Risankizumab for previously treated active psoriatic arthritis [ID 1399]. A Fast-Track Appraisal.

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Kate Ren critiqued the statistical aspects of the submission. Aline Navega Biz critiqued the economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse event
bDMARD	Biological disease-modifying anti-rheumatic drug
BIO-IR	bio-experienced patients
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CFB	Change from Baseline
cPAS	Comparator Patient Access Scheme
CrI	Credible interval
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CS	Company submission
DMARD	Disease-modifying anti-rheumatic drug
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence review group
FAS	Full analysis set
FTA	Fast track appraisal
GUS	guselkumab
HAQ-DI	Health assessment questionnaire disability index
HRQoL	Health-related quality of life
IgG1	Immunoglobulin G1
IL	Interleukin
ITC	Indirect treatment comparison
JAK	Janus kinase
MAIC	Matching-adjusted indirect comparison
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
MTX	Methotrexate
NA	Not available
NMA	Network meta-analysis
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drugs

OR	Odds ratio
PAS	Patient Access Scheme
PASI	Psoriasis area severity index
PBO	Placebo
PDE	Phosphodiesterase
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria
PSS	Personal Social Services
QALY	Quality-adjusted life year
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
Q12W	Once every 12 weeks
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SJC	Swollen joint count
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
TA	Technology appraisal
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom

1. SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

- The description of the underlying problem and the pathway presented at the company's submission (CS)[1] appear to be appropriate.
- The technology being appraised is risankizumab, an IL-23 inhibitor. The licensed indication for risankizumab in Psoriatic Arthritis (PsA) is for the treatment of adults with active disease who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).[2] The company is seeking a positive recommendation for risankizumab in patients with active PsA and moderate to severe psoriasis who had two previous conventional synthetic DMARDs [csDMARDs] and at least one previous biological DMARD [bDMARD],[3] which is narrower than the eligible population covered by the marketing authorisation and the population defined in the final NICE scope.[4] This proposed positioning is, however, in the same indication for which guselkumab obtained a recommendation in 2021. Guselkumab is pharmacologically similar to risankizumab (IL-23 inhibitor) and the only drug specifically recommended for this specific population.
- The criteria for choosing the comparator under the NICE Fast Track Appraisal (FTA) process includes the selected comparator adequately representing the NICE recommended treatments as a whole, and having a significant market share.[5] Even though the company expects that guselkumab does not currently have a significant market share for PsA as a consequence of its recent approval, the Evidence review group (ERG) believes that overall the choice of guselkumab as the comparator in the CS meets NICE's criteria, considering the specific population they are seeking a recommendation for.
- All the relevant trials were included in the CS. No head-to-head trials of risankizumab and guselkumab (or risankizumab and any other bDMARDs) are available, and clinical equivalence is based on the results from network meta-analyses (NMAs). Although the population used in the NMAs was restricted to patients who had received prior biologic therapy (bio-experienced patients [BIO-IR]), this is a broader population compared to the population of interest for this appraisal.
- The ERG has concerns about the generalisability of the treatment effect and safety of risankizumab in the BIO-IR population to the specific subgroup relevant to this appraisal. In the previous appraisal for guselkumab, the committee accepted the use of the same efficacy and safety data for the biologic-experienced population in the cost-effectiveness model regardless of psoriasis severity.
- Psoriatic Arthritis Response Criteria (PsARC) and health assessment questionnaire disability index (HAQ-DI) change from baseline conditional on PsARC response were two of the key outcomes

used in the cost-effectiveness analysis of guselkumab in TA711.[3] However, there are no results for these endpoints from the NMAs comparing risankizumab and guselkumab because there were no data available for guselkumab in the BIO-IR subpopulation.

- NMAs were conducted under a Bayesian framework for the following outcomes: Psoriasis area severity index (PASI) 50/70/90, HAQ-DI change from baseline, American College of Rheumatology (ACR) 20/50/70 response, adverse events (AEs) and serious adverse events (SAEs). Appropriate statistical models were used in the NMAs.
- The point estimates of odds ratios (ORs) were close to 1.0 and the point estimates of mean difference were close to 0 at Week 24 and they were slightly away from 1.0 for ORs at Week 16. Although none of the NMA results were statistically significant, the credible intervals (CrIs) were wide indicating large uncertainty in the estimates. The ERG notes that the absence of statistical significance does not necessarily imply clinical equivalence.
- Nonetheless, the ERG's clinical advisor stated that the adverse event (AE) profiles for risankizumab and guselkumab in clinical practice are likely to be similar and has not raised any concerns in terms of toxicity.
- The company presents a cost-comparison analysis where the drug acquisition cost for risankizumab is lower than the costs for guselkumab. The analysis is based on the assumption of clinical equivalence between the two treatment groups from the NMAs. The structure and parameters of the analysis are similar to the economic analyses in TA711;[3] however, it is based only on the PsARC rate and does not include costs of subsequent lines of therapy or those associated with the management of psoriasis and arthritis, based on the this assumption of equivalence between the two treatment groups. The analysis assumes that except for drug acquisition, all other costs are the same between the treatment groups. The ERG's clinical advisor agrees that healthcare resource usage, including those associated with drug administration, monitoring, managing AEs and subsequent treatment after patients progress whilst receiving risankizumab or guselkumab, are likely to be similar. The ERG believes that if the assumption of clinical equivalence between risankizumab and guselkumab is accepted by the Appraisal Committee, the company's cost-comparison analysis is adequate.

2. CRITIQUE OF THE COMPANY'S DECISION PROBLEM

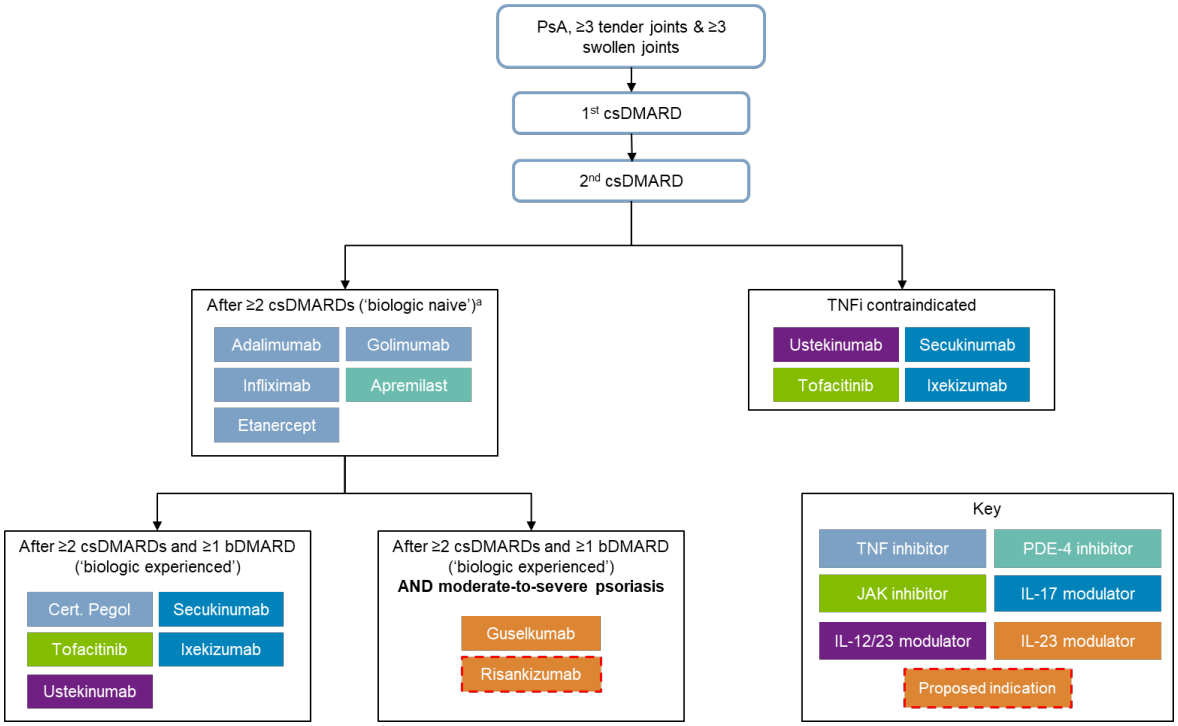
The description of the underlying health problem as presented in the company's submission (CS)[1] is considered appropriate and relevant to the decision problem. The decision problem addressed by the company is presented in Table 1 and Section B.1.1 of the CS. A summary of the points addressed, including the Evidence review group (ERG)'s critique, is presented in subsequent sections.

2.1 Population

The CS[1] provides an accurate description of the underlying health condition. Psoriatic Arthritis (PsA) is a chronic, progressive and complex inflammatory autoimmune disease which combines musculoskeletal arthropathy with skin disease psoriasis. The pathogenesis of PsA is multifactorial. Symptoms vary from mild to very severe, and can include inflammation within and around joints, fatigue, uveitis and inflammatory bowel disease. The impact of the disease on mortality is unclear, but it is associated with comorbidities which exacerbates the patient burden and impacts adversely on patients of working age (30–50 years). The disease can lead to impaired function with marked impact on work, social life and relationships and health-related quality of life (HRQoL).[6-8] There are over approximately 130,000 patients living with PsA in the UK (prevalence of 0.19%).[9]

The clinical pathway of care for patients with PsA is presented in Section B.1.3.3 of the CS.[1] Current treatment for PsA includes non-steroidal anti-inflammatory drugs (NSAIDs), combined with intra-articular corticosteroid injections, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs, such as methotrexate, sulfasalazine and leflunomide). For patients with active PsA who have not responded to at least two csDMARDs, biological DMARDs (bDMARDs) are available, which include tumour necrosis factor inhibitor (TNFi) therapies such as adalimumab, etanercept, infliximab,[10] golimumab[11] and certolizumab pegol,[12] or phosphodiesterase (PDE)-4 inhibitor (apremilast).[13] After failure of TNFi therapy or when TNFi therapies are contraindicated, patients are eligible to receive an anti-interleukin-17 antibody drug (IL-17, ixekizumab or secukinumab),[12, 14] janus kinase (JAK) inhibitor (tofacitinib or upadacitinib),[15, 16] or IL-12/23 inhibitor (ustekinumab).[17] Patients with moderate to severe psoriasis, peripheral arthritis with three or more tender joints and three or more swollen joints, and who have already received at least one bDMARD after failing two csDMARDs are eligible to receive guselkumab,[3] an interleukin-23 protein (IL-23) inhibitor, which has the same mechanism of action as risankizumab. Figure 1 shows the proposed positioning of risankizumab within this pathway (reproduced from CS, Figure 4).

Figure 1: Treatment pathway for psoriatic arthritis (PsA), showing proposed position of risankizumab (reproduced from CS, Figure 4)



bDMARD: biological disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; IL: Interleukin; JAK: Janus kinase; PDE: phosphodiesterase; PsA: psoriatic arthritis; TNFi: tumour necrosis factor inhibitor.
"[a]Certolizumab pegol, tofacitinib, secukinumab and ixekizumab were specified in the NICE final scope for this subpopulation but are only recommended by NICE following treatment failure of at least one TNFi or when TNFis are contraindicated (excluding certolizumab pegol), so have not been presented in this subpopulation."

The population addressed in the final NICE scope[4] represents *"adults with active PsA whose disease has not responded adequately to previous biological therapies or csDMARDs, or for whom biological therapies or csDMARDs are not tolerated or for whom DMARDs are contraindicated."* The population addressed in the CS[1] is more restrictive than that defined in the NICE scope, and relates to adults with active PsA whose disease has not responded adequately to DMARDs or who cannot tolerate them, only if they have:

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

2.2 Intervention

The intervention considered in the CS[1] is risankizumab. Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody selective to the IL-23 protein (IL-23 inhibitor).[2] The marketing authorisation issued by the European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) for risankizumab states that this drug is indicated alone or in

combination with methotrexate (MTX) for the treatment of active PsA in adults who have had an inadequate response or who have been intolerant to one or more DMARDs.[2, 18-20] In their response to clarification question A1,[21] the company confirmed that their intended positioning of risankizumab is as monotherapy or in combination with MTX. The ERG notes that the cost-comparison of risankizumab and guselkumab relates only to the use of these drugs as monotherapy, and it is not clear what percentage of patients are expected to receive the risankizumab in combination with MTX.

Risankizumab is available as 150 mg/1 ml solution for injection in a pre-filled syringe or pen. The recommended dose for this indication is 150 mg by subcutaneous (SC) injection on weeks 0, 4 and every 12 weeks thereafter. The Summary of Product Characteristics (SmPC) for risankizumab states that *"consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment."*[2, 19, 20] The NHS indicative price for each pack of risankizumab is £3,326.09, irrespective of the dose. A Patient Access Scheme (PAS) discount is available for risankizumab, resulting in a discounted cost per pack of [redacted] ([redacted] discount).

The positioning of risankizumab intended by the company is narrower than its marketing authorisation and the final NICE scope, and is identical to the positive recommendation received by guselkumab from NICE in the same disease area (TA711).[3]

2.3 Comparator

Guidance from NICE on the FTA process states that in a cost-comparison FTA, a comparison needs to be made only against one of the comparators listed in the scope. However, the selected comparator should: (i) adequately represent the NICE recommended treatments as a whole both in terms of its cost and effects; and (ii) have a significant market share. The guidance document notes that the market share criterion is in place to *"ensure that the selected comparator is relevant and part of established practice for the whole population"* rather than to a subgroup of patients, and that any positive recommendation from the committee in a cost-comparison case would usually mirror the recommendation for the comparator.[5]

The CS[1] includes a single comparator: guselkumab, which is also an IL-23 inhibitor. The SmPC for guselkumab states that it is indicated as monotherapy or in combination with MTX for the treatment of active PsA who have had an inadequate response or who have been intolerant to a prior DMARD therapy.[22] Guselkumab is available as 100 mg/1mL solution for injection in pre-filled syringe, and the recommended dose is 100mg by SC injection at weeks 0, 4, and every 8 weeks thereafter. The SmPC for guselkumab also states that treatment discontinuation should be considered in patients with no response after 24 weeks of treatment initiation with guselkumab and that *"for patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered"*.

However, the CS does not include this alternative schedule of dosing for guselkumab, which would be associated with higher frequency of doses, and consequently, higher costs for the comparator. The NHS indicative price for guselkumab is £2,250.00 per pack. A comparator Patient Access Scheme (cPAS) discount is available; details of this discount and results of the cost-comparison analysis using the cPAS discount are presented in a separate confidential appendix to this ERG report.

The company considers guselkumab to represent the only relevant comparator for the patient population addressed in the CS as it is the only drug in PsA that is specifically recommended to this restricted population of patients with active PsA and moderate to severe psoriasis who have had two cDMARDs and at least one bDMARD.[1] The final NICE scope[4] also lists best supportive care (BSC) and upadacitinib '(subject to ongoing NICE appraisal)' as comparators for people whose disease has not responded adequately to conventional DMARDs and 1 or more biological DMARDs, or for whom these are not tolerated. The company, however, claims that these comparators *"are recommended for broader patient populations which do not align to the positioning of risankizumab in clinical practice"*.[1] Clinical advice received by the ERG suggests that the treatment pathway for PsA has changed in recent years, and BSC alone would be reserved only for the very few patients who cannot tolerate injections or for whom the IL-23 would be contraindicated. Upadacitinib has only been approved very recently by NICE (February 2022) and was not yet available in the NHS at the time of writing this report; therefore it was not considered a comparator.

The company also justifies the choice of guselkumab on the grounds that, despite guselkumab having limited market share in the overall PsA population, as it has only been recently recommended by NICE for this indication (2021), an increasing market share can be observed in countries where guselkumab was launched earlier than the UK. Recent data provided as part of the company's reference pack show a very modest market share for guselkumab in one specific European country.[23] The company also notes that in a previous NICE appraisal for risankizumab for treating moderate to severe plaque psoriasis (TA691), guselkumab was accepted as the comparator for the FTA although its market share was likely to be low. The ERG considers that taking into consideration that the intended positioning for risankizumab is aligned with the restricted population of patients for which guselkumab has a positive recommendation, the choice of this comparator is generally in line with NICE's criteria for the comparator choice in an FTA. The ERG's clinical advisor agreed that guselkumab is an appropriate comparator for risankizumab in the population of patients considered in this appraisal.

2.4 Outcomes

The final NICE scope[4] lists the following outcomes:

- disease activity

- functional capacity
- disease progression
- periarticular disease (for example enthesitis, tendonitis, dactylitis)
- axial outcomes
- mortality
- adverse effects of treatment
- health-related quality of life

Section B.3.5 of the CS[1] reports data from the pivotal study of risankizumab. The ERG notes that the company did not presented results for mortality as this outcome was not considered relevant by the company because patients with PsA have only a slightly higher risk of mortality compared to the general population.[1] The ERG's clinical advisor confirmed the view of the company that most studies in this disease area have a short follow-up duration and do not capture effects on survival, and instead typically focusing on capturing differences in disease activity. The company also confirmed that the Phase III KEEPsAKE-2 study, which provides most of the evidence on clinical efficacy for risankizumab in this appraisal, has not measured mortality. The CS[1] also does not report results on axial outcomes, with the justification that these have not been requested in any previous NICE appraisals for this disease area (TA445, TA537, TA543 and TA711). The ERG notes that the only outcomes reported in the trial that provide evidence for the cost-comparison base-case analysis is disease activity (assessed using Psoriatic Arthritis Response Criteria [PsARC]).

2.5 Economic analysis

The CS[1] reports the methods and results of a model-based cost-comparison analysis which estimates the incremental costs of risankizumab versus guselkumab from the perspective of the NHS and Personal Social Services (PSS) over 10 years. The company's cost-comparison is underpinned by an assumption of equivalence between risankizumab and guselkumab for all efficacy endpoints based on the results of the network meta-analyses (NMAs) and additional assumptions regarding disease management costs. Further details of the company's cost-comparison analysis are presented in Section 4 of this report.

2.6 Subgroups

The NICE final scope states that *"if evidence allows the following subgroups will be considered:*

- *the reason for previous treatment failure (for example due to lack of efficacy, intolerance, or adverse events)*
- *mechanism of action or number of previous treatments*
- *presence or severity of concomitant psoriasis (no psoriasis, mild, moderate, or severe psoriasis)*

- *presence or severity of axial involvement".*

The CS does not present any analyses of subgroups, on the basis that the patient population for whom the company is seeking a positive recommendation already represents a specific subgroup of the population specified in the final NICE scope and the marketing authorisation. The ERG agrees with the company's position; however, as stated in Section 3.2.2, the evidence presented from KEEPsAKE-2 relates to 'biologic experienced' patients who in its majority have not been exposed to two previous csDMARDs and did not have moderate to severe psoriasis at baseline (clarification response, question A4).[21]

2.7 Equality considerations

The CS[1] states that no equality issues are anticipated.

3. ERG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1 Summary of company's systematic review methods

The company conducted systematic literature searches across a variety of sources (three databases including hand-searching), to identify randomised controlled trials (RCTs) of risankizumab and relevant comparators in adults with moderate to severe PsA (CS Appendices, Section D). An initial search (inception until August 2019) followed by six update searches were carried out (August 2019-May 2020/September 2020, September 2020-March 2021, March-July 2021, July-November 2021, November-December 2021). It is unclear to the ERG what terms (subject heading and free-text terms) were reviewed and updated for all subsequent review updates, because only the strategies for the most recent electronic database update (December 2021) were provided by the company (CS Appendix D.2.3).[1] The most recent update search strategy is comprehensive (with no consequential errors) and the ERG is not aware of any relevant RCTs for risankizumab and their relevant comparators that have been missed.

The selection criteria used in the systematic literature review (SLR) comprised the following inclusion criteria, which were broader than for the decision problem.

Intervention:

In the SLR, the inclusion criteria related to the intervention were not restricted by dose, whilst the intervention included in the decision problem was risankizumab 150 mg administered as a SC injection at week 0, week 4, and every 12 weeks thereafter (as monotherapy or with MTX).

Comparator:

The inclusion criteria used by the company in the SLR included other bDMARD treatments than guselkumab and were not restricted by dose. The cost-comparison analysis includes only guselkumab 100 mg administered by SC injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks (as monotherapy or with MTX). Because guselkumab is the only comparator in this appraisal and no feedback loops were formed by considering other bDMARD treatments in the NMA, the ERG notes it would be sufficient to only include comparator trials related to guselkumab in the NMA.

Population:

The inclusion criteria used in the SLR for the population was adult patients (≥18 years of age) with moderate to severe PsA, which is broader in terms of the previous treatment received but is more restrictive in terms of disease severity than the population in the NICE scope. The population addressed in the CS[1] was more restricted than in the NICE scope and marketing authorisation, and in line with the

population for which guselkumab had received a positive recommendation from NICE, that is, restricted to: active PsA (defined as ≥3 tender joints and ≥3 swollen joints); and moderate to severe psoriasis (a body surface area of at least 3% affected by plaque psoriasis and a PASI score greater than 10); and had two prior csDMARDs and at least one prior bDMARD.

Outcomes:

In the technology appraisal that recommended the use of guselkumab in this indication (NICE TA711),[3] the outcomes related to clinical effectiveness included in the economic analysis of the technology were PsARC, HAQ-DI change from baseline conditional on PsARC response and PASI scores. The company included all these outcomes and adverse events (AEs) outcomes in the NMAs. However, only NMA results comparing to guselkumab 100mg once every 8 weeks (Q8W) for ACR20/50/70, PASI 50/75/90/100, HAQ-DI change from baseline, AEs and serious adverse events (SAEs) were available due to the lack of relevant data for guselkumab for PsARC and HAQ-DI change from baseline conditional on PsARC response.

3.2 Summary of company's indirect treatment comparison (ITC)

3.2.1 Summary of the ITC methods

An NMA was conducted to estimate the comparative efficacy and safety of risankizumab 150mg versus guselkumab 100mg Q8W in the BIO-IR patient subgroup population in the absence of head-to-head RCTs. The primary NMA analysis was conducted at Week 24 with scenario analysis at Week 16.

The NMA included 10 trials with a wide range of treatments (CS Section B3.8.1).[1] Figure 1 and Figure 2 show the network diagram for PASI and ACR at Week 24. The network diagram for other outcomes can be found in CS Appendix D.8.2. A summary of the included trials can be found in CS Appendix D.8. The CS states that there was some heterogeneity among the included trials in the NMAs. To account for heterogeneities in the NMAs, both fixed effect and random effects model were fitted; a supportive anchored matching-adjusted indirect comparison (MAIC) only using KEEPsAKE-2 and DISCOVER-1 with placebo as the common comparator adjusting for differences in trial populations was also conducted. A Bucher ITC was also conducted before matching. The company's conclusion of clinical equivalence was based on the NMA results.

Figure 2: Network diagram for PASI among the BIO-IR population at Week 24 (reproduced from CS Appendix D)

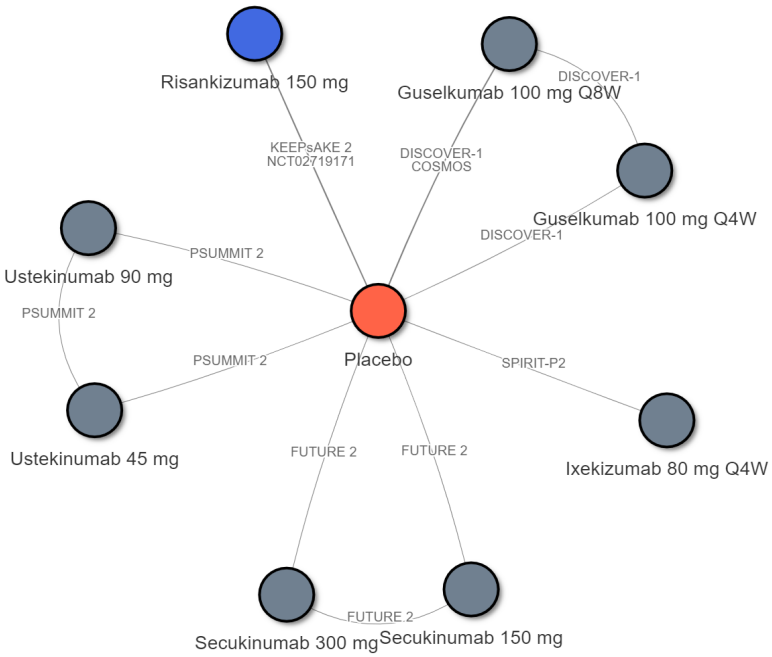
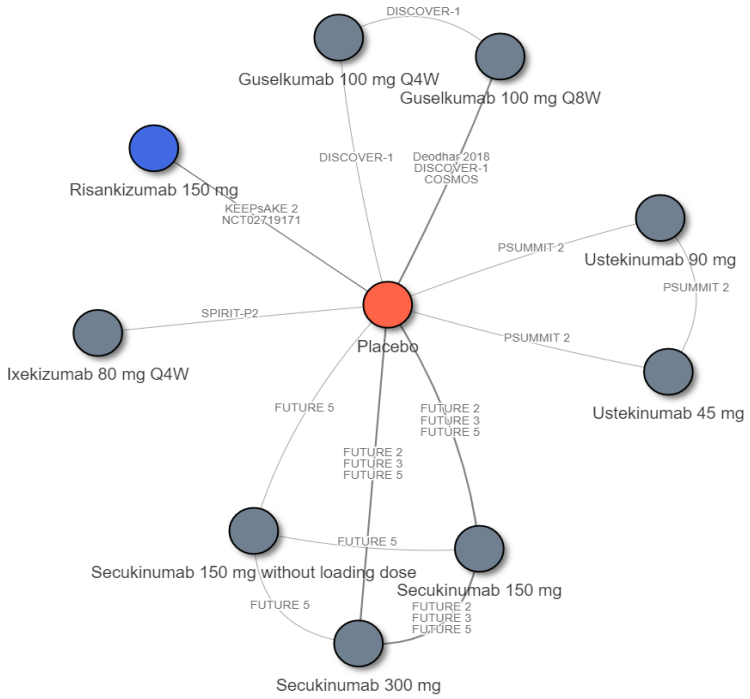


Figure 3: Network diagram for ACR among the BIO-IR population at Week 24 (reproduced from CS Appendix D)



3.2.2 Summary of the trial evidence

The trials providing data for risankizumab were KEEPsAKE-2 and NCT02719171,[24, 25] whilst the trials providing data for guselkumab were COSMOS and DISCOVER-1 and Deodhar 2018 (see ERG Clinical Appendix).[26-28]

3.2.2.1 KEEPsAKE-2

KEEPsAKE-2 was a Phase III RCT of PsA. The trial population was not restricted to the population eligible for this FTA: i.e. not restricted to patients who were bDMARD experienced; or those with moderate to severe psoriasis (BSA≥3% affected by plaque psoriasis and a PASI score >10); or those who had two prior csDMARDs. It was an international, multicentre trial, with 7 of 99 centres in the UK.[29]

Patients in KEEPsAKE-2 were randomised to placebo (PBO) or risankizumab 150mg SC at weeks 0, 4 and 16. Randomisation was stratified by current csDMARD use (0 versus ≥1), number of prior biological therapies (0 versus ≥1) and extent of psoriasis (≥3% versus <3% BSA affected by psoriasis). There was a 24-week double blind period, followed by an open-label extension study of risankizumab 150 mg once every 12 weeks (Q12W) up to week 208 (with follow-up up to week 228).

Baseline characteristics for the trial population (n=443) are shown in CS Table 7.[1] The baseline characteristics of the bDMARD experienced (BIO-IR) subgroup (n=206) were similar to those of the whole population.[30] According to the ERG's clinical advisor, the characteristics of the KEEPsAKE-2 trial population were in general representative of eligible UK population, except for having a higher swollen joint count (SJC) than would be seen in clinical practice.

For the NMAs for this FTA, the KEEPsAKE-2 population used was the BIO-IR subgroup: n=105 in risankizumab group, and n=101 in PBO group. These patients did not all meet the inclusion criteria for the decision problem ((BSA≥3% and PASI>10), two prior csDMARDs). As part of their clarification response (question A4),[21] the company provided more details about the subgroup in the KEEPsAKE-2 study who had received prior biologic therapy (the 'BIO-IR subgroup'). In this group, only [redacted] of patients in the risankizumab arm and [redacted] receiving placebo had moderate to severe psoriasis (BSA≥3% and PASI>10) at baseline, whilst [redacted] and [redacted] also had prior treatment with two csDMARDs, respectively. Patients in this subgroup who had moderate to severe psoriasis and prior treatment with two csDMARDs corresponded to [redacted] and [redacted], respectively.

It is unclear if the evidence from the 'biologic experienced' subgroup of patients from the KEEPsAKE-2 study is generalisable to the targeted population for which the company is seeking a positive recommendation. The majority of patients in the 'biologic experienced' subgroup of the trial have not

been exposed to two previous csDMARDs and do not have moderate to severe psoriasis, which does not seem to reflect the population seen in clinical practice in the UK that would be currently eligible for guselkumab (or risankizumab if recommended).

In response to clarification question A7,[21] the company states that in the appraisal of guselkumab (TA711) in this indication, data for the biologic-experienced subgroup of DISCOVER-1 was used to inform the efficacy of guselkumab in this same population. The ERG notes that during TA711, the ERG also had concerns regarding the differences between the populations in the DISCOVER-1 and DISCOVER-2 trials and patients seen in the NHS, regarding previous exposure to biological therapies and csDMARDs and the severity of psoriasis disease. However, in TA711, the Appraisal Committee accepted the use of the same efficacy and safety data for the biologic-experienced population in the cost-effectiveness model, regardless of psoriasis severity.[3]

3.2.2.2 NCT02719171

NCT02719171 was a Phase II, international, dose-ranging study, in which 185 patients were randomised to placebo (PBO) or to one of four doses of risankizumab, for 16 weeks.[31] The patients were followed-up following treatment, and those reaching the week 24 visit having taken all doses of study drug were able to enter the open-label single-arm extension (open-label risankizumab 150 mg SC at Weeks 0, 12, 24, and 36).[29] The trial population was not restricted to the population eligible for this FTA. For the NMAs undertaken to inform this FTA, the NCT02719171 population used was the bDMARD experienced population (BIO-IR): in the relevant risankizumab dose (150mg SC at weeks 0, 4 and 16) [redacted]; in the PBO group [redacted] (clarification response, question A11).[21]

3.2.3.3 Clinical trials that included guselkumab

DISCOVER-1 was a Phase III, PBO-controlled RCT, of 381 randomised patients; the BIO-IR subgroup had n=38 guselkumab 100 mg once every 4 weeks (Q4W); n=41 guselkumab 100 mg Q8W; and n=39 PBO.[27] COSMOS was a Phase III, PBO-controlled RCT, in which all patients in the trial had prior TNFi; n=189 in guselkumab group, n=96 in PBO group.[26] Deodhar 2018 was a Phase II, PBO-controlled RCT, of 149 randomised patients; in the BIO-IR subgroup there were n=9 in the guselkumab group, and n=4 in the PBO group.[28]

In response to clarification question A20,[21] the company provided an updated table comparing the baseline characteristics between KEEPsAKE-2 and DISCOVER-1 in the BIO-IR subgroup. The table shows that age, body mass index (BMI), PsA disease duration, BSA, C-reactive protein (CRP), DMARD use at baseline and PASI mean were deemed to be clinically significantly different between the two trials. In response to clarification question A20,[21] it also states that the company's UK clinical experts suggest that patients in the risankizumab group are harder to treat. The ERG notes that it's not

clear if "the risankizumab group" refers to the both arms in KEEPsAKE-2 or just the risankizumab arm as the comparisons in baseline characteristics were made by pooling the data for KEEPsAKE-2 and DISCOVER-1 across both treatment arms.

3.2.3 Summary of the ITC results

A summary of the company's ITC results is presented in Table 1 (efficacy outcomes including PsARC response, ACR 20/50/70, PASI 50/75/90/100 and HAQ-DI change from baseline at Week 24), Table 2 (efficacy outcomes including PsARC response, ACR 20/50/70, PASI 50/75/90/100 and HAQ-DI change from baseline at Week 16) and Table 3 (safety outcomes including AE, SAE and AEs leading to discontinuation at Week 24). Only the results for ACR 20/50/70 were from a random effects model. A fixed effect model was used for the other endpoints.

The OR results for ACR and SAEs at Week 24 were incorrectly reported in the CS and corrected in response to clarification questions A15 and A16.[21] The ERG also noticed that the relative result for HAQ-DI change from baseline at Week 24 was reported incorrectly in the CS; this has been corrected in Table 1.

In the factual accuracy check of the ERG report,[32] the company reported the following errors made in the CS:

- "*In the company submission, the random effects model was reported as the optimal model and selected for ACR outcomes, however, based on model diagnostic statistics, the random-effects model with placebo response adjustment is the optimal model*"
- "*HAQ-DI CFB for guselkumab was reported incorrectly in the company submission*".
- "*PASI response rates were reported incorrectly and were flipped for risankizumab and guselkumab*"
- *"the PsARC response rate for risankizumab was reported incorrectly as the placebo response rate."*

The company provided updated results for ACR outcomes and HAQ-DI CFB for guselkumab at Week 24, and PASI outcomes and PsARC response rate at Week 16 in the fact check Appendix A,[32] which are included in Table 1 and Table 2 (the original ERG report included the results from the CS which are not presented in this updated version).

In the factual accuracy check of the ERG report, the company also provided updated NMA results for AEs and SAEs incorporating additional published data.[32] However, the company did not provide enough information about this update to allow for the ERG to check the accuracy of the results. The ERG notes that the original safety NMA results are presented in Table 3.

The point estimates were close to 1.0 for the OR measure and close to 0 for the mean difference measure (favouring risankizumab for HAQ-DI change from baseline, and favouring guselkumab for ACR and PASI outcomes) at Week 24 for the efficacy outcomes. The results at Week 16 were slightly further away from 1.0 for the OR measure (favouring risankizumab for PASI outcomes and favouring guselkumab for ACR outcomes and HAQ-DI change from baseline). The point estimates of odds ratios (ORs) for the safety outcomes were not close to 1.0, favouring guselkumab for AEs and favouring risankizumab for SAEs. None of the results were statistically significant.

In response to clarification question A17,[21] the company updated the NMAs using an informative prior distribution for the between-study heterogeneity parameter to allow for more plausible analysis using a random effects model for the endpoints PASI 50/75/90/100 and HAQ-DI change from baseline at Week 24. The results of the random effects models show similar point estimates as the fixed effect models and slightly wider credible intervals (CrIs) which reflects the heterogeneity among the included studies.

During the clarification stage, the ERG asked the company to provide the results of the probability of the point estimate being within the interval where clinical equivalence could be claimed for each of the endpoints analysed using the CODA samples from the NMAs (clarification response, question A18).[21] In response, the company provided estimates of the probabilities of clinical equivalence for risankizumab relative to guselkumab for the PASI and ACR endpoints. The company used an approach for the non-inferiority trial design for the calculations. The aim of a non-inferiority trial is to show that the amount by which the test treatment is inferior to the active control is less than some pre-specified margin. The company determined the margin (M2) as a proportion of a margin (M1), where M1 is obtained using a fixed effect meta-analysis with response rate difference as the effect measure for guselkumab Q8W vs. placebo. The company conducted sensitivity analysis with M2 defined as 50% or 20% of M1. The results are presented in Table 14 of the clarification response.[21] The probability of clinical equivalence among the PASI and ACR endpoints varies from [redacted] to [redacted] when M2 was defined as 50% of M1 and varies from [redacted] to [redacted] when M2 was defined as 20% of M1. The probability of clinical equivalence is low for the outcome PASI 100, ACR 50 and ACR 70.

Table 1: Summary of company's ITC analyses for efficacy outcomes of risankizumab 150mg versus guselkumab 100mg Q8W at Week 24 (adapted from Table 11 of the CS, Tables 10 from the clarification response, and factual accuracy check Appendix A, Table 1)

Endpoint	Response rates % (95% CrI)		NMA	After matching MAIC	Before matching Bucher ITC
	Risankizumab	Guselkumab	OR (95% CrI)		
PsARC response	[redacted]	[redacted]	[redacted]		
ACR 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR 70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	[redacted]	[redacted]	[redacted]		
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Posterior median (95% CrI)		MD (95% CrI)		
HAQ-DI CFB	[redacted]	[redacted]	[redacted]		

Note: *A fixed effect model was selected for PsARC, PASI 50/75/90/100 and HAQ-DI CFB. A random effects model with placebo response adjustment was selected for ACR 20/50/70. No result was available versus guselkumab for PsARC response as no trials were identified reporting the treatment effect of guselkumab on this outcome.*

Abbreviations: *ACR: American College of Rheumatology; CrI: credible interval; NA: not available; OR: odds ratio; MD, mean difference; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area Severity Index; CFB: change from baseline; HAQ-DI: health assessment questionnaire disability index; NMA: Network Meta Analysis; Q8W: once every 8 weeks; MAIC, matching-adjusted indirect comparison; ITC, indirect treatment comparison.*

Table 2: Summary of company's ITC analyses for efficacy outcomes of risankizumab 150mg versus guselkumab 100mg Q8W at Week 16 (adapted from Table 13 of the CS, Tables 84 and Table 85 from the CS appendix, and factual accuracy check Appendix A, Table 2)

Endpoint	Response rates % (95% CI)		NMA
	Risankizumab	Guselkumab	OR (95% CrI)
PsARC response	[redacted]	[redacted]	[redacted]
ACR 20	[redacted]	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]	[redacted]
ACR 70	[redacted]	[redacted]	[redacted]
PASI 50	[redacted]	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]	[redacted]
	Posterior median (95% CrI) [redacted]		MD (95% CrI)
HAQ-DI CFB	[redacted]	[redacted]	[redacted]

Note: *A fixed effect model was selected for PsARC, PASI 50/75/90/100 and HAQ-DI CFB. A random effects model was selected for ACR 20/50/70. No result was available versus guselkumab for PsARC response as no trials were identified reporting the treatment effect of guselkumab on this outcome.*
Abbreviations: *ACR: American College of Rheumatology; CrI: credible interval; NA: not available; OR: odds ratio; MD, mean difference; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area Severity Index; CFB: change from baseline; HAQ-DI: health assessment questionnaire disability index; NMA: Network Meta Analysis; Q8W: once every 8 weeks; MAIC, matching-adjusted indirect comparison.*

Table 3: Summary of company's ITC analyses for safety outcomes of risankizumab 150mg versus guselkumab 100mg Q8W at Week 24 (adapted from Table 14 of the CS and Table 11 of the clarification response)

Endpoint	Rates % (95% CrI)		NMA	Bucher ITC
	Risankizumab	Guselkumab	OR (95% CrI)	OR (95% CrI)
AE	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *AE: adverse event; CrI: credible interval; OR: odds ratio; SAE: serious adverse event; NMA: Network Meta Analysis; NR, not reported; ITC, indirect treatment comparison.*

3.2.4 Critique of company's ITC

3.2.4.1 Trial evidence used in the ITC

The ERG notes that all relevant trials were included in the NMAs, and the trials are generally at low risk of bias. The majority of trials had adequate randomisation and allocation concealment (ERG Clinical Appendix Tables 13-15), and all were double-blind. All reported either intent-to-treat (ITT) or modified-ITT (all randomised patients receiving at least one dose of study drug).

For most trials, the trial populations were broader than those of the CS decision problem. COSMOS and SPIRIT-P2 trials had a BIO-IR population, whereas others also included bDMARD-naïve patients. Of the trials with mixed populations (with the exception of PSUMMIT-2), they had stratified randomisation by prior bDMARD use (see ERG Clinical Appendix, Tables 13-14), and so intervention and placebo groups would be expected to be balanced in terms of baseline characteristics. The PSUMMIT-2 trial that did not stratify randomisation by prior bDMARD use, published the baseline demographics of the BIO-IR group, and baseline characteristics appear to be balanced between the groups. Trials were international, with a minority of centres in the UK, with the exception of DISCOVER-1 and Deodhar 2018 [redacted] (ERG Clinical Appendix, Table 16-17).

Comparing the BIO-IR groups of KEEPsAKE-2 and DISCOVER-1, baseline characteristics differed significantly in age, swollen joint counts, BSA affected, HAQ-DI, CRP (a marker of inflammation), DMARD use at baseline and PASI (CS Appendix D and clarification response, question A20).[21]

In the 24-week double-blind period of KEEPsAKE-2, in the whole trial ITT population (i.e. bDMARD naïve and bDMARD experienced), there were SAEs in 9/224 (4.0%) of the risankizumab group, and in 12/219 (5.5%) of the PBO group.[30] There were AEs in 124/225 (55.4%) of the risankizumab group, and in 120/219 (54.8%) of the PBO group.[30]

In 24 weeks of the DISCOVER-1 trial whole population (i.e. bDMARD naïve and bDMARD experienced), SAEs were reported by 0/128 (0%) in the guselkumab Q4W group, 4/127 (3.1%) in the guselkumab Q8W group, and 5/126 (4.0%) in the PBO group.[27] AEs were reported by 71/128 (55.5%) in the guselkumab Q4W group, 68/127 (53.5%) in the guselkumab Q8W group, and 75/126 (59.5%) in the PBO group.[27] Of the bDMARD experienced patients treated with either dose of GUS, 45/79 (57.0%) patients experienced any AE.[27]

Across all treatment groups in both trials, the most common AEs were infections.[1]

The ERG considers the following limitations of the included trial evidence:

- No head-to-head trials of risankizumab and guselkumab (or risankizumab and any other bDMARD) are available
- There is a lack of PsARC and HAQ-DI change from baseline conditional on PsARC response data for the guselkumab BIO-IR population

- Although data in NMAs are limited to the BIO-IR population, these data were not all also limited by moderate to severe psoriasis as defined by a BSA ≥ 3% affected by plaque psoriasis and a PASI score >10; and had two prior csDMARDs.

3.2.4.2 Representativeness of the subpopulation used in the ITC

In the absence of data for the subgroup of relevance to this appraisal (i.e., adult patients with active PsA who have moderate to severe psoriasis and have had two csDMARDs and at least one bDMARD), the company assumed that the relative efficacy of risankizumab versus guselkumab in the overall BIO-IR subgroup is the similar to this restricted subgroup. The ERG notes that there could be some difference in treatment effect between the BIO-IR and csDMARD-IR subgroup, and by psoriasis severity. Figures 22 and 27 of the CS show that a greater improvement compared with placebo was observed in the BIO-IR subgroup compared to the csDMARD-IR subgroup for ACR20 at Week 24, and CS Appendix D.9.2. states that it was determined that BSA ≥3% and PASI are treatment effect modifiers which were included in the MAIC.[1] The company argues that: (1) because the two treatments share a therapeutic class, it is expected that the potential treatment effect modifiers have a similar impact on the efficacy of the two treatments; (2) TA711 accepted the assumption that the efficacy in the BIO-IR population is generalisable to this restricted subgroup.[1] The ERG's clinical expert also shares a similar view.

3.2.4.3 Models used in the ITC

The appropriate link function was chosen for each of the NMA. When a network contains insufficient number of trials to appropriately estimate the between-study heterogeneity, a fixed effect model was chosen as the primary model. In the presence of between-study heterogeneity, the use of a fixed effect model would underestimate the uncertainty associated with the treatment effect. The company updated the analysis for the endpoints PASI 50/75/90/100 and HAQ-DI change from baseline at Week 24 using a random effects model with an appropriate informative prior distribution for the between-study heterogeneity parameter (clarification response, question A17).[21]

A logit link was used when modelling the efficacy outcomes ACR20/50/70 and PASI 75/90/100 using the MAIC and Bucher ITC approaches. The ERG believes that this is not the appropriate model choice because the data are ordered categorical and a probit link function should be applied just as in the NMAs.

3.2.4.4 Clinical equivalence

The ERG believes that the company's approach of using a non-inferiority margin to determine the probability of clinical equivalence (clarification response A18)[21] is not appropriate. The U.S. Food and drug administration (FDA) guidance for industry on non-inferiority clinical trials to establish effectiveness[33] states that the intent of a non-inferiority trial is not to show that the test treatment is

equivalent to the active control treatment, and if the lower limit of the confidence interval for the relative effect of the test treatment relative to the active control was only slightly negative (note that the outcome is continuous in this case), a judgement on similarity would be possible. The company used response rate difference to obtain the margin. However, ORs were presented as the measure for the relative treatment effect (CS, Table 11).[1] It is not clear whether ORs or rate differences were used to compare with the margin to obtain the probability of clinical equivalence.

The ERG believes that a better approach is to obtain the probability of the point estimate for the relative treatment effect falling within a clinical equivalence range using the CODA samples from the NMAs. The ERG used the CODA sample for efficacy and safety endpoints at Week 24 provided by the company (clarification response, question A9)[21] to obtain the probability of clinical equivalence. A scenario analysis was conducted to obtain the probability for a range of clinical equivalence range (Table 4 - Table 7).

Table 4: Probability of clinical equivalence for risankizumab vs. guselkumab Q8W at Week 24 for ACR20/50/70

	Fixed effect model			Random effects model		
	ACR 20	ACR 50	ACR 70	ACR 20	ACR 50	ACR 70
[0.9, 1.1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.8, 1.2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.7, 1.3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.6, 1.4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.5, 1.5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Probability of clinical equivalence for risankizumab vs. guselkumab Q8W at Week 24 for PASI50/75/90/100

	Fixed effect model				Random effects model			
	PASI 50	PASI 75	PASI 90	PASI 100	PASI 50	PASI 75	PASI 90	PASI 100
[0.9, 1.1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.8, 1.2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.7, 1.3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.6, 1.4]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[0.5, 1.5]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Probability of clinical equivalence for risankizumab vs. guselkumab Q8W at Week 24 for HAQ-DI change from baseline

	Fixed effect model	Random effects model
	HAQ-DI change from baseline	HAQ-DI change from baseline
[-0.1, 0.1]	[redacted]	[redacted]
[-0.2, 0.2]	[redacted]	[redacted]
[-0.3, 0.3]	[redacted]	[redacted]
[-0.4, 0.4]	[redacted]	[redacted]
[-0.5, 0.5]	[redacted]	[redacted]

Table 7: Probability of clinical equivalence for risankizumab vs. guselkumab Q8W at Week 24 for any AE and SAE

	Fixed effect model	
	Any AE	SAE
[0.9, 1.1]	[redacted]	[redacted]
[0.8, 1.2]	[redacted]	[redacted]
[0.7, 1.3]	[redacted]	[redacted]
[0.6, 1.4]	[redacted]	[redacted]
[0.5, 1.5]	[redacted]	[redacted]

The ERG notes that large uncertainty remains in whether risankizumab is clinical equivalent to guselkumab because of the lack of indirect comparisons in the two key outcomes PsARC and HAQ-DI change from baseline conditional on PsARC response, and wide CrIs for the estimates of efficacy and safety outcomes.

4. ERG'S CRITIQUE OF THE COMPANY'S COST-COMPARISON ANALYSIS

4.1 Summary of the cost-analysis scope, model structure and assumptions

4.1.1 Population, intervention and comparator

The company submitted a cost-comparison analysis for risankizumab versus guselkumab for patients with active PsA and moderate to severe psoriasis who have been previously treated with two csDMARDs and at least one bDMARD.[1] The executable model developed in Microsoft Excel® uses a 10-year time horizon and 4-week cycles to estimate the cost savings for risankizumab. The model does not include discounting, in line with the user guide for cost-comparison FTAs.[34] The company's analyses presented in the CS include the PAS discount for risankizumab and the list price for guselkumab. The results of the company's analyses including the cPAS discount for guselkumab are provided in a separate confidential appendix to this ERG report.

The intervention assessed within the cost-comparison is risankizumab, which is assumed to be administered via SC injections at a dose of 150mg in Weeks 0 and 4, and every 12 weeks thereafter. It is not clear what proportion of patients would be receiving MTX in combination with risankizumab, as recommended in its SmPC (see Section 2.2). However, the ERG notes that the analysis only includes the costs of risankizumab as monotherapy. The comparator included within the company's analysis is guselkumab administered via SC injections at 100mg per administration in Week 0, Week 4, and every 8 weeks thereafter. As presented in Section 2.3 of this report, the company has chosen not to include an alternative dosage schedule of dosing for guselkumab of 100 mg every 4 weeks for patients at high risk for joint damage,[22] nor have they included the costs of MTX as part of the combination therapy, similarly to the approach adopted for risankizumab.

The chosen comparator was selected on grounds of: guselkumab being the only drug specifically recommended for this restricted population of patients with active PsA and moderate to severe psoriasis previously treated with two cDMARDs and at least one bDMARD; its similar mechanism of action to risankizumab, and it being one of the most recent technologies recommended by NICE for this clinical indication. The ERG believes that the choice of comparator is appropriate based on NICE's guidance on undertaking cost-comparison.

4.1.2 Company's model structure

The company's model logic is presented in Section B.4.2.1 of the CS.[1] All patients enter the model in the 'Treatment Trial Period' where they receive therapy with risankizumab or guselkumab according to each treatment schedule and all patients are assumed to remain on treatment until the point of treatment response assessment (24 weeks) or death, which comes first. At the treatment response

assessment timepoint, patients who have responded adequately to treatment based on PsARC response criteria enter the "maintenance treatment" phase and are assumed to remain on treatment until they discontinue or die, whichever comes first. Patients who have not responded adequately to treatment are assumed to stop therapy and transition to the 'no treatment' state. Patients in the model are assumed not to incur further costs after they have stopped responding to treatment or discontinued.

4.1.3 Assumptions

The company's base-case analysis makes the following assumptions:

(i) Risankizumab and guselkumab are assumed to be clinically equivalent in terms of mortality, treatment response (based on PsARC rate from KEEPsAKE-2), treatment discontinuation rates (from previous NICE appraisals in PsA) and AEs.

(ii) The only difference in costs between the treatment groups relates to costs associated with drug acquisition. Costs related to drug administration, subsequent treatments, monitoring and management of the disease, and AEs are assumed by the company to be the equivalent in both treatment groups, and therefore are not included in the base-case analysis. Drug administration and monitoring costs are included as part of scenario analyses.

(iii) The model assumes that patients remaining alive during the trial period do not discontinue treatment, and patients achieving treatment response at 24 weeks are subject to a constant discontinuation rate which is applied in all subsequent cycles.

(iv) The risk of death during each model cycle is assumed to be the same as the age- and sex-matched mortality risks in the general population (from UK life tables). The model does not include a standardised mortality rate (SMR) for patients with PsA as a simplification of the analysis and considering the minimal impact on results given the assumption of clinical equivalence between the treatment groups adopted, the short time horizon and the approaches used in previous NICE appraisals in plaque psoriasis.[1]

4.2 Evidence used to inform the model parameters

The parameter values and evidence sources used to inform the company's cost-comparison analysis are summarised in Table 8. These are discussed in more detail in the subsequent sections.

Table 8: Evidence sources used to inform the company's cost-comparison model

Parameter	Value (base-case)	Value (scenario)	Source
Time horizon (years)	10	5	-
Cycle length (days)	28	Not varied	-
Population characteristics (age)	53	53	KEEPsAKE-2
Population characteristics (percentage female)	55.1%	55.1%	KEEPsAKE-2
Time until response assessment (weeks)	24	16	KEEPsAKE-2
Response rate (PsARC 24W or 16W)	[redacted]	[redacted]† (16W); 0.663 (TA711)[3]	Company's NMAs (24W and 16W);[1] TA711[3] (unadjusted FE model in the BIO-IR population)
Cost per pack – risankizumab	List price: £3,326.09 PAS price: [redacted]	Not varied	BNF[35]
Cost per pack – guselkumab	List price: £2,250.00 cPAS price: see confidential appendix	Not varied	BNF[36]
Discontinuation rate (annual)	16.5%	18.7%	Rodgers *et al.* (2011)[37] and previous NICE appraisals,[11-14, 17] TA511 (scenario analysis)[38]
RDI – both treatment groups	Not included		-
Administration costs	Not included	£42	PSSRU[39]
Monitoring costs (trial treatment period)‡	Not included	£60.26	TA711;[3] NHS Reference Costs 2019/2020[40]
Monitoring costs (maintenance treatment period)‡	Not included	£24.09	TA711;[3] NHS Reference Costs 2019/2020[40]
Subsequent treatment	Not included		-
AE frequencies and unit costs	Not included		-

ERG - Evidence Review Group; PAS - Patient Access Scheme; cPAS - comparator PAS; RDI - relative dose intensity; SA - sensitivity analysis; BNF - British National Formulary; AE - adverse event; NMA – network metanalysis
† During the factual check process, the company clarified that the PsARC response at 16 weeks from the NMA was incorrectly reported in the CS, and provided the correct value. The cost comparison analysis uses 2 decimal places for the estimates PsARC 24W and 16 W from the NMA).
‡Detailed monitoring costs are presented in Table 19 of the CS.

4.2.1 Patient characteristics

The characteristics of the modelled patient population were assumed to reflect the baseline characteristics of patients from the ITT population of KEEPsAKE-2, whereby the median age of the patients across both arms was 53 years and 55.1% were female.[24] These are similar to the baseline characteristics of the patient population in the risankizumab arm in the BIO-IR subgroup of the trial (CS Appendices, Table 18).[1] It is assumed that these characteristics are broadly comparable to the target

population of patients for this appraisal. The clinical expert consulted by the ERG noted that patients recruited in KEEPsAKE-2 (and DISCOVER-1 trial) had a higher swollen joint count than patients that would be eligible to receive risankizumab usually seen in clinical practice, which suggests that the patients in these studies had more severe rheumatological disease.

4.2.2 Treatment response rate

The company has selected PsARC as the outcome used in the cost-comparison analysis to evaluate the treatment response. The timepoint selected for the response assessment in the base-case was 24 weeks. Whilst the treatment response is assumed equivalent between the two treatment groups, this outcome drives the duration of initial treatment and the rate of discontinuation at this timepoint, and therefore costs. The CS states that *"PsARC has been used as the measure of response in economic analyses submitted in all prior appraisals and accepted by the committee. Therefore, PsARC was selected as the most appropriate outcome for the base-case analysis."*[1] The ERG notes, that in TA711, the outcome used to evaluate treatment response in the base-case economic analysis was also PsARC.[3] The company in the present appraisal has also presented the results of the cost-comparison using 16-weeks as a scenario analysis.

Nonetheless, the ERG notes the following points for consideration:

(i) The company has used an outcome for which the result of the NMA versus guselkumab for the BIO-IR subgroup was not available; this was justified by the lack of published data for guselkumab. Instead, the company has used the data for this outcome from KEEPsAKE-2 for both treatment groups, based on the assumption of clinical equivalence between risankizumab and guselkumab.

(ii) The timepoint of the treatment assessment is based on the information in the SmPC for guselkumab; however, the EMA European Public Assessment Report (EPAR) for risankizumab considers a different timepoint of 16 weeks for discontinuing treatment in patients who have shown no response. The choice of the timepoint of 24 weeks seems to disfavour the cost results for risankizumab, since patients who would have already shown no response at 16 weeks would continue to receive treatment for longer. The impact of adopting different timepoints in the analysis is unclear, since the model submitted does not allow for the use of separate values and different timepoints for each treatment group. In TA711, the company had initially included different timepoints for treatment response assessment, according to treatment received. However, the ERG considered this could benefit the results for biologic treatments with longer trial periods, since the treatment benefits accrued instantly upon entering the trial period are assumed not to be lost until the response timepoint is reached (unless the patient dies).[3] The ERG notes, nonetheless, that in TA711, a full model was developed with different

characteristics, and treatment response and length of the initial trial also impacted on costs of disease related management and benefits in terms of HRQoL.

(iii) The ERG for TA711 noted that NICE, in previous recommendations for other technologies in this disease, has also given consideration to the possibility of continuation of treatment for patients whose PsARC response does not justify continuation of treatment but who show a PASI 75 response.[3] The clinical expert consulted by the ERG noted that PSARC is a measure that looks only to the rheumatologic aspect of PsA, but other specialists such as dermatologists would look at benefits on skin condition to evaluate treatment response. The company has not included in the analysis any assessment related to the extension of response in terms of the skin condition.

In the factual accuracy check of the ERG report,[32] the company indicated that the PsARC response rate for risankizumab at 16W was reported incorrectly in the CS, and provided the correct estimate (presented in Table 2). The ERG notes that this corrected is much closer to the estimate at 24 weeks ([redacted] for 16W and [redacted] for 24W). Nonetheless this change impacts the total costs for risankizumab and guselkumab and the cost difference estimates, it does not alter the overall conclusions of the report.

4.2.3 Mortality

The cost-comparison analysis assumes that patients have the same risk of death as the general population of the UK. The company in TA711 included a SMR of 1.05 to account for increased mortality observed in patients with PsA; this was deemed consistent with previous PsA models.[3] For the risankizumab cost-comparison analysis, no adjustment factor has been included by the company. The CS justifies this exclusion stating that *"given the shorter time horizon of this cost-comparison model, and in line with cost-comparison analyses in moderate to severe plaque psoriasis (TA596, TA521 and TA723), an SMR was not included for simplicity."*[1] The ERG notes that mortality has very little impact on the difference in costs given the assumption of clinical equivalence between risankizumab and guselkumab (see Table 9).

4.2.4 Drug acquisition and administration costs

In line with their SmPCs, risankizumab and guselkumab are assumed to be administered via SC injections at fixed doses of 150mg and 100mg per administration, respectively. Risankizumab is assumed to be administered in Week 0, Week 4, and every 12 weeks thereafter, whilst guselkumab is assumed to be administered in Week 0, Week 4, and every 8 weeks thereafter.[2, 22]

The list price for risankizumab is £3,326.09 per 150 mg dose of pre-filled pens or syringes with 150mg/1ml solution for injection. A PAS for risankizumab is available in the form of a simple discount of approximately [redacted] of the list price, resulting in a discounted cost of [redacted] per 150mg dose.

The list price for guselkumab is £2,250.00 per 100 mg dose. Unit costs were taken from the British National Formulary (BNF).[35, 36]

Discontinuation of treatment with risankizumab and guselkumab during the post-trial period is assumed at an annual probability of 16.5% from Rodgers *et al.* (2011)[37]. This value has been used in prior NICE appraisals, including in the ERG-preferred analyses in TA711.[3, 11-14, 17] The annual probability applied in the model has been converted to a 4-weekly probability of 1.37%, assuming a constant rate.

Additional costs associated with wastage were not included in the model. The company assumes that since risankizumab and guselkumab are administered at fixed doses, using pre-filled syringes or pens, vial sharing is not possible. The company has further clarified that dose escalations or alterations of dose intervals are not within the marketing authorisation and were not permitted in the KEEPsAKE-2 trial (clarification response, question B9).[21] The ERG believes that, considering the assumption made in the cost-comparison analysis that patients' mortality follows the age and sex-matched general population risk of death, the impact of omitting wastage is likely minimal.

Administration costs were not included in the base-case analysis, based on the similar pattern of administration followed for both treatment groups. The company assumes that risankizumab and guselkumab, given their administration routes via pre-filled SC injections, will be initially administered in the clinic or community setting, and patients may be trained by a physician to self-inject the drug thereafter. Subsequent injections (after the initial 24 weeks) would be administered at home with homecare service provided and funded by the manufacturers of the drugs. A scenario analysis is explored by the company whereby administration costs are incorporated into the model only during the trial period. The ERG notes that there might be a proportion of patients who would not be eligible for self-administered injections; however, this discrepancy is likely to be minor.

The ERG also notes that, in contrast to what has been assumed in the scenario analyses, the administration costs for each treatment group might be different given the treatment schedules for risankizumab and guselkumab, as guselkumab is administered more frequently than risankizumab. In the company's scenario analyses where these costs are included, the company accounts for the same number of administrations within the 24-week trial period; however, guselkumab would account for one additional dose administration within that period, compared to risankizumab. The impact of this change is very small; nonetheless, it would increase the costs savings for risankizumab.

4.2.5 Monitoring and subsequent treatment costs

The model assumes that patients receiving risankizumab will not require any additional tests or follow-up appointments when compared to guselkumab and any potential concomitant medication use during

treatment would also be similar for both treatment groups. Therefore, costs related to the management of the disease have not been included in the base-case cost-comparison.[1] The ERG's clinical advisor shares the view that these would be similar in both treatment groups.

A scenario analysis including these costs was explored; details regarding the type of interventions and tests used and their frequencies are presented in CS, Table 19.[1] Risankizumab and guselkumab are described in the CS as requiring some forms of monitoring which includes clinical visits, blood, image and DNA tests, based on the previous NICE appraisal for guselkumab in the same indication (TA711) and NHS Reference Costs 2019-2020.[3, 40] The frequency per cycle of use of these healthcare resources is assumed to be higher in the treatment trial period compared to the maintenance period. The ERG notes that because the frequencies of the additional resources included in the analysis are assumed to be the same, this analysis does not have an impact on the cost difference between treatment groups, although the estimated total costs would rise for both groups.

The ERG also notes that other types of disease management costs, such as those associated with the management of arthritis and psoriasis were excluded from the cost-comparison analysis. These costs were included in TA711, and were intended to capture the impact of both arthritis and psoriasis severity on healthcare costs, being calculated based on absolute HAQ-DI scores and the proportion of patients achieving a PASI 75 response.[3] However, given the assumption of clinical equivalence adopted in the cost-comparison analysis, the inclusion of these costs would not impact on the cost difference between groups.

Costs associated with subsequent treatment after patients discontinue treatment with risankizumab and guselkumab were also not included in the analysis, based on the assumption that *"given that the response rates and discontinuation rates for risankizumab and guselkumab are assumed to be identical for this cost-comparison, it follows that future costs of alternative therapies would also be identical"*. Nonetheless, the company states that in practice patients would likely receive an alternative treatment upon failure of biological therapy with risankizumab or guselkumab. The ERG's clinical advisors confirmed the company's view that patients receiving either risankizumab or guselkumab are likely to be considered for the same treatment options upon loss of treatment response or discontinuation, and that downstream costs and outcomes would likely be similar for both groups.

4.2.6 Adverse event costs

In the cost-comparison analysis, AEs associated with the use of risankizumab and guselkumab are assumed to be identical, based on the results of the NMA analyses for AEs that did not indicate a statistically significant difference between the treatments in the AE and SAE outcomes (See Section 3.2.3). The company justified this approach on the basis that it was also applied in the previous NICE

appraisals for risankizumab and guselkumab in plaque psoriasis (TA596 and TA521). The CS also mentions that this assumption has been validated by clinicians; however, no further details of this validation process are provided. The ERG notes that the company in TA711 had initially included in the economic analysis treatment specific AEs with associated costs and quality-adjusted life year (QALY) losses. However, the ERG report highlighted that AEs had not been included in previous appraisals, and the ERG-preferred analysis did not include them. The ERG's clinical advisor stated that patients receiving risankizumab and guselkumab usually experience similar AEs, and there are no additional concerns in relation to toxicity for one drug compared to the other.

Overall, the ERG considers the assumptions used by in the cost-comparison analysis to be appropriate.

4.3 Company's model results

The results of the company's base-case analysis and sensitivity analyses using the discounted price for risankizumab and list price for guselkumab are presented in Table 9.

Table 9: Results of company's cost-comparison (adapted from CS, Table 25)

Scenario	Risankizumab	Guselkumab	Incremental
Company's base-case	[redacted]	£45,733	[redacted]
SA1 - time horizon 5 years	[redacted]	£34,444	[redacted]
SA2 - Treatment discontinuation rate based on TA511	[redacted]	£42,599	[redacted]
SA3 – Excludes mortality	[redacted]	£46,364	[redacted]
SA4 - Includes drug administration costs	[redacted]	£45,859	[redacted]
SA5 - Includes monitoring costs	[redacted]	£47,513	[redacted]
SA6 - Treatment response assessment at 16 weeks (PsARC response rate from NMA ([redacted]))	[redacted]	£43,725	[redacted]
SA7 - Treatment response assessment at 24 weeks (PsARC response rate TA711 (0.663))	[redacted]	£52,490	[redacted]

SA - sensitivity analysis; NMA - network meta-analysis; PsARC - Psoriatic arthritis response criteria; TA - technology appraisal

The company's base-case analysis suggests that risankizumab will generate estimated cost savings of [redacted] per patient compared to guselkumab. These costs saving are directly derived from the differences in the drug acquisition costs, and as a consequence of the assumption of equivalence adopted by the company. Scenario analyses that do not have an impact on drug acquisition costs (such as the inclusion of drug administration costs or monitoring costs) do not change the estimated costs savings generated by risankizumab. The estimated cost savings for risankizumab are reduced if the model adopts: a higher treatment discontinuation rate for both treatments, which leads to patients spending less time on treatment; the PsARC response rate for the shorter trial treatment period (from the NMA for the PsARC 16-weeks parameter); or a shorter time horizon (5 years). Conversely, adopting a higher PsARC response rate at 24 weeks (from TA711) leads to an increase on the estimated cost savings for

risankizumab. The company also presented results for one-way sensitivity analysis in Figure 29 of the CS,[1] where the PsARC response rate was the parameter with biggest impact on the cost difference between treatment groups.

The ERG notes that these analyses are not meaningful for decision-making as they do not include the cPAS discount for guselkumab. The results including the PAS discounted prices for risankizumab and guselkumab are presented by the ERG in a separate confidential appendix to this report.

4.4 ERG's critique of the company's economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted cost-comparison analysis. These included:

- Assessing whether the company's analysis is in line with NICE's guidance on undertaking cost-comparison FTAs[5]
- Verification of the calculations used in the cost-comparison model, which included double-programming the base-case and sensitivity analyses to check for errors
- Scrutinising the assumptions underpinning the cost-comparison model and discussing these with clinical experts
- Checking the correspondence between the description of the model reported in the CS[1] and the company's executable model and key parameter values used in the company's model against their original data sources (where possible).

The ERG double-programmed the company's cost-comparison model was able to generate the same results as those presented in the CS for the base-case analysis and each of the sensitivity analyses presented. The ERG believes that the company's analyses are not subject to programming errors. The ERG believes that the evidence sources and that the values applied in the executable model are consistent with their original sources. The company has mostly used previous assumptions and approaches accepted by the Appraisal Committee in TA711;[3] therefore, the sources used to obtain these parameter values are deemed appropriate by the ERG for this appraisal.

4.4.1 Adherence to NICE guidance on cost-comparison FTAs

The ERG believes that the company's analysis is broadly in line with NICE's guidance for undertaking cost-comparison FTAs.

4.4.2 Appropriateness of base-case model assumptions

As discussed in Sections 3.2.2 and 3.2.4.2, the ERG has some concerns relating to how the evidence from KEEPsAKE-2 and DISCOVER-1 were used by the company to inform the decision making is generalisable for the population for which the company is seeking a positive recommendation for

risankizumab. The proportion of patients with moderate to severe psoriasis in the BIO-IR subgroup of KEEPSAKE-2 was only [redacted] in the risankizumab arm and [redacted] in the placebo arm (clarification response, question A9), and only [redacted] patients in this group had received two prior csDMARDs.[21]

In addition, there are concerns related to the heterogeneity in psoriasis severity between the studies included in the ITC. The baseline characteristics of the patients in the biologic experienced subgroup in KEEPSAKE-2 that have been included in the NMA performed by the company, suggest that there might be significant differences in some of the characteristics related to disease extension or severity (Table 18 of the CS appendices), but it is unclear how these differences overall could affect the results of the NMA. It is also unclear how generalisable the results from the NMA are to the target population in which the company is seeking a positive recommendation for risankizumab (Section 3.2.4.2).

The ERG has some concerns regarding some of the base-case model assumptions, in particular:

- Trial populations may not be representative of population seen in UK clinical practice
- The trial used for risankizumab to inform the evidence for this appraisal had patients displaying more severe levels of disease of the disease than usually seen in the clinical practice in the UK, and lower prior use of cDMARDs. A similar issue was raised by the ERG in the guselkumab appraisal (TA711)[3]
- Treatment response, and in consequence treatment discontinuation after the initial period of 24 weeks is defined based solely on the PsARC response. However, the ERG in TA711 brought to attention the possibility of continuation on treatment for patients whose PsARC response does not justify continuation but who demonstrate a PASI 75 response.[3] However, it is unclear how a combined measurement would impact the results of the cost-comparison if clinical equivalence was not assumed for all clinical outcomes.
- Administration costs should be included consistently with the approach used for drug acquisition. This also has a minor impact on the cost difference between treatment groups.

The ERG also notes that the company has used as a source for the general population mortality the life tables for the UK instead of England. This is considered a minor issue and has not been addressed by the ERG in exploratory analyses.

The key difference between the company's preferred assumptions and the ERG's preferred assumptions is the inclusion of administration costs. These costs were applied only during the trial period as per the company scenario analysis; however, the ERG applied to these costs the same approach for calculating acquisition costs, which corresponds to applying the full administration cost (£42.00) at the cycles patients receive each drug dose. The ERG's preferred assumptions are aimed at ensuring consistency

within the analysis, the different treatment schedules for risankizumab and guselkumab, and with previous appraisals TAs in PsA. The ERG notes that, whilst the annual health care costs associated with management of arthritis and psoriasis were included in TA711, the ERG was unable to explore the inclusion of these costs in the cost-comparison, since the analysis structure does not account for changes in PASI-75 and HAQ-DI scores. Due to the absence of data from the NMA for the PSARC outcome, the ERG was also unable to explore an alternative approach to treatment response assessment.

4.4.3 ERG Exploratory analysis

The ERG undertook one additional exploratory analysis using the company's original submitted Excel model. The analysis presented in this section reflects the Patient Access Scheme (PAS) discount price for risankizumab and list price for guselkumab. The results of the analysis including cPAS discounts for guselkumab are presented in a separate confidential appendix to this report.

EA1: ERG-preferred analyses: Inclusion of drug administration costs using the ERG's approach

The model was amended to include drug administration costs for both risankizumab and guselkumab during the trial period, at the cycles at which patients are assumed to receive the drugs.

ERG exploratory analysis – results

Table 10 presents the results of the ERG's preferred analyses for the comparison of risankizumab versus guselkumab. The results indicate that the inclusion of the amendment for the drug administration costs lead to different total costs for risankizumab and guselkumab and to a small increase in the estimates of cost-savings for risankizumab compared with the company's base case analysis. Nonetheless, it does not change the overall conclusions of the economic analysis.

Table 10: ERG preferred analysis, risankizumab versus guselkumab

Option	Costs	Inc. costs	Conclusion
Company's base case			
Risankizumab	[redacted]	[redacted]	[redacted]
Guselkumab	£45,733	-	
EA1: ERG preferred analysis – Inclusion of drug administration costs using the ERG's approach			
Risankizumab	[redacted]	[redacted]	[redacted]
Guselkumab	£45,901	-	-

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Appendix 1 - Appendix for clinical section

Table 11: Trials included in NMAs, data at 24 weeks (reproduced from CS Appendix D, Table 10 and Figure 19 and Figure 20)

Trial	Treatments	PsARC	PASI	HAQ-DI	HAQ-DI change conditional on PsARC response	ACR	AEs	SAEs
Deodhar 2018 NCT02319759[28]	Guselkumab Q8W Placebo					ACR20 Week 24		Any SAE at week 24
DISCOVER-1 NCT03162796[27]	Guselkumab SC 100 mg Q8W Guselkumab SC 100 mg Q4W Placebo		75/90/100 Week 24			ACR20/50/70 Week 24		Any SAE at week 24
COSMOS NCT03796858[26]	Guselkumab SC 100 mg Q8W Placebo		75/90/100 Week 24	Week 24		ACR20/50/70 Week 24	Any AE at week 24	Any SAE at week 24
SPIRIT-P2 NCT02349295[41]	Ixekizumab SC 80 mg Q4W Placebo	Week 24	75/90/100 Week 24	Week 24		ACR20/50/70 Week 24	Any AE at week 24	Any SAE at week 24
KEEPsAKE 2 NCT03675308[30]	Risankizumab SC 150 mg Q12W Placebo	Week 24	50/75/90/100 Week 24	Week 24	Week 24	ACR20/50/70 Week 24	Any AE at week 24	Any SAE at week 24
NCT02719171[31]	Risankizumab SC 150 mg Q12W Placebo	Week 24	90/100 Week 24	Week 24	Week 24	ACR20/50/70 Week 24		
FUTURE 2 NCT01752634[42]	Secukinumab SC 150 mg Q4W Secukinumab SC 300 mg Q4W Placebo		75/90 Week 24	Week 24		ACR20/50/70 Week 24		
FUTURE 3 NCT01989468[43]	Secukinumab SC 150 mg Q4W Secukinumab SC 300 mg Q4W Placebo					ACR20/50 Week 24		
FUTURE 5 NCT02404350[44]	Secukinumab SC 300 mg Secukinumab SC 150 mg Secukinumab SC 150 mg without Loading Dose Placebo					ACR20/50/70 Week 24		
PSUMMIT 2 NCT01077362[45]	Ustekinumab SC 45 mg Q12W Ustekinumab SC 90 mg Q12W Placebo	Week 24	75 Week 24	Week 24	Week 24	ACR20/50/70 Week 24	Any AE at week 24	Any SAE at week 24
ASTRAEA[46]	Abatacept SC 125mg Placebo						Any AE at week 24	Any SAE at week 24

Table 12: Trials included in NMAs, data at 16 weeks (reproduced from CS Appendix D, Table 14)

Trial	Treatments	PsARC	PASI	HAQ-DI	HAQ-DI | PsARC	ACR
DISCOVER-1 NCT03162796[27]	Guselkumab SC 100 mg Q8W Guselkumab SC 100 mg Q4W Placebo					20/50/70 Week 16
COSMOS NCT03796858[26]	Guselkumab SC 100 mg Q8W Placebo		100 Week 16	Week 16		20/50 Week 16
SPIRIT-P2 NCT02349295[41]	Ixekizumab SC 80 mg Q4W Placebo		75/90/100 Week 16			20/50/70 Week 16
KEEPsAKE 2 NCT03675308[30]	Risankizumab SC 150 mg Q12W Placebo	Week 16	50/75/90/100 Week 16	Week 16	Week 16	20/50/70 Week 16
NCT02719171[31]	Risankizumab SC 150 mg Q12W Placebo	Week 16	50/75/90/100 Week 16	Week 16	Week 16	20/50/70 Week 16
FUTURE 2 NCT01752634[42]	Secukinumab SC 150 mg Q4W Secukinumab SC 300 mg Q4W Placebo					20 Week 16
FUTURE 3 NCT01989468[43]	Secukinumab SC 150 mg Q4W Secukinumab SC 300 mg Q4W Placebo					20/50 Week 16
FUTURE 4 NCT02294227[47]	Secukinumab SC 150 mg Q4W Secukinumab SC 150 mg without LD Placebo					20/50 Week 16
FUTURE 5 NCT02404350[44]	Secukinumab SC 150 mg Q4W Secukinumab SC 300 mg Q4W Secukinumab SC 150 mg without LD Placebo					20/50/70 Week 16
PSUMMIT 2 NCT01077362[45]	Ustekinumab SC 45 mg Q12W Ustekinumab SC 90 mg Q12W Placebo					20 Week 16

Table 13: Risankizumab trials quality assessment

	CS QA	ERG QA	CS QA	ERG QA
Study name Author (reference)	**KEEPsAKE 2**	**KEEPsAKE 2**	**NCT02719171**	**NCT02719171**
	Phase 3, PBO-controlled RCT		**Phase 2, dose-ranging, PBO-controlled RCT**	
Was randomisation adequate?	Yes; IRTS	Yes; IRTS. stratified by current csDMARD use (0 vs ≥1), number of prior biological therapies (0 vs ≥1) and extent of psoriasis (≥3% vs <3% body surface area)	Unclear [29]	Unclear [29] [redacted]
Was allocation adequately concealed?	Yes; IRTS	Yes; IRTS	Unclear	Unclear [29] [redacted]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	yes	Yes	[redacted]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes; double-blind	yes	Yes; double-blind	yes
Were there unexpected imbalances in dropouts between groups?	No	no	No	no
Were any outcomes measured but not reported?	No	Not for the whole study population (biologic-naïve and biologic-experienced). Clinical trials gov lists outcomes from the protocol, and reports results from each outcome. Not all outcomes published For biologic-experienced subgroup, although Ostler 2021b has baseline demographics and ACR20 point estimates. However, CS Doc B reports (CiC) other outcomes for the biologic-experienced subgroup (CS Doc B Table 9).	No	Not for the whole study population (biologic-naïve and biologic-experienced). Clinical trials gov lists outcomes from the protocol, and reports results from each outcome. For biologic-experienced subgroup, not published (but CiC data provided by CS clarification response A9)[21]
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes; ITT	For whole study population, mITT "all randomised patients who received at least one dose of study drug" (in practice, all but one patient who had been randomised to PBO).	Yes; ITT (FAS)	For whole study population, ITT results on clinical trials gov [29]

Table 14: Guselkumab trials quality assessment

	CS QA	ERG QA	CS QA	ERG QA	CS QA	ERG QA
Study name Author (reference)	**COSMOS**	**COSMOS**	**Deodhar 2018**	**Deodhar 2018**	**DISCOVER-1**	**DISCOVER-1**
	Phase 3, PBO-controlled RCT		**Phase 2, PBO-controlled RCT**		**Phase 3, PBO-controlled RCT**	
Was randomisation adequate?	Unclear	Unclear	Yes; central IWRS	yes	Yes; computerised IWRS	yes
Was allocation adequately concealed?	Unclear	Unclear	Yes; IWRS	yes	Yes; computerised IWRS	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	yes, except numerically "higher proportion of females and a lower mean body weight in the guselkumab" group [26]	Yes	Yes, except "Mean body surface area affected by plaque psoriasis and PASI scores seemed higher in the guselkumab group" "and numerically more patients in the guselkumab group had dactylitis or enthesitis" [28]	Yes	yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes; double-blind	yes	Yes; double-blind	yes	Yes; double-blind	yes
Were there unexpected imbalances in dropouts between groups?	No	no	No	no	No	no
Were any outcomes measured but not reported?	No	no	No	no	No	not for whole population
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes; ITT	yes ITT (note that mITT planned (all randomly assigned patients who received at least one dose) but in practice all randomised patients received study treatment and were included in the analyses)	Yes; ITT	yes ITT (note that mITT planned (all randomly assigned patients who received at least one dose) but in practice all randomised patients received study treatment and were included in the analyses)	Yes; ITT	mITT (all randomly assigned patients who received at least one dose)

Table 15: Other trials in NMAs quality assessment

	CS QA	ERG QA	CS QA	ERG QA	CS QA	ERG QA	CS QA	ERG QA	CS QA	ERG QA	CS QA
Study name Author (reference)	**FUTURE 2**	**FUTURE 2**	**FUTURE 3**	**FUTURE 3**	**FUTURE 4**	**FUTURE 4**	**FUTURE 5**	**FUTURE 5**	**PSUMMIT-2**	**PSUMMIT-2**	**SPIRIT- P2**
	Phase 3, PBO-controlled RCT		**Phase 3, PBO-controlled RCT**		**Phase 3, PBO-controlled RCT**		**Phase 3, PBO-controlled RCT**		**Phase 3, PBO-controlled RCT**		**Phase 3, PBO-controlled RCT**
Was randomisation adequate?	Yes; IVRS/IWSRS	yes	Yes; IVRS	yes	Yes; IVRS	yes	Yes; IVRS	yes	Yes; IVRS/IWRS	yes	Yes; computer generated random sequence
Was allocation adequately concealed?	Yes; Triple masking was done	yes	Yes; IVRS	yes	Yes; IVRS	yes	Yes; IVRS	yes	Yes; IVRS/IWRS	yes	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, except for imbalances in baseline PASI score and the proportion of female patients, patients with psoriasis affecting ≥3% BSA, and patients with dactylitis or enthesitis.	yes	Yes	yes	Yes	yes	Yes	yes	Yes	yes	Yes
Were the care providers, participants and outcome assessors blind to	Yes; double-blind	yes	Yes; double-blind	yes	Yes; double-blind	yes	Yes; double-blind	yes	Yes; double-blind	yes	Yes; double-blind

treatment allocation?											
Were there unexpected imbalances in dropouts between groups?	No	no	No	no	No	no	No	no	No	no	Unclear; withdrawals not reported
Were any outcomes measured but not reported?	No	no	No	no	No	no	No	no	No	no	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT	Yes; ITT

Table 16: Risankizumab and guselkumab trials in NMAs

	KEEPsAKE 2		NCT02719171		COSMOS		DISCOVER-1			Deodhar 2018	
Treatment group	RIS 150mg weeks 0, 4 and 16	PBO	RIS 150mg weeks 0, 4 and 16	PBO	GUS 100 mg Q8W	PBO	GUS 100 mg Q4W	GUS 100 mg Q8W	PBO	GUS 100 mg Q8W	PBO
Number of patients with prior bDMARDs	105 any prior bDMARD (103 prior TNFi) Prior failed bDMARDS: 72 failure of one bDMARD; 15 failure of more than one bDMARD) [30]	101 any prior bDMARD (100 prior TNFi) Prior failed bDMARDS: 64 failure of one bDMARD; 23 failure of more than one bDMARD) [30]	NR [31] [redacted] (CS clarification response A11)[21]	NR [31] [redacted] (CS clarification response A11)[21]	189 (167 one prior TNFi; 22 two prior TNFi) [48]	96 (85 one prior TNFi; 11 two prior TNFi)] [48]	38 (33 one prior TNFi; 5 two prior TNFi) [27]	41 (34 one prior TNFi; 7 two prior TNFi) [27]	39 (35 one prior TNFi; 4 two prior TNFi) [27]	9 (one prior TNFi) [28]	4 (one prior TNFi) [28]
Was randomisation stratified by biologic-naïve/biologic-experienced?	Yes [30]		unclear [31] [redacted] [25]		NA, all patients in trial prior TNFi (although stratified by number of prior TNFi (1 or 2)) [48]		Yes [27]			Yes [28]	
No. of UK patients/centres?	7 centres [29] N=NR		[redacted] [25]		5 centres[48] N=8 [49]		0 centres [27]			0 centres [28]	

Table 17: Other trials in NMAs

	FUTURE 2	**FUTURE 2**	**FUTURE 2**	**FUTURE 3**	**FUTURE 3**	**FUTURE 3**	**FUTURE 4**	**FUTURE 4**	**FUTURE 4**	**FUTURE 5**	**FUTURE 5**	**FUTURE 5**	**FUTURE 5**	**PSUMMIT-2**	**PSUMMIT-2**	**PSUMMIT-2**	**SPIRIT- P2**	**SPIRIT - P2**
Treatment group	Secukinumab 300 mg	Secukinumab 150 mg	Placebo	Secukinumab 300 mg	Secukinumab 150 mg	Placebo	Secukinumab SC 150 mg Q4W	Secukinumab SC 150 mg without LD	Placebo	Secukinumab SC 150 mg Q4W	Secukinumab SC 300 mg Q4W	Secukinumab SC 150 mg without LD	Placebo	Ustekinumab SC 45 mg Q12W	Ustekinumab SC 90 mg Q12W	Placebo	Ixekizumab 80mg Q4W	Placebo
Number of patients with prior bDMARDs	33 (1 prior TNFi n=16; 2or3 prior TNFi n=17)[42]	37 (1 prior TNFi n=26; 2or3 prior TNFi n=11)[42]	35 (1 prior TNFi n=16; 2or3 prior TNFi n=19)[42]	44[43]	44[43]	44[43]	27 [47]	27[47]	27[47]	65 (1 prior TNFi n=43; 2+ prior TNFi n=22)[44]	68 (1 prior TNFi n=45; 2+ prior TNFi n=23)[44]	64 (1 prior TNFi n=44; 2+ prior TNFi n=20)[44]	98 (1 prior TNFi n=65; 2+ prior TNFi n=33)[44]	60 [45]	58 [45]	62 [45]	122 [41]	118 [41]
Was randomisation stratified by biologic-naïve/biologic-experienced?	Yes[42]			Yes [43]			Yes [47]			Yes [44]				No [45] (however, baseline characteristics appear similar across treatment groups, Ritchlin suppl data TableS1) [45]			NA, all patients in trial prior TNFi (although stratified by "inadequate response to one TNF inhibitor, inadequate response to two TNF inhibitors, or intolerance to TNF inhibitors"[41]	
No. of UK patients/ centres?	12 centres [29] n=NR			13 centres [29] n=NR			1 centre[29] n=NR			21 centres[29] n=NR				10 centres[29] n=NR			6 centres , n=11 [29]	

NR=not reported; TNFi= Tumour necrosis factor inhibitor

Appendix 2 – Technical Appendix

ERG exploratory analysis 1 (ERG preferred analysis)

In the company's model, change the following formulas in the worksheet 'Base-case results':

- In cell R32 to '=I32*N32*Costs_admin*IF(E32<p_Controls_response,1,0)'
- In cell V32 to '=I32*O32*Costs_admin*IF(E32<p_Controls_response,1,0)'

Drag the formulas down to row 554.