PRAC) from EMA stated, *"In view of the seriousness of the emerging data, as well as the comparable mode of action of these five JAK inhibitors, a safety review on MACE, VTE, serious infections, malignancies, and mortality should be performed for the JAK inhibitors authorised in inflammatory diseases. The impact of these serious events on the benefit/risk balance in all authorised indications should correspondingly be assessed (9)."*

- In February 2022, followed by EMA announcement the French Health Authority (ANSM) asked manufactures to suspend all promotional activities related to JAK inhibitors, in all indications, until PRAC conclude the assessment, which is for June 2022(16).

Further details on the post-authorisation study (13) may be valuable for the Committee, given its importance in the important safety communications issued by MHRA, EMA and FDA. The study looked at tofacitinib versus TNFi in patients with rheumatoid arthritis, who were ≥50 years of age and had at least one cardiovascular risk (such as smoking, hypertension, diabetes and cardiovascular disease family history). The co-primary outcomes were incidence of major adverse cardiovascular events and incidence of malignancies excluding non-melanoma skin cancer (NMSC). The safety study enrolled 4,362 patients who were randomised to receive tofacitinib

(5mg and 10 mg doses) and TNFi, and patients were followed up for a period of up to 72 months. The study did not meet the non-inferiority criterion, hence patients treated with both doses of tofacitinib demonstrated a higher incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, and a higher incidence of myocardial infarctions compared to patients treated with TNFi. This confirms the importance of raising safety concerns during the Original Submission and highlights the changing clinical context for tofacitinib which is relevant to this Rapid Review. We note that as when the first EMA special warning was published shortly before the FAD, we did request a short delay to NICE publication timelines in order for the Committee to consider the new information.

Since publication of the TAG the FDA, and MHRA warnings have also been published, while a complete EMA benefit-risk assessment of all JAK inhibitors has started , emphasising the risks of continuing to use tofacitinib as a routine comparator in PsA. There are now a sizable group of patients who cannot take tofacitinib or for who tofacitinib may no longer be appropriate, and therefore for whom tofacitinib is not a comparator. Even within those patients who are not strictly prevented from taking tofacitinib, our knowledge of costs and outcomes have materially changed since the original submission and this might impact patient and clinician choice of treatment substantially.

We believe the Committee is at material risk of using an outdated standard-of-care landscape if tofacitinib is included as a comparator without additional consideration of these points. Therefore, we request the Committee consider recommendations in light of the fact that guselkumab represents an appropriate treatment option for all PsA patients, while tofacitinib can and will only be used in limited circumstances now.

B.3 Cost effectiveness

B.3.2 Economic analysis

As with the clinical data, we conclude that since this Rapid Review does not alter the fundamental structure of the model in any way, and that model was determined to be “appropriate for decision making” in the FAD (6), including extensive detail on the

model in this Rapid Review would not serve the Committee since it would repeat information the Committee has already assessed which is irrelevant to the decision problem.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

A detailed table of base-case analysis inputs is provided in Appendix A. The Committee was satisfied with all inputs made in the original submission with the exception of treatment-specific discontinuation rates, which is removed in this Rapid Review and replaced with the Committee's preferred static 16.5% discontinuation rates.

Assumptions

A summary of assumptions in the model is given in Table 17 of Appendix A. The Committee was satisfied with all assumptions except the assumption that all patients would receive three lines of targeted therapy before transitioning to BSC. The Committee explained that in UK clinical practice treatment sequencing was highly variable and it might be possible for patients to receive more or fewer lines of treatment. However, the Committee agreed that this assumption was consistent with previous submissions and therefore acceptable for decision-making.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

All biologic naïve population

Complete results of the fully incremental analysis for biologic naïve (2 cDMARD failure) patients are shown in Appendix A, Table 4 – Table 7. These results are better than those initially seen by the Committee , in the sense that guselkumab is not extendedly dominated by etanercept, as shown in Table 2.

Table 2: Base-case results – Bio-naïve

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER (Fully Incremental)	ICER (pairwise vs BSC)
BSC	[redacted]	5.02				
GUS	[redacted]	7.393	[redacted]	2.370	[redacted]	[redacted]
ETA	[redacted]	7.776	[redacted]	2.753	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

The Committee indicate that they would prefer to see results broken down by psoriasis severity and this is presented in Table 3. At the increased simple discount guselkumab is plausibly cost-effective in the Bio-Naïve, Mod-Sev PsO subpopulation. Whether etanercept or guselkumab represents a better use of NHS resources in this subpopulation depends on the certainty with which the extra-QALY benefit for etanercept can be established (that is, the ICER for etanercept lies between £20,000 and £30,000 per QALY, which means that increasingly stronger evidence of effectiveness would be required to consider it cost-effective).

Table 3: Base-case results by PsO severity – Bio-naive, No PsO

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER (Fully Incremental)	ICER (pairwise vs BSC)
BSC	[redacted]	5.414				
GUS	[redacted]	7.703	[redacted]	2.289	[redacted]	[redacted]
ETA	[redacted]	8.129	[redacted]	0.426	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 4: Base-case results by PsO severity – Bio-naive, Mild-Mod PsO

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER (Fully Incremental)	ICER (pairwise vs BSC)
BSC	[redacted]	5.274				
GUS	[redacted]	7.599	[redacted]	2.325	[redacted]	[redacted]
ETA	[redacted]	8.007	[redacted]	0.408	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 5: Base-case results by PsO severity – Bio-naive, Mod-Sev PsO

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER (Fully Incremental)	ICER (pairwise vs BSC)
BSC	[redacted]	4.369				
GUS	[redacted]	6.863	[redacted]	2.494	[redacted]	[redacted]

ETA	[redacted]	7.179	[redacted]	0.316	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

All biologic experienced population

Results of the fully incremental analysis for biologic experienced (2 cDMARD failure, 1 previous biologic) patients are shown in Table 6. These results are significantly better than those initially seen by the Committee, as they include an additional simple discount for guselkumab, which is a key purpose of this Rapid Review.

Table 6: Base-case results – Bio-experienced

Treatment	Total Costs	Total QALYs	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	4.265			
Guselkumab	[redacted]	5.524	[redacted]	1.259	[redacted]
Certolizumab	[redacted]	5.173	[redacted]	-0.350	[redacted]
Tofacitinib	[redacted]	5.143	[redacted]	-0.031	[redacted]
Ustekinumab	[redacted]	5.134	[redacted]	-0.009	[redacted]
Ixekizumab	[redacted]	5.292	[redacted]	0.158	[redacted]
Secukinumab	[redacted]	5.262	[redacted]	-0.030	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

As discussed above, the Committee indicate that they would prefer to see results broken down by psoriasis severity. These results are displayed in Table 7 - Table 9. These indicate no material difference to the results in the original submission – guselkumab is still cost-effective vs BSC in all subpopulations, but the increased simple discount makes this case more effectively.

Table 7: Base-case results by PsO severity – Bio-experienced, No PsO

Treatment	Total Costs	Total QALYs	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	5.442			
Guselkumab	[redacted]	6.685	[redacted]	1.243	[redacted]
Certolizumab	[redacted]	6.349	[redacted]	-0.336	[redacted]
Tofacitinib	[redacted]	6.332	[redacted]	-0.016	[redacted]

Ustekinumab	[redacted]	6.306	[redacted]	-0.026	[redacted]
Ixekizumab	[redacted]	6.443	[redacted]	0.136	
Secukinumab	[redacted]	6.423	[redacted]	-0.019	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 8: Base-case results by PsO severity – Bio-experienced, Mild-Mod PsO

Treatment	Total Costs	Total QALYs	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	4.143			
Guselkumab	[redacted]	5.360	[redacted]	1.216	[redacted]
Certolizumab	[redacted]	5.023	[redacted]	-0.336	
Tofacitinib	[redacted]	5.001	[redacted]	-0.022	
Ustekinumab	[redacted]	4.981	[redacted]	-0.020	
Ixekizumab	[redacted]	5.124	[redacted]	0.143	
Secukinumab	[redacted]	5.107	[redacted]	-0.017	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 9: Base-case results by PsO severity – Bio-experienced, Mod-Sev PsO

Treatment	Total Costs	Total QALYs	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	3.503			
Guselkumab	[redacted]	4.842	[redacted]	1.339	[redacted]
Certolizumab	[redacted]	4.458	[redacted]	-0.385	
Tofacitinib	[redacted]	4.402	[redacted]	-0.056	
Ustekinumab	[redacted]	4.426	[redacted]	0.024	
Secukinumab	[redacted]	4.565	[redacted]	0.140	
Ixekizumab	[redacted]	4.630	[redacted]	0.065	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

TNFi contraindicated population

Results of the fully incremental analysis for TNFi contraindicated (2 cDMARD failure, 0 previous biologic) patients are shown in Table 10. As with the biologic experienced population, these results are significantly better than those initially seen by the Committee, as they include an additional simple discount for guselkumab, which is a key purpose of this Rapid Review.

Table 10: Base-case results – TNFi contraindicated

Treatment	Total Cost	Total QALY	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	5.022			
Guselkumab	[redacted]	7.393	[redacted]	2.370	[redacted]
Tofacitinib	[redacted]	6.980	[redacted]	-0.413	[redacted]
Secukinumab	[redacted]	7.380	[redacted]	0.400	[redacted]
Ustekinumab	[redacted]	7.382	[redacted]	0.002	[redacted]
Ixekizumab	[redacted]	7.179	[redacted]	-0.203	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

As for the other subpopulations, results by psoriasis subpopulation are displayed below in Table 11 – Table 13. As with the bio-experienced results, these results are qualitatively similar but quantitatively improved over the equivalent model runs in the original submission, since the increased simple discount improves guselkumab's ICER.

Table 11: Base-case results by PsO severity – TNFi contraindicated, No PsO

Treatment	Total Cost	Total QALY	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC	[redacted]	5.414			
Guselkumab	[redacted]	7.703	[redacted]	2.289	[redacted]
Secukinumab	[redacted]	7.719	[redacted]	0.016	[redacted]
Tofacitinib	[redacted]	7.324	[redacted]	-0.395	[redacted]
Ustekinumab	[redacted]	7.707	[redacted]	0.383	[redacted]
Ixekizumab	[redacted]	7.479	[redacted]	-0.228	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 12: Base-case results by PsO severity – TNFi contraindicated, Mild-Mod PsO

Treatment	Total Cost	Total QALY	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC		5.274			
Guselkumab		7.599		2.325	
Secukinumab		7.609		0.011	
Tofacitinib		7.205		-0.404	
Ustekinumab		7.596		0.391	
Ixekizumab		7.368		-0.228	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 13: Base-case results by PsO severity – TNFi contraindicated, Mod-Sev PsO

Treatment	Total Cost	Total QALY	Inc. Cost	Inc. QALY	ICER (Fully Incremental)
BSC		4.369			
Guselkumab		6.863		2.494	
Tofacitinib		6.397		-0.465	
Ustekinumab		6.830		0.433	
Ixekizumab		6.688		-0.143	
Secukinumab		6.797		0.110	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

B.3.8 Sensitivity analyses

Deterministic sensitivity analysis

As described above, the only difference between the Rapid Review model and the Original Submission model is the inclusion of a larger simple PAS. We note that the Original Submission model was largely agreed to be acceptable by the Committee, the ERG and Janssen (the only outstanding point of disagreement was regarding the appropriateness of differential-by-treatment versus static treatment discontinuation

rates, and we have adopted the Committee's preferred assumption of static 16.5% discontinuation rates here to be conservative). Consequently we conclude that there is no outstanding material structural uncertainty with the economic model, and that therefore presenting extensive scenario or one-way deterministic sensitivity analysis would not be of interest to the Committee, since these results would not meaningfully help address uncertainty in the submission.

This notwithstanding, we note that the FAD is clear that guselkumab is not cost effective at conventional thresholds in most subpopulations, and conclude from this that one or more competitor must have a confidential discount affecting the results of the analysis. Since the exact level of competitor discount was not explored in the Original Submission model and the Committee may find this analysis useful, Table 16– Table 19of Appendix A display scenario analysis results in all subpopulations for secukinumab, ixekizumab and tofacitinib respectively (all other treatments either do not have confidential discounts or have discounts which are known to Janssen, for example because Janssen manufactures these products).

We note that the calculated discount for tofacitinib does not take into account the serious safety concerns raised in Section B.2.1. These safety concerns may translate to additional monitoring costs, a higher propensity to discontinue treatment or – in extreme cases – costs and QALY impact of very serious adverse events stemming from the use of JAK inhibitors. We note that the Committee has not considered these issues as the ERG requested that Janssen remove adverse events from the economic model, which will bias against guselkumab given the serious economic and quality of life impact of the adverse events associated with tofacitinib. More fundamentally, these concerns indicate that there is significant uncertainty over the estimates of cost-effectiveness versus tofacitinib included in the model below, which can reasonably be considered entirely downside risk given the serious nature of the safety concerns raised by the relevant authorities. Consequently we believe that guselkumab is likely to be cost-effective in the full bio-experienced population at any level of tofacitinib discount, since HTA requires that value for money be assessed on incremental costs and benefits between reasonable alternatives. We are concerned that this leaves the Committee at material risk of making decisions on

the basis of an outdated standard of care landscape unless these points are given due consideration.

Probabilistic sensitivity analysis

We note above that additional deterministic sensitivity analysis is unlikely to be of use to the Committee since there are no outstanding material structural uncertainties with the model. This does not strictly apply to investigations of parameter uncertainty (i.e. probabilistic sensitivity analysis) since the improved confidential discount alters the probability of cost-effectiveness at various parameters. Therefore probabilistic sensitivity analysis distributions are presented in Figure 3 - Figure 6 of Appendix A. These distributions are quantitatively improved from – although qualitatively similar to - the same distributions from the Original Submission.

B.3.9 Subgroup analysis

As described in Section B.1.1, one issue on which we request NICE issue clear guidance in the process of this Rapid Review is on the status of the q4w dose, which is a secondary dose which may be given to a small number of patients.

The Committee concluded that it was difficult to evaluate the cost-effectiveness of the q4w dose because:

- The doubled cost of the q4w dose reduced cost-effectiveness
- There is no standard definition for ‘high risk of joint damage’
- Assessment of the clinical effectiveness of the q4w dose was based on its performance in the DISCOVER trials, where it was given to the full PsA population rather than a specifically high-risk population

In response to the first point, the company have proposed a complex PAS where the q4w regimen is provided at the same cost as a q8w regimen by making every other q4w dose available free of charge to the NHS.

In response to the second point, we note that the FAD concludes “this [i.e. the company definition of ‘high risk’] seemed reasonable” but that “a precise definition

was probably not possible, given the accepted variation in clinical judgement". Given the agreed reasonability of the company approach and the accepted lack of any better alternative, we propose that extensive deterministic sensitivity analysis (such as that included in Table 16-Table 21).

There is some evidence of a miscommunication regarding the third point, since we agree with the ERG that "there was no evidence that the 4-weekly dose was more effective than the 8-weekly dose" and that "it [is] reasonable to assume that both doses would also have the same effectiveness for people at high risk of joint damage" and it is unclear why the ERG present these as objections / uncertainties with the q4w dose. Table 14 and Table 15 reproduce the q8w and q4w data as a reference for the Committee, demonstrating substantial and consistent agreement between the q8w and q4w doses.

Table 14: Results by trial arm from DISCOVER-1; FAS1

End point at week 24	Placebo	DISCOVER 1 q8w	DISCOVER 1 q4w
	N=126	N=127	N=128
ACR 20	22.2%	52.0% (p<0.001)	59.4% (p<0.001)
ACR 50	8.7%	29.9% (p<0.001)	36.7% (p<0.001)
ACR 70	5.6%	11.8% (p=0.069)*	20.3% (p<0.001)
PASI 75	14.1%	75.6% (p<0.001)	86.5% (p<0.001)
PASI 90	11.5%	50.0% (p<0.001)	62.9% (p<0.001)
PASI 100	6.4%	25.6% (p<0.001)	44.9% (p<0.001)
PsARC	31.0%	59.8% (p<0.001)	72.7% (p<0.001)
HAQ-DI score (LS mean, 95% CI)	-0.09 (-0.17, -0.00)	-0.31 (-0.40, -0.23)	-0.38 (-0.46, -0.30)
MDA	11.1%	22.8% (p=0.012)	30.5% (p<0.001)
Discontinuation	9.5%	3.1%	2.3%

* indicates nominal p-value. The p-values (nominal) for DISCOVER-1 are based on the CMH test, stratified by baseline use of cDMARD (yes, no) and prior exposure to TNFi agents (yes/no). Patients with missing data are assumed to be non-responders.

Table 15: Results by trial arm from DISCOVER-2 based on composite estimand; FAS1

End point at week 24	Placebo	DISCOVER 2 q8w	DISCOVER 2 q4w
	N=246	N=248	N=245
ACR 20	32.9%	64.1% (p<0.001)	63.7% (p<0.001)
ACR 50	14.2%	31.5% (p<0.001)*	33.1% (p<0.001)
ACR 70	4.1%	18.5% (p<0.001)*	13.1% (p<0.001)
PASI 75	23.0%	79.0% (p<0.001)	78.3% (p<0.001)
PASI 90	9.8%	68.8% (p<0.001)	60.9% (p<0.001)
PASI 100	2.7%	45.5% (p<0.001)	44.6% (p<0.001)
PsARC	44.7%	72.6% (p<0.001)	68.6% (p<0.001)
HAQ-DI score (LS mean, 95% CI)	-0.13 (-0.19, -0.07)	-0.38 (-0.44, -0.32)	-0.39 (-0.45, -0.33)
MDA	6.1%	25.0% (p<0.001)	18.8% (p<0.001)
Discontinuation	5.2%	3.2%	3.7%

* indicates nominal p-value. The p-values (nominal) for DISCOVER-2 are based on the CMH test, stratified by baseline use of cDMARD (yes, no) and CRP prior to randomisation (<2.0 mg/dL vs ≥2.0 mg/dL). Patients with missing data are assumed to be non-responders.

We believe the main point of this objection is that the SmPC indicates that the q4w dose should be used in a 'high risk of structural damage' population, but the DISCOVER trial's q4w arm was conducted in a general PsA population. This objection appears underdeveloped since:

- All **other** PsA treatments are used in a high-risk population, since they were studied in all patients that met the trial inclusion criteria, whether high risk or not. Therefore, this eligible population includes high-risk by definition. It is inconsistent to ask for specific evidence of cost-effectiveness in a high-risk population for guselkumab when the same evidence was not requested for all other treatments.
- The essence of the objection is exactly risk neutral; the ERG have no evidence or argumentation that guselkumab is likely to underperform in a high-risk population, and therefore it is equally reasonable to imagine that guselkumab will overperform in a high-risk population. In fact Janssen have presented some evidence that guselkumab performs approximately equally well in a high- or normal-risk population (XXXXXXX2 and XXXXXXX3), but this evidence notwithstanding there is no reason not to accept the q4w dose on the basis of the risk generated by the uncertainty.

- Notwithstanding the above, we note that the q4w dose will be used in response to clinical judgement only. Therefore, the q4w dose will likely overperform in the real world compared to a trial conducted in high-risk patients, since the only high-risk patients who will receive q4w in the NHS will be those who their clinician believes will benefit from it. Therefore, it is not clear why the conservative assumption of using DISCOVER trial data is inappropriate for the purpose of decision making, given that the q4w dose appears cost-effective even with this conservative assumption.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Under these circumstances, the objections raised by the ERG; Table 16 - Table 21 shows that there is almost no difference in ICER between a scenario where 0% of patients take the q4w option (i.e. the base case) and a scenario where 100% of patients that the q4w option (i.e. an extreme q4w case where q4w is used exactly as

per the DISCOVER trials on the full PsA population, and also including the Complex PAS).

Table 16: Base-case results - Bio-naïve, 0% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	5.02			
GUS	[redacted]	7.393	[redacted]	2.370	[redacted]
ETA	[redacted]	7.776	[redacted]	2.753	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 17: Extreme-case results - Bio-naïve, 100% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	5.022			
GUS	[redacted]	7.402	[redacted]	2.379	[redacted]
ETA	[redacted]	7.776	[redacted]	0.374	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 18: Base-case results - Bio-experienced, 0% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	4.265			
GUS	[redacted]	5.524	[redacted]	1.259	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 19: Extreme-case results - Bio-experienced, 100% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	4.265			
GUS	[redacted]	5.677	[redacted]	1.412	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 20: Base-case results – TNFi contraindicated, 0% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	5.02			
GUS	[redacted]	7.393	[redacted]	2.370	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

Table 21: Extreme-case results – TNFi contraindicated, 100% q4w results

Technology	Total costs	Total QALY	Inc. Costs	Inc. QALY	ICER
BSC	[redacted]	5.022			
GUS	[redacted]	7.402	[redacted]	2.379	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Net price for guselkumab, list price for comparators

In conclusion, we believe the q4w and q8w doses are effectively equivalent for all primary and major secondary outcomes, but that a small number of patients and clinicians might have a preference for one over the other. We believe most patients with such a preference will prefer the q8w dose for its additional convenience, but that some patients or clinicians will prefer the q4w dose since it has a slightly better clinical profile with respect to preventing structural damage than the q8w dose. We do not claim that the q4w dose offers significantly better primary or major secondary treatment outcomes for patients at high risk of joint damage, but in the interests of patients' and clinicians' choice Janssen is committed to make both doses schemes available to patients, since both doses are acceptable under the SmPC. While we agree the ERG make an interesting academic point about the generalisability of the eligible population in the DISCOVER trial to a high-risk population, we strongly request that the Committee consider that this point makes absolutely no difference in practice; historic recommendations of treatments in eligible populations prove that the Committee has set a precedent to resolve this uncertainty in favour of patient and clinician choice, the new PAS demonstrates a strong Commitment from Janssen to resolve this uncertainty even despite this precedent.

B.3.11 Interpretation and conclusions of economic evidence

Broadly, this Rapid Review document requests that the Committee consider three points:

- Has the improved simple PAS made a material difference to the cost-effectiveness of guselkumab compared to alternative PsA treatments, particularly in respect to full access in the bio-experienced population?
- Has the improved complex PAS (along with clarification regarding the miscommunication about generalisability) made a material difference to the acceptability of the optional dose-escalation q4w dose as an adjunct to the main q8w dose?
- Has the new evidence made available at the time of the original assessment of guselkumab made a difference to the Committee's reasoning regarding either of the above points:

- The MHRA, EMA and FDA safety concerns regarding JAK inhibitors fundamentally change the reasonability of tofacitinib (itself a JAK inhibitor) as a comparator. Does this alter the cost-effectiveness of guselkumab?
- Feedback from clinicians is that the requirement of a PASI score before prescribing guselkumab creates an equalities issue, since it requires patients who could benefit from guselkumab to live in an area where rheumatologists and dermatologists work closely together. Does this alter the case for full access in at least the bio-experienced population (and the TNFi contraindicated population), taking into account the improved simple PAS?

We note that the FAD is clear that PsA has a substantially detrimental impact on quality of life, and that guselkumab would be welcomed by clinicians as an option in their armamentarium, particularly for patients who desire strong holistic control of symptoms, patients who desire a treatment with a strong safety profile or patients who desire a treatment with a low discontinuation rate (notwithstanding the technical reasons that mean that guselkumab's low observed discontinuation rate cannot be included in the economic modelling).

The FAD is further clear that the reason the Committee chose to issue an optimised recommendation was on grounds of cost-effectiveness, likely in relation to southwest quadrant treatments like tofacitinib in the bio-experienced subpopulation. We hope that the improved simple PAS increases the case for guselkumab on cost-effectiveness grounds, and while we are disappointed that fewer patients can benefit from tofacitinib than was believed during the appraisal process, we note that the MHRA, EMA and FDA judgements significantly decrease the case for tofacitinib to be considered as a reasonable comparator at the margin.

Janssen is committed to ensuring that patients have appropriate access to innovative treatments such as guselkumab, and we thank the Committee for the opportunity to address this through a Rapid Review.

B.4 References

1. Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P T. 2010;35(12):680-9.
2. Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheumatic diseases clinics of North America. 2015;41(4):545-68.
3. Mease PJ, Gladman DD, Papp KA, Khraishi MM, Thaçi D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. Journal of the American Academy of Dermatology. 2013;69(5):729-35.
4. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Annals of the rheumatic diseases. 2005;64 Suppl 2:ii14-7.
5. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. Journal of the American Academy of Dermatology. 2008;58(5):851-64.
6. NICE [TA711]. Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs 2021 [Available from: https://www.nice.org.uk/guidance/TA711.
7. MHRA. Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies 2021 [Available from: https://www.gov.uk/drug-safety-update/tofacitinib-xeljanzv-new-measures-to-minimise-risk-of-major-adverse-cardiovascular-events-and-malignancies.
8. EMA. Xeljanz: EPAR - Product information. 2021.
9. PRAC. EMA: PRAC List of questions To be addressed by the marketing authorisation holder(s) for Xeljanz, Cibinqo, Olumiant, Rinvoq and Jyseleca 2022 [Available from: https://www.ema.europa.eu/en/documents/referral/janus-kinase-inhibitors-jaki-article-20-referral-prac-list-questions_en.pdf.
10. FDA. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions 2021 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death.
11. Coates LC, on behalf of BSRCAC, Standards A, Guidelines Working G, the B, Tillett W, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology. 2013;52(10):1754-7.
12. NICE [TA521]. Guselkumab for treating moderate to severe plaque psoriasis 2018 [Available from: https://www.nice.org.uk/guidance/ta521.
13. ClinicalTrials.Gov. Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis. 2021.
14. PRAC. PRAC recommendations on signals: Adopted at the 7-10 June 2021 PRAC meeting. 2021.
15. AEMPS. Xeljanz (tofacitinib): nuevas precauciones de uso 2021 [Available from: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2021-seguridad-1/xeljanz-tofacitinib-nuevas-precauciones-de-uso/?lang=en.

16. ANSM. Lancement d’une réévaluation des données de sécurité sur les inhibiteurs de Janus Kinase (JAK) utilisés dans les maladies inflammatoires chroniques. 2022.

B.5 Appendices

Appendix A – Decision problem and additional economic evidence, including fully incremental analysis at new confidential discount, deterministic and probabilistic analysis.

Appendix B – Feedback from clinicians regarding the appropriateness of the PASI criteria

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs (rapid review of TA711) [ID4013]

Clarification questions

May 2022

File name	Version	Contains confidential information	Date
ID4013 - Company response to clarification questions		No	04/05/2022

Cost-effectiveness clarification questions

1. **We have been unable to replicate the results reported in Table 6 (company evidence submission) and Table 8 (Appendix A) for the comparators ixekizumab and secukinumab for the bio-experienced full population. We suspect this may be due to the company selecting the q2w dose for ixekizumab rather than selecting a mixed dose.**

Thank you for these clarification questions, we apologise for the confusion the oversight in the treatment dosing regimen selection has caused.

As noted in the clarification question, the dosing regimens selected for ixekizumab in Table 6 (company evidence submission) and Table 8 (Appendix A) were not appropriate for the bio-experienced full population. The new submission documents will include an updated version of Table 6 (company evidence submission) and Table 8 (Appendix A) based on a mixed dose scenario for ixekizumab.

The dose regimens for ixekizumab as per SPC are described in the table below.

Treatment / Dosing regimen	ixekizumab[1]
For patients with psoriatic arthritis	160 mg by subcutaneous injection (2×80 mg injections) at week 0, followed by 80 mg (1 injection) every 4 weeks thereafter.
For patients with psoriatic arthritis and concomitant moderate to severe plaque psoriasis	160 mg by subcutaneous injection (2×80 mg injections) at week 0, followed by 80 mg (1 injection) at weeks 2, 4, 6, 8, 10 and 12, then maintenance dosing of 80 mg (1 injection) every 4 weeks.

[1] MHRA. Summary of product characteristics of Ixekizumab [Available from: https://mhraproducts4853.blob.core.windows.net/docs/e3d36793cef2c6897a337f0bd24b1450c64726a3

2. **We have been unable to replicate the results reported in Table 10 (company evidence submission) for the comparators ustekinumab, ixekizumab and secukinumab for the TNFi contraindicated full population. We suspect this may be due to the total costs and QALYs reported by the company for ustekinumab actually being for secukinumab, the total costs and QALYs reported by the company for ixekizumab actually being for ustekinumab and the total costs and QALYs reported by the company for secukinumab actually being for ixekizumab.**

The treatment labels in the first column of Table 10 (company evidence submission) were incorrect. An updated version of Table 10 will be included in the new documents to be submitted.

3. **We have been unable to replicate the results reported in Table 12 (company submission) and Table 14 (Appendix A) for the comparators ixekizumab and secukinumab for the TNFi contraindicated, mild-moderate population. We suspect this may be due to the company selecting the 300mg dose for secukinumab rather than the 150mg dose, and the company selecting the q2w dose for ixekizumab rather than the q4w dose.**

The dosing regimens selected for ixekizumab and secukinumab were incorrect, as noted. Table 12 (company evidence submission) and Table 14 (Appendix A) will be updated accordingly in the new submission documents.