NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Contents:

The following documents are made available to consultees and commentators:

Final Scope and Final Stakeholder list

1. **Technical Briefing**

2. **Company cost comparison submission** from AbbVie

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Psoriasis Association
   b. Psoriasis and Psoriatic Arthritis Alliance

5. **Expert personal perspectives** from:
   a. Ms Helen McAteer – patient expert, nominated by the Psoriasis Association
   b. Mr David Chandler – patient expert, nominated by the Psoriasis and Psoriatic Arthritis Alliance

6. **Evidence Review Group report** prepared by ScHARR

7. **Evidence Review Group report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Risankizumab for previously treated active psoriatic arthritis

Fast track appraisal

ERG: School of Health and Related Research

(ScHARR), The University of Sheffield

Technical team: Tom Jarratt

Risankizumab

Marketing authorisation	Risankizumab is indicated, alone or in combination with methotrexate, for the treatment of adults with active PsA who have had an inadequate response or who have been intolerant to one or more DMARDs.
Mechanism of action	Risankizumab is an anti-interleukin-23 (IL-23) antibody drug that reduces inflammation by blocking the action of the IL-23 protein
Administration	Subcutaneous injection
SmPC	The recommended dose for PsA is 150 mg administered as a subcutaneous (SC) injection at week 0, week 4, and every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.
Price	List - £3,326 per 150 mg dose [redacted]

FTA: cost-comparison

A cost-comparison FTA can be used if the drug provides similar/greater benefits at a similar/lower overall cost than a NICE-recommended comparator

Company submitted a cost-comparison against guselkumab (TA711):

- Positively recommended by NICE.
- Company is positioning risankizumab in the same subgroup (patients with active PsA who have moderate-to-severe psoriasis and have had 2 conventional DMARDs and ≥1 biological DMARD).

Market share of guselkumab:

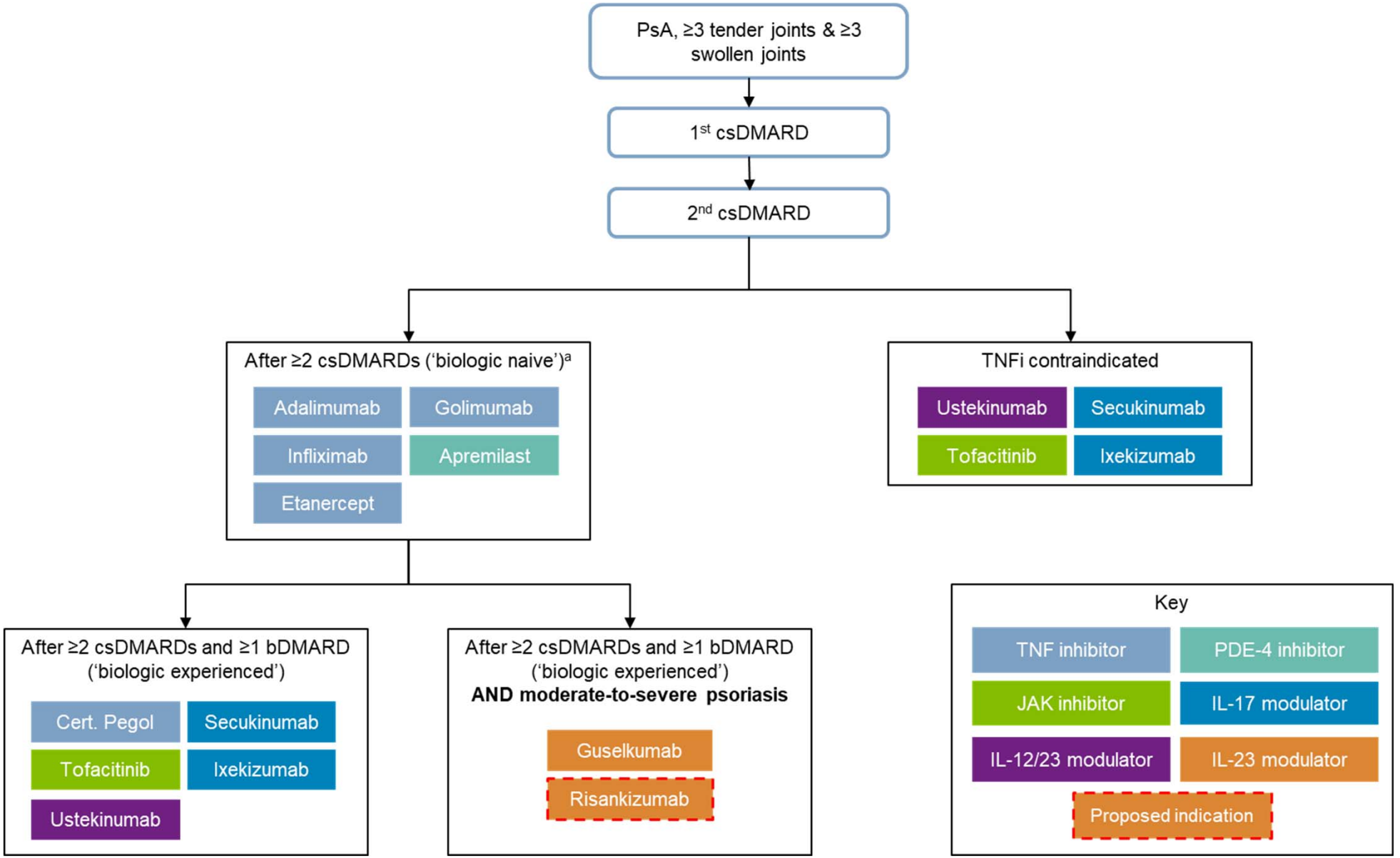
- Small in overall PsA population as relatively new in UK.
- Expected to increase in subgroup of biologic-experienced people with moderate-severe psoriasis.
- Company: guselkumab accepted as the comparator in the fast-track appraisal of risankizumab in plaque psoriasis (TA596), although market share was low.

Mechanism of action:

- risankizumab and guselkumab both work by inhibiting interaction with the IL-23 receptor.

Scrutiny panel view – chosen comparator appropriate for subgroup company in company's positioning.

Treatment pathway



NICE

Patient experts and professional groups

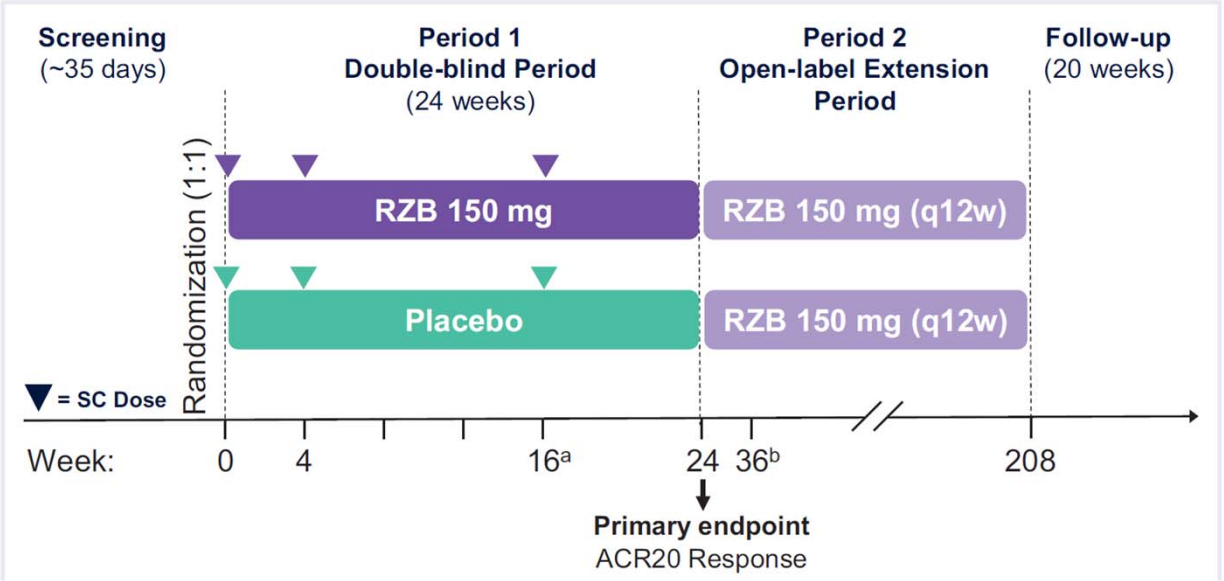
Patient experts

- There are few treatments for psoriatic arthritis and treatments often fail. Expanding the number of options is important.
- The pen device allowing easy self-administration is of great value.
- Mode of action of risankizumab is similar to other injectable same class treatments, and safety profiles look similar.
- Comorbidities such as fatigue, sleep disturbance, impacted mental health, pain, diminished work capacity and social participation should be included when assessing adequate treatment response.

Company

- Risankizumab has more convenient maintenance dosing schedule than guselkumab (12 weekly vs 8 weekly).

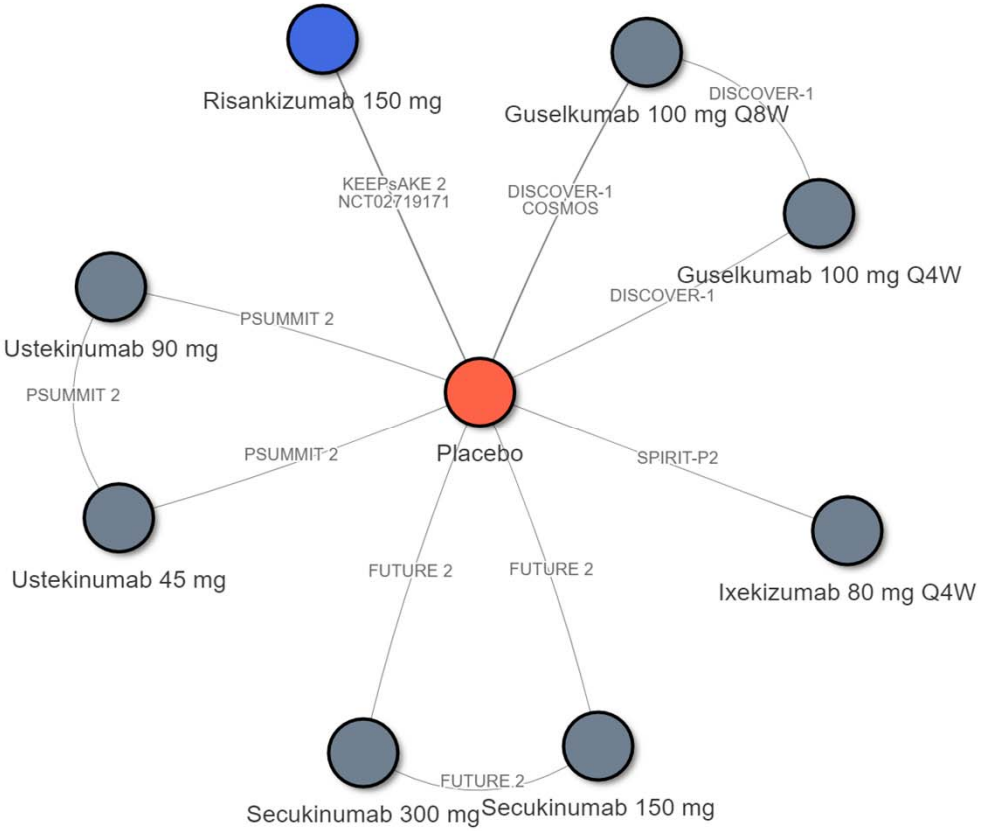
Clinical trials: KEEPsAKE-2



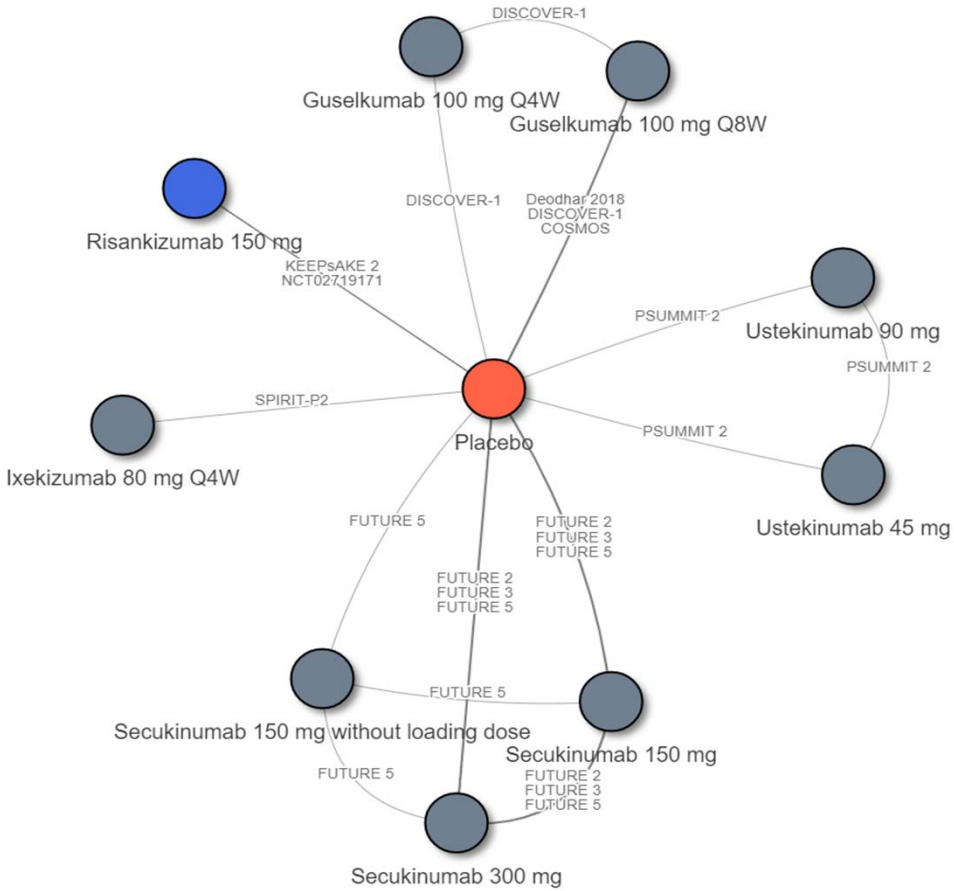
	KEEPsAKE-2
Population	Active PsA with inadequate response or intolerance to ≥1 biologic DMARD(s) and/or have had an inadequate response to ≥1 conventional synthetic DMARD(s).
Participants	443
Key results	• Significantly more patients in the risankizumab arm achieved ACR20 at week 24 compared to placebo (51.3% and 26.5%, respectively) • Secondary endpoints (HAQ-DI, PASI 90, MDA, SF36 physical component and FACIT fatigue at week 24) all significantly improved in risankizumab arm.

ACR20: ≥20% improvement in American College of Rheumatology score; q12w: every 12 weeks; RZB: risankizumab; HAQ-DI: Health assessment questionnaire disability Index; PASI: Psoriasis area and severity index; MDA: Minimal Disease Activity; SF36: Short-form 36; FACIT: Functional assessment of chronic illness therapy

Indirect treatment comparison: NMA



PASI network



ACR network

NICE

Indirect treatment comparison: Effectiveness

A network meta-analysis compared risankizumab vs guselkumab

Company:

- Results suggest clinical equivalence between risankizumab and guselkumab.

ERG:

- The point estimates of the odds ratios for the key outcomes of ACR and PASI at 24 weeks were close to 1, suggesting no difference.
- Wide confidence intervals (large uncertainty).

Endpoint	Response rates % (95% CrI)		NMA	After matching MAIC	Before matching Bucher ITC
At w24:	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]		

Scrutiny panel concluded that there were issues with applicability of the trial population and missing data for key outcomes. However, they noted that no differences were statistically significant.

Indirect treatment comparison: Safety

A network meta-analysis compared risankizumab vs guselkumab

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

Company:

- Results show that both options have similar tolerability.

ERG:

- Uncertainty in results due to wide confidence intervals.
- Effect estimates not close to 1.
- But all comparisons non-significant.

Scrutiny panel concluded that although there is uncertainty, the adverse event profile of risankizumab is likely to be similar to that of guselkumab

Issue 1: Trial population

Previous treatments

- KEEPsAKE-2 trial included people who previously had a biological DMARD **but only 51.0% of these patients had also received at least 2 conventional DMARDs**. Therefore, trial population is broader than population of interest
- TA711 for guselkumab also assumed that the efficacy in the biological experienced group is generalisable to the more restricted population. ERG clinical expert agrees with this view.

Disease severity

- Company defines moderate to severe psoriasis as a BSA ≥3% and a PASI score >10.
- Baseline characteristics of KEEPsAKE-2 show 54.6% had a BSA ≥3.
- The proportion with moderate to severe psoriasis in the biologic experienced subgroup of KEEPsAKE-2 was [redacted] in the risankizumab arm and [redacted] in the placebo arm. [redacted] people with moderate to severe psoriasis had received 2 prior csDMARDs.
- ERG notes the committee in TA711 accepted the use of the same efficacy and safety data for the biologic-experienced population in the cost-effectiveness model regardless of psoriasis severity.

Issue 2: Response assessment

- Company base case: response assessment at 24 weeks for risankizumab and guselkumab → aligned with primary outcome in trial and guselkumab recommendation
  - Scenario analysis with response assessment at 16 weeks for both treatments
- Guselkumab recommendation:
  - Assess the response to guselkumab from 16 weeks. Stop guselkumab at 24 weeks if psoriatic arthritis has not responded adequately using the Psoriatic Arthritis Response Criteria. If PsARC response does not justify continuing treatment but there is a PASI 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response
- Guselkumab SmPC:
  - Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment
- Risankizumab SmPC:
  - Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.

Issue 2: Response assessment

ERG:

- Model does not allow separate values and different timepoints for each treatment
- In TA711 (guselkumab), the company 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
- The recommendations for TA711 note that if PsARC response does not justify continuing treatment but there is a PASI 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response
  - the company has not included in the analysis any assessment related to the extension of response in terms of the skin condition.

Company's key assumptions

1) **Risankizumab and guselkumab are assumed to be clinically equivalent in mortality, treatment response, treatment discontinuation rates and AEs.**

ERG: While 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.

2) The only difference in costs is in drug acquisition (drug administration and monitoring costs are included as part of scenario analyses).

3) 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.

4) 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.

Scrutiny panels agrees that healthcare resource usage associated with drug administration, monitoring, managing AEs and subsequent treatment after patients progress whilst receiving risankizumab or guselkumab, are likely to be similar

Company's assumptions: admin and monitoring costs

Company:

- Company base case assumes people may self-inject after having initial training from a healthcare professional. It funds a homecare service so did not include administration costs in its base-case but included £42 for administration in scenario analysis for treatment administered during the trial period.

ERG:

- A proportion of people might not be eligible but consider a minor discrepancy.
- Guselkumab's administration costs should account for 1 more dose. The impact of this is very small.

Company:

- The company did not include monitoring costs in its base case because clinical expert advice confirmed healthcare resource use for risankizumab and guselkumab were similar but included a scenario analysis, assuming the healthcare resource use and costs based on those considered in TA711 and NHS Reference Costs 2019-2020.

ERG:

- The ERG notes the frequency per cycle of use is assumed to be higher in the treatment trial period compared to the maintenance period. This would mean estimated total costs would rise for both groups.

Company cost-comparison

Includes treatment and comparator discounts

Drug	Risankizumab (150 mg dose)	Guselkumab (100 mg dose)
List price	£3,326.09	£2,250.00
Average cost of a course of treatment	£46,646 (list price)	£45,733 (list price),
PAS price	[redacted]	[redacted]
Average cost of a course of treatment	[redacted]	[redacted]

	Dosing		
Risankizumab	Week 0	Week 4	Every 12 weeks
Guselkumab	Week 0	Week 4	Every 8 weeks

ERG exploratory analysis

- Included drug administration cost (£42) for both risankizumab and guselkumab during the trial period, for the cycle people would receive each dose.

- This leads to a small increase in the estimates of cost-savings for risankizumab compared with the company's base case analysis. But it did not change the overall conclusions.

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

Company's scenarios analyses

Scenario	Risankizumab	Guselkumab	Incremental
Company's base-case	[redacted]	[redacted]	[redacted]
SA1 - time horizon 5 years	[redacted]	[redacted]	[redacted]
SA2 - Treatment discontinuation rate based on TA511	[redacted]	[redacted]	[redacted]
SA3 – Excludes mortality	[redacted]	[redacted]	[redacted]
SA4 - Includes drug administration costs	[redacted]	[redacted]	[redacted]
SA5 - Includes monitoring costs	[redacted]	[redacted]	[redacted]
SA6 – Treatment response assessment at 16 weeks (PsARC response rate from NMA ([redacted])	[redacted]	[redacted]	[redacted]
SA7 –Treatment response assessment at 24 weeks (PsARC response rate TA711 (0.663))	[redacted]	[redacted]	[redacted]

Scrutiny panel conclusions

- Issues with generalisability of study populations.
- NMA shows no significant differences between treatments in effectiveness or safety, but confidence intervals are wide.
- Company base-case and ERG exploratory analysis suggest that risankizumab is cost saving compared to guselkumab
- 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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Document B

Company evidence submission

February 2022

File name	Version	Contains confidential information	Date
ID1399_Risankizumab PsA_Document B_ACIC	Final	Yes	08/02/2022

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse event
ANA	Antinuclear antibody
ASDAI	Ankylosing Spondylitis Disease Activity Score
bDMARD	Biological disease-modifying anti-rheumatic drug
BIO-IR	Biologic inadequate responder
BMI	Body mass index
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSR	British Society of Rheumatology
CASPAR	Classification Criteria for Psoriatic Arthritis
CFB	Change from Baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
csDMARD-IR	Conventional synthetic disease modifying anti-rheumatic drug – inadequate responder
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DB	Double-blind
DIC	Deviance information criterion
DMARD	Disease-modifying anti-rheumatic drug
DNA	Double stranded DNA
EMA	European Medicines Agency
EPAR	European public assessment report
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FACIT-Fatigue	functional assessment of chronic illness therapy-fatigue
FAS	Full analysis set
FTA	Fast track appraisal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health assessment questionnaire-disability index
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein

IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IgG1	Immunoglobulin G1
IL	Interleukin
ITC	Indirect treatment comparison
JAK	Janus kinase
LDI	Leeds dactylitis index
LEI	Leeds enthesitis index
LOCF	Last observation carried forward
LS	Least squares
MAA	Marketing authorisation application
MACE	Major adverse cardiac event
MAIC	Matching-adjusted indirect comparison
MAPP	Multinational Assessment of Psoriasis and Psoriatic Arthritis survey
MDA	Minimal disease activity
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed-effect model repeated measures
mNAPSI	Median nail psoriasis severity index
MTA	Multiple technology assessment
mTSS	Modified total sharp score
MTX	Methotrexate
N/A	Not applicable
NA	Not available
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NR	Not reported
NRI	Non-responder imputation
NRI-C	Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PAS	Patient access scheme
PASI	Psoriasis area severity index
PBO	Placebo
PDE	Phosphodiesterase
PE	Point estimate
PGA	Physician’s global assessment
PGA-F	Physician's global assessment of fingernails
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria

PsO	Psoriasis
PSW	Propensity score weighting
PT	Preferred term
PtGA	Patient's global assessment
PY	Patient year
QALY	Quality adjusted life year
QXW	Every x weeks
RCT	Randomised controlled trial
RZB	Rizankizumab
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SF-36 PCS	Short form-36 physical component summary
SJC	Swollen joint count
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SOC	System organ class
STA	Single technology appraisal
TAG	Technology appraisal guidance
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th	T-helper
TJC	Tender joint count
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
UK	United Kingdom
US	United States
VAS	Visual analogue score
VAT	Value added tax
WPAI	Work productivity and activity impairment

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

B.1.1 Decision problem

Population

Risankizumab has received a licence alone or in combination with methotrexate for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).[1] Risankizumab is positioned for use as an alterative to guselkumab. The submission therefore focuses on a subgroup of the technology's anticipated marketing authorisation, in order to align to the population for which guselkumab has received a positive recommendation from NICE. This population is adult patients with PsA who have[2]:

- 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 Psoriasis Area and Severity Index [PASI] score greater than 10) and
- had two conventional synthetic DMARDs (csDMARDs) and at least one biological DMARD (bDMARD).

This population represents patients with active PsA who have previously received csDMARD and bDMARD therapy and also have moderate-to-severe psoriasis. Guselkumab is the only technology recommended for this population specifically; no other treatments for PsA are recommended in this restricted subgroup, in which risankizumab is positioned for use.

Comparator

The manufacturer is proposing that the appraisal of risankizumab be considered under the NICE Fast Track Appraisal (FTA) process. The NICE user guide for FTA states that a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published technology appraisal guidance for the same indication.[3] Criteria for the selection of an appropriate comparator state that the selected comparator must fulfil the following:

- It adequately represents the NICE recommended treatments as a whole both in terms of costs and effects
- It has significant market share
- It is recommended in published NICE technology appraisal guidance for the same indication

Based on these criteria, guselkumab can be deemed the most appropriate comparator for this appraisal. This is consistent with the selection of guselkumab as the only relevant comparator in appraisal of risankizumab in moderate-to-severe plaque psoriasis (TA596), which was informed by a cost-comparison analysis.[4]

In addition a series of indirect comparisons were conducted to estimate the relative efficacy of risankizumab against the full range of comparators specified in the final scope (please refer to

Section B.3.8 for further details), with a focus on guselkumab. Evidence from the indirect comparisons demonstrates that risankizumab has similar efficacy to guselkumab.

Guselkumab is the only technology recommended in the restricted subgroup of patients with PsA who are 'biologic-experienced' and have moderate-to-severe psoriasis (TA711), in which risankizumab is positioned for use.[2] Guselkumab therefore represents the most relevant comparator used in clinical practice in this specific population, with other bDMARDs recommended for broader patient populations that do not align to the positioning of risankizumab. In addition, guselkumab is one of the most recent technologies to be recommended by NICE for patients with PsA (June 2021); the cost-effectiveness of guselkumab has therefore been established by NICE when compared to all other treatments that could be considered established practice in this restricted population, as per the NICE scope (ustekinumab, secukinumab, certolizumab pegol, tofacitinib and ixekizumab). The committee and ERG in TA711 also agreed that guselkumab appeared to be very similar in effectiveness to other interleukin inhibitors (secukinumab and ixekizumab).[2] As discussed, risankizumab provides similar health benefits at similar or lower cost than guselkumab, eliminating the need for comparisons to other treatments to be replicated in this appraisal and making guselkumab the only relevant comparator.

As guselkumab is relatively new to the UK market for PsA, it is not expected that guselkumab has a significant market share in the overall PsA population at present. However, increasing market share can be observed for guselkumab in PsA in countries where guselkumab launched earlier than the UK.[5] It is expected that the market share in the UK will increase within the subgroup of patients with moderate-to-severe psoriasis and who are 'biologic-experienced', as guselkumab is the only technology currently recommended for this population specifically. The criteria of increasing market share was endorsed by the committee in TA596.[4]

The decision problem addressed within this submission is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active PsA whose disease has not responded adequately to previous biological therapies or conventional synthetic DMARDs (csDMARDs), or for whom biological therapies or csDMARDs are not tolerated or for whom DMARDs are contraindicated.	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 of at least 3% affected by plaque psoriasis and a PASI score greater than 10) • had 2 csDMARDs and ≥1 bDMARD This population can be referred to as biologic-experienced with moderate-to-severe psoriasis.	The submission will align exactly to the population for which guselkumab has received a recommendation from NICE (narrower than the licensed indication/marketing authorisation of risankizumab).[2] This population is broadly in line with the subgroup of patients from the KEEPsAKE-2 trial, which provides the clinical evidence for risankizumab in this indication, who had received prior csDMARD and prior biologic therapy (biologic-experienced).
Intervention	Risankizumab	Risankizumab	N/A – in line with the NICE final scope
Comparator(s)	For people who have only received 1 previous conventional DMARD • Conventional DMARDs For people whose disease has not responded adequately to at least 2 conventional DMARDs: • Biological DMARDs (with or without methotrexate including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab) • Apremilast • Tofacitinib • Upadacitinib (*subject to ongoing*	Guselkumab	Risankizumab is positioned as an alternative to guselkumab in UK clinical practice for treatment of active PsA in a restricted subgroup of patients for which only guselkumab is specifically recommended (patients with moderate-to-severe psoriasis who have had 2 conventional DMARDs and at least 1 bDMARD). The patient population addressed in the submission is in line with this restricted population, where guselkumab represents the most relevant comparator. Other comparators in the NICE final scope are recommended for broader patient populations which do not

	NICE appraisal) For people whose disease has not responded adequately to conventional DMARDs and 1 or more TNF-alpha inhibitors: • Ustekinumab • Secukinumab • Certolizumab pegol • Tofacitinib • Ixekizumab • Guselkumab • Best supportive care • Upadacitinib (*subject to ongoing NICE appraisal*) For people in whom TNF-alpha inhibitors are contraindicated or not tolerated: • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Guselkumab • Best supportive care • Upadacitinib (*subject to ongoing NICE appraisal*) For people whose disease has not responded adequately to conventional DMARDs and 1 or more biological DMARDs, or for whom these are not tolerated: • Guselkumab • Best supportive care • Upadacitinib *(subject to ongoing NICE appraisal)*		align to the positioning of risankizumab in clinical practice. Guselkumab is considered the only relevant comparator within the scope of the FTA for the following reasons: • Guselkumab is one of the most recent technologies to be recommended by NICE for patients with PsA; the cost-effectiveness of guselkumab has therefore been established by NICE when compared to all other treatments that could be considered established practice in this restricted population[2] • Evidence from the indirect comparisons demonstrates that risankizumab has similar efficacy to guselkumab (Section 3.8). As risankizumab and guselkumab share a mechanism of action, clinicans would likely consider them as alternative treatment options • Increasing market share can be observed for guselkumab in PsA in countries where guselkumab launched earlier than the UK[5] • Guselkumab was the only relevant comparator in the appraisal of risankizumab in moderate-to-severe plaque psoriasis (TA596), which was informed by a cost-comparison analysis[4]

			In the final scope published by NICE, the positioning of guselkumab is not consistent with the recommendation from NICE, which is for 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 • had 2 conventional DMARDs and ≥1 bDMARD
Outcomes	The outcome measures to be considered include: • 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	Outcome measures include: • Disease activity (assessed using PASI, PsARC and ACR response) • Functional Capacity (HAQ-DI) • Radiographic progression (mTSS) • Periarticular disease (enthesitis and dactylitis resolution) • Adverse effects of treatment • Health-related quality of life (assessed using SF-36 and FACIT-Fatigue)	AbbVie do not consider mortality to be a relevant outcome. Patients with PsA have been reported to have slightly higher risk of mortality compared to the general population and generally have a good prognosis in terms of mortality.[6] Therefore, the goal of treatment in psoriatic arthritis is to manage symptoms and reach a state of remission, or low disease activity, rather than improve life expectancy.[7] Furthermore, studies in rheumatic conditions are typically conducted over 24 weeks in order to capture meaningful differences in disease activity, which does not provide enough time to capture sufficient mortality events. Mortality was therefore not assessed in the Phase 3 KEEPsAKE-2 trial, which provides the evidence base for this submission. Axial outcomes are not included in the submission as this outcome has not been requested in any previous NICE appraisals for PsA (TA445, TA537, TA543 and TA711]).[2, 8-10]

			Radiographic progression was not assessed in KEEPsAKE-2 however it was assessed in KEEPsAKE-1. KEEPsAKE-1 was conducted in a biologic-naïve population and provides supporting evidence for risankizumab in this submission (presented in Appendix I).
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered. The availability of any managed access arrangement for the intervention will be taken into	• A cost-comparison analysis has been conducted in Microsoft Excel to estimate the incremental costs of risankizumab versus guselkumab • The time horizon for assessing costs was set to 10 years, which is sufficiently long to capture the majority of costs associated with the use of risankizumab. • Costs were considered from an NHS and Personal Social Services perspective • A patient access scheme (PAS) for risankizumab has been included as part of the analysis	The manufacturer believes that risankizumab can be appropriately assessed through the NICE FTA process due to the similarities in terms of both effectiveness and costs with guselkumab and as such, a cost-comparison has been submitted. The cost-comparison compares the drug acquisition costs for risankizumab versus guselkumab. A 10-year time horizon was adopted to align with ERG and Committee preferences in previous appraisals that employed cost-comparison analyses (TA596, TA521 and TA723) in moderate-to-severe plaque psoriasis (in the absence of cost-comparison precedence in PsA).[4, 11, 12]

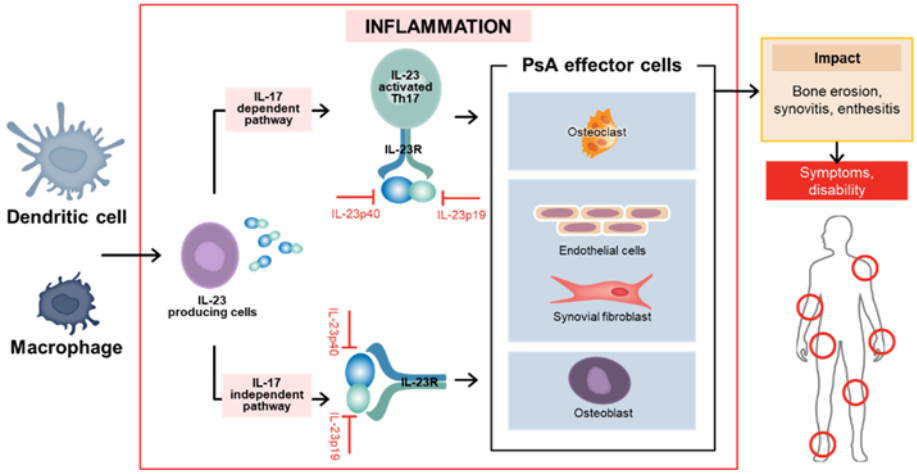
	account		
Subgroups to be considered	If evidence allows the following subgroups will be considered: • the reason for previous treatment failure (for example due to lack of efficacy, intolerance, or adverse events) • mechanism of action or number of previous treatments • presence or severity of concomitant psoriasis (no psoriasis, mild, moderate, or severe psoriasis) • presence or severity of axial involvement	No further subgroup analyses have been conducted.	The patient population addressed in this submission represents a specific subgroup of the population specified in the NICE final scope and the licenced indication. Therefore, no further subgroup analyses are of relevance.

Abbreviations: ACR: American College of Rheumatology; bDMARD: biological disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; ERG: Evidence Review Group; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; IL: Interleukin; mTSS, modified Total Sharp Score; NHS: National Health Service; PAS: patient access scheme; PASI: Psoriasis Area and Severity Index; PsA: Psoriatic Arthritis; PsARC: Psoriatic Arthritis Response Criteria; SF-36: 36 Item Short-Form Health Survey.
Sources: Risankizumab NICE final scope [ID1399];[13] AbbVie Data on File KEEPsAKE-1 CSR;[14]; AbbVie Data on File KEEPsAKE-2 CSR.[15]

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with risankizumab for the treatment of adults with active PsA with moderate-to-severe psoriasis who have previously received two csDMARDs and at least one bDMARD is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Risankizumab (Skyrizi®)
Mechanism of action	Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 (without binding to IL-12) and inhibits its interaction with the IL-23 receptor complex.[16] IL-23 is a cytokine that is involved in inflammatory and immune responses; it is referred to as a 'master cytokine' because it regulates cells which themselves further promote inflammation.[17] For example, IL-23 binds to T-helper (Th)-17 cells and macrophages which in turn promote the release of other cytokines, such as IL-17, IL-6, IL-1, IL-22 and tumour necrosis factor (TNF).[17] This IL-23-Th17-IL17 pathway is believed to be crucial in the development of skin and joint manifestations in PsA (Figure 1).[14, 15, 18] By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.[16] The control of the 'upstream' causes of PsA by IL-23 inhibition therefore offer patients an efficacious, durable response by controlling inflammation. **Figure 1: Risankizumab mechanism of action**  **Abbreviations**: IL: interleukin; PsA: psoriatic arthritis; Th: T-helper.
Marketing authorisation/CE mark status	A marketing authorisation application (MAA) for risankizumab alone or in combination with methotrexate, for the treatment of active PsA in adult patients who have had an inadequate response or have been intolerant to

	one or more DMARD therapies was submitted to the European Medicines Agency (EMA) via the centralised procedure in April 2021,[19] and a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) was adopted on 14th October 2021.[20] The marketing authorisation for risankizumab in this indication was approved by the EMA on 16th November 2021 and approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on the 18th November 2021.[16, 21]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The Summary of Product Characteristics (SmPC) for risankizumab in this indication is provided in Appendix C. Risankizumab is indicated:[16] • alone or in combination with methotrexate, for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more DMARDs • for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy Contraindications include: • Hypersensitivity to the active substance or to the listed excipients: Sodium acetate trihydrate; Acetic acid; Trehalose dihydrate; Polysorbate 20; Water for injections • Clinically important active infections (e.g. active tuberculosis). Risankizumab should be used with caution in patients with a chronic infection, a history of recurrent infection, or known risk factors for infection[16] Full details of contraindications can be found in the SmPC.[16]
Method of administration and dosage	Risankizumab is available as 150 mg/1 ml solution for injection in a pre-filled pen or syringe.[22] Risankizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of PsA. The recommended dose for PsA is 150 mg administered as a subcutaneous (SC) injection at week 0, week 4, and every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.[16]
Additional tests or investigations	In accordance with routine clinical practice for the use of biologics, prior to initiation of therapy, patients should be evaluated for tuberculosis infection and completion of all appropriate immunisations should be considered according to current immunisation guidelines. No additional tests or investigations are stipulated within the license.
List price and average cost of a course of treatment	The list price of risankizumab for one 150 mg dose is £3,326.09.[22]
Patient access scheme (if applicable)	Risankizumab is available under a confidential PAS discount in the treatment of plaque psoriasis. It is anticipated the [redacted] will apply to PsA. This with-PAS net pack price for risankizumab is [redacted], and the cost per patient is [redacted] in the first year and [redacted] in subsequent years (assuming no treatment discontinuation).

Abbreviations: PsA: Psoriatic Arthritis; IL-23: Interleukin-23 DMARD: Disease-modifying antirheumatic drug; PAS: Patient access scheme; TNF: Tumour necrosis factor; Th17: T-helper 17; IgG1: Immunoglobulin G1;SC: Subcutaneous.

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

Summary of the health condition

- Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease with co-existing musculoskeletal and dermatological manifestations.[23]
- PsA is progressive and can cause permanent joint and tissue damage and ultimately disability. However, the disease course may be erratic, with flare-ups and remissions.[24]
- The precise pathophysiology of PsA is not yet well understood.[25] It is known to be an immune-mediated disease caused by complex interactions between genetic and environmental factors. As the pathogenesis of PsA is multifactorial, there is substantial heterogeneity in clinical presentation.[26, 27]
- In the UK, the prevalence of PsA has been reported to be 0.19% (approximately 130,000 patients) with males and females being affected equally.[28, 29]
- PsA is associated with high symptom, psychosocial and economic burden:
    - Joint and skin symptoms range from mild to very severe, and include painful joint inflammation, debilitating skin psoriasis, dactylitis, enthesis and nail disease.[7, 23, 30] PsA is also associated with debilitating comorbidities such as cardiovascular disease and metabolic syndrome.[31-33]
    - As a result, patients with PsA experience significantly reduced HRQoL compared with the general population.[34] Key drivers of reduced HRQoL are joint pain and swelling, skin involvement and associated sleep problems.[30, 35]
    - The variable clinical burden requires substantial use of multiple healthcare resources resulting in high direct healthcare costs. The combination of physical and psychological symptoms experienced by patients with PsA contributes to lost productivity and unemployment. The economic burden of PsA is therefore substantial due to both direct healthcare costs and indirect costs.

Unmet need

- As PsA is a lifelong, relapsing, and remitting disease, multiple therapies are needed to provide patients and clinicians with a range of effective treatment options.[30, 36]
- Despite several available treatment options, there remains a burden of unmet need amongst the PsA population. [30, 37]
- Treatment options for individual patients are determined/limited by disease presentation, contraindications, comorbidities, adverse effects and prior treatment history.[38]
- The unmet need is heightened in the biologic experienced population as patients are likely to have experienced multiple treatment discontinuations due to adverse events (AEs) or lack/loss of effect of biologics.[39]

Position of risankizumab in the treatment pathway

- Risankizumab is positioned as an alternative to guselkumab for biologic-experienced patients with moderate-to-severe psoriasis. This is the population for which guselkumab has received a positive recommendation from NICE; risankizumab and guselkumab share a therapeutic class and have been shown to have similar costs and health benefits.
- Risankizumab offers an additional treatment option that effectively sustains skin clearance and addresses joint symptoms, with a favorable safety profile, predictable and convenient dosing regimen, and minimal budget impact.

B.1.3.1 Health condition

Disease background

PsA is a chronic, progressive, inflammatory arthropathy associated with the skin disease psoriasis.[26] Between 30% and 40% of people with psoriasis go on to develop PsA, usually within 5 to10 years of cutaneous disease onset.[40] PsA often leads to impaired function and a reduced quality of life.[24-26] Although PsA is a progressive condition, its course may be erratic, with flare-ups and remissions; 'active' PsA means a patient is currently experiencing tenderness in at least three joints and swelling in at least three joints.[41]

The precise pathophysiology of PsA is not yet fully understood.[25] As with other chronic inflammatory autoimmune conditions, it is known that PsA is the result of complex interactions between genetic and environmental factors.[26, 27] PsA is immune-mediated and possibly shares pathogenic mechanisms with psoriasis.[42] Research has highlighted that environmental factors appear to impact individuals with genetic susceptibility PsA.[43] These include infections, trauma, stress, obesity and smoking.[43] The pathogenesis of PsA is multifactorial and tends to vary between affected anatomical sites, thus resulting in heterogenous clinical presentation at different sites affected.

Characteristic symptoms include inflammation within and around joints and extra-articular manifestations such as skin and nail disease, uveitis and inflammatory bowel disease (IBD).[23] PsA can cause permanent joint and tissue damage and ultimately disability. However, the disease can be modulated by immunosuppressive therapy; patients with moderate-to-severe disease require timely disease management with effective treatments.[24]

Diagnosis and severity

There is no specific test for diagnosing PsA, with diagnosis involving a mixture of multispecialty assessment, patient-reported measures, clinical history, physical examination and imaging tests.[40] The Classification of PsA (CASPAR) criteria can be used as a diagnostic aid which incorporates clinical presentation, history, and radiographic and laboratory evidence.[44] PsA may be categorised according to disease severity as either mild, moderate or severe, although there are no set definition for these categories. In general, mild disease has minimal impact on quality of life; moderate disease affects a person's ability to perform daily tasks of living and physical functions; and severe disease causes major pain and dysfunction.[45]

Assessment of the severity of disease is generally informed by the number of joints affected and patient's responsiveness to treatment. The Psoriatic Arthritis Response Criteria (PsARC) is recommended in the assessment and monitoring of PsA and incorporates tender/swollen joint count with patient/physician global assessment of disease activity.[46] Several other tools have been developed to measure disease activity and patient-reported outcomes in PsA, as described in Section B.3.3.1.

Epidemiology

In the UK, the prevalence of PsA has been reported to be 0.19% (approximately 130,000 patients).[28, 29] Males and females are affected equally. PsA is especially likely to manifest in and adversely affect patients of working age (30–50 years).[29] It should be noted that the disproportionate impact of the disease on people of working age is not captured in the cost-comparison analysis but is nevertheless an important concern to patients. Studies reporting on

the mortality rates of patients with PsA are conflicting; some studies have demonstrated an increased risk of mortality, while others have highlighted no impact on mortality when compared to the general population.[47-50]

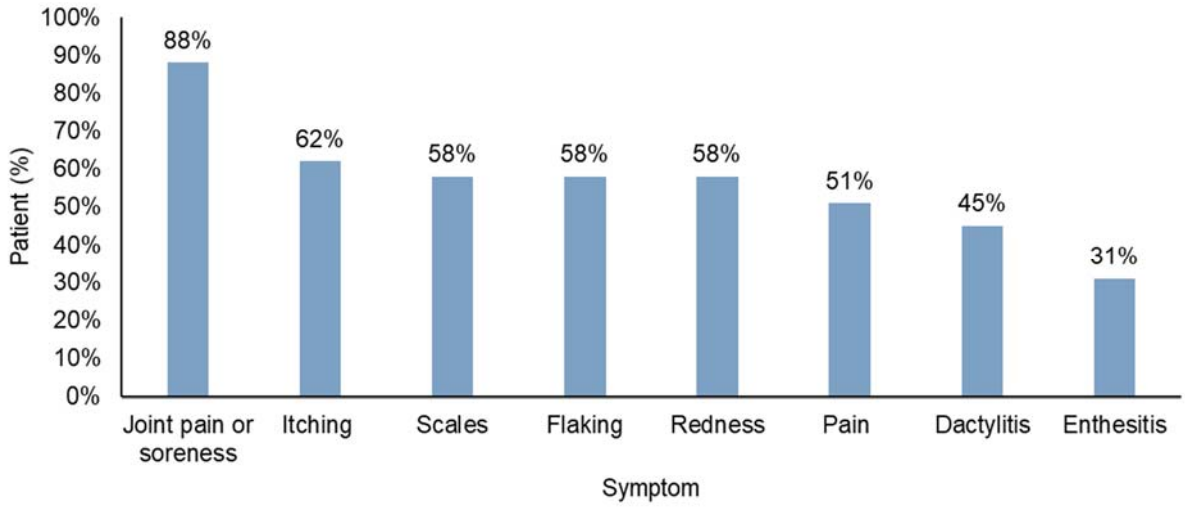
B.1.3.2 Disease burden

Symptom burden and comorbidities

The disease has a heterogeneous clinical presentation; joint and skin symptoms range from mild to very severe and do not always correlate with each other.[31] Joint symptoms typically include tenderness and swelling; dactylitis (severe inflammation of the fingers or toes) is found in 40–50% patients with PsA in clinical practice and enthesitis (inflammation of the attachment sites for tendons or ligaments) is observed in 30–50% of patients with PsA in clinical practice, with the Achilles tendon being the most frequently affected joint.[26] Skin disease is also common in PsA. An estimated 80% of PsA patients have skin psoriasis, characterised by erythematous, flaking, scaling skin,[23] which can severely affect patients' health-related quality of life (HRQoL).[35] With coexisting skin and joint features, the symptom burden in PsA is substantial. Patients have emphasised that there is a compounding burden of skin and joint symptoms; both contribute to psychological and functional burden.[51]

Figure 2 shows the symptoms reported by patients, despite current treatments, in the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey which examined the impact of PsA symptoms on patients' activities of daily living; 3,426 patients participated in the survey, including 712 (21%) who identified themselves as having PsA. 88% of patients reported current joint pain or soreness, 31% of patients reported symptoms resembling enthesitis, 45% of patients reported symptoms resembling dactylitis, whilst 21% of patients reported nail symptoms. Additionally, more than half of patients reported on symptoms associated with psoriatic skin lesions.[30]

Figure 2: PsA symptoms reported by patients in the MAPP survey



Abbreviations: MAPP: Multinational Assessment of Psoriasis and Psoriatic Arthritis study; PsO: psoriasis.
Source: Kavanaugh *et al.* (2016)[30]

PsA is also associated with a range of debilitating comorbidities including cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, Crohn's disease, ophthalmic disease, depression, and anxiety. More than half of PsA patients have at least one comorbidity.[32]

The high number and severity of these comorbidities exacerbates the patient burden in PsA. The need to be treated for these multiple comorbidities also increases the treatment burden faced by patients with PsA and the use of healthcare resources, and these are associated with a known mortality impact.[33]

Quality of life impact and psychosocial burden

Patients with PsA experience significantly reduced HRQoL compared with the general population.[34] Clinical features of PsA, including comorbid conditions and erratic disease activity, contribute to reduced self-perceived health status and physical and emotional functioning.[52] Key drivers of reduced HRQoL are joint pain and swelling, skin involvement and associated sleep problems.[30, 35] Inflammatory joint pain causes physical dysfunction and immobility, and represents one of the largest contributing factors to self-perceived disease severity.[30] Moreover, skin manifestations represent a key HRQoL impediment.[53] Survey evidence indicates that painful, inflamed, or broken skin is extremely bothersome for patients.[30, 35] In a multinational patient survey, increased skin involvement in psoriatic disease had a greater impact on HRQoL when compared to joint symptoms, even in milder forms of the disease, indicating a moderate to extremely large effect of psoriasis on HRQoL.[53]

Physical functioning scores, as measured using the Health Assessment Questionnaire Disability Index (HAQ-DI), generally worsen as the number of inflamed joints and disease activity increases, reducing both the capacity to carry out daily activities and HRQoL.[54] HAQ-DI assesses patients' physical functioning in 20 questions pertaining to eight domains: dressing, rising, eating, walking, hygiene, reach, grip, and common daily activities. Patients with enthesitis/dactylitis and patients with a higher body surface area affected by psoriasis report particularly high HAQ-DI scores relative to the background population, suggesting these are especially burdensome symptoms.[30] Patients also report significantly lower HRQoL compared with the general population, as measured using the short form-36 (SF-36) health questionnaire.[54] The SF-36 assesses health status across eight domains: physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health. Patients with PsA display considerably lower mean SF-36 scores (0.651) than age and gender matched controls (0.848).[55] Additionally, all domains of the SF-36 were lower in patients with PsA than age and gender matched controls.

PsA is associated with substantial psychosocial burden.[35, 51, 54] Patients suffer from sleep disorders, fatigue, depression, anxiety and mood/behavioural changes.[51, 56] Depression and anxiety have been reported in 22% and 30% of PsA patients respectively.[57] Moreover, skin lesions cause impaired confidence and psychological well-being, leading to reduced social participation.[34]

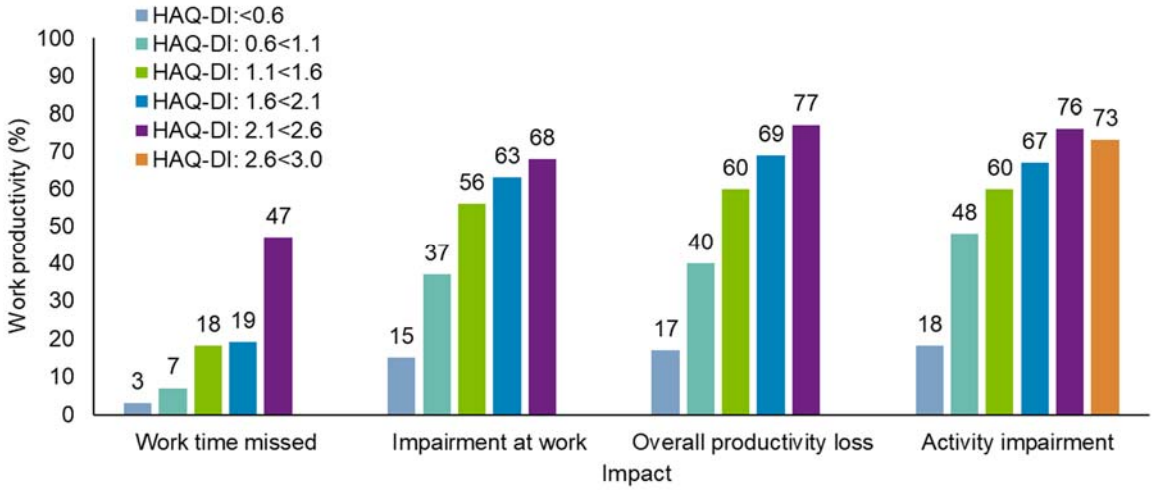
Economic burden

The economic burden of PsA is substantial due to both direct healthcare costs and indirect costs.[58] In order to manage the variable clinical burden and symptoms of PsA, patients require substantial use of multiple healthcare resources. A study investigating healthcare costs among biologic-naïve PsA patients in the UK estimated the mean annual direct healthcare costs per patient to be £1,446 (SD: £1,756).[59] Prescription costs and secondary care episodes accounted for more than a third of total care costs each (38% and 34%, respectively), and total healthcare costs significantly increases with increasing disease severity (as measured by HAQ-DI).[59] New

treatments which effectively manage PsA may substantially reduce healthcare costs through avoiding flares and reducing the need for secondary care visits.

The combination of physical and psychological symptoms experienced by patients with PsA contributes to lost productivity and unemployment. Absenteeism is common among PsA patients who have an impaired ability to work; a multinational patient survey found that more than 30% of patients with PsA reported that they had missed work in the last 12 months because of their disease and a similar proportion reported that PsA impacted their ability to work full-time.[30] In a large UK multicentre study in 236 PsA patients of working age assessing work disability and the factors affecting it, 14% of participants reported presenteeism (working with impaired productivity) whilst 39% of patients reported absenteeism.[60] Absenteeism was associated with a worse joint activity and hence worse functional impairment.[61] A large real-world study of 16 countries (n=1,499 patients of working age) reported that the increasing rate of work time missed, impairment at work and overall work productivity loss was directly proportionate to increasing disease severity, as measured by HAQ-DI scores (Figure 3).[62] Patients are typically diagnosed with PsA at working age, and thus effective management can have substantial indirect economic benefits if treatment allows patients to continue working at full or increased capacity.

Figure 3: Impact of functional disability (HAQ-DI) on work productivity (mean % of WPAI scores) in PsA patients



Based on employed patients only: Work time missed, impairment at work and overall productivity loss.
Abbreviations: HAQ-DI: health assessment questionnaire disability index; PsA: psoriatic arthritis; WPAI: work productivity and activity impairment.
Source: Conaghan *et al.* (2016).[62]

B.1.3.3 Current treatment pathway and proposed positioning of risankizumab

There are currently no UK-specific guidelines for the management of PsA. UK healthcare practitioners refer to international guidelines, particularly the European Alliance of Associations for Rheumatology (EULAR) 2019 recommendations and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2021 recommendations.[7, 63, 64] Guidelines recognise that the primary goal of treatment is to maximise HRQoL through the control of symptoms including joints and skin, prevention of structural damage and the normalisation of functional and social participation.[7, 63-66] GRAPPA Guidelines include IL-23 inhibitors within the first line biologic and advanced therapy recommendations for the PsA domains of peripheral arthritis, enthesitis, dactylitis, skin and nails.[64] Guidelines are available

from the British Society of Rheumatology (BSR) but are outdated, with an update in development.[67] It is expected that the updated BSR guidelines will include IL-23 inhibitors as a treatment option following a TNF- or IL17- inhibitor.

Treatment aims

There is currently no cure for PsA, therefore the aim of treatment is to minimise disease activity, prevent joint damage, stop swelling, reduce pain and improve HRQoL.[68] Ideally, PsA treatment leads to long-term remission and a reduction in disease symptoms. However, over time, patients may experience disease flares and may become unresponsive or intolerant to treatments. As such, patients require additional therapeutic options that provide suppression of disease symptoms with a favourable safety profile. Owing to heterogeneity in phenotypic presentation of PsA, treatment varies substantially by patient, with many patients requiring multi-disciplinary treatment.Treatment plans are highly individualised, depending on the disease presentation and patient choices.[7, 26]

EULAR recommends that rheumatologists and in the case of skin manifestations, rheumatologists and dermatologists, should collaborate in the diagnosis, treatment and management of disease.[7] Additional clinical specialists are consulted in order to manage the range of comorbidities and extra-articular manifestations associated with PsA.[7, 23, 65]

Current treatment options

For patients with a mild presentation, non-steroidal anti-inflammatory drugs (NSAIDs), combined with intra-articular corticosteroid injections, can be effective. For patients whose disease is not controlled, csDMARDs, such as methotrexate, sulfasalazine and leflunomide, are prescribed. In the UK patients who do not respond to or are not suitable for treatment with at least two different types of csDMARD are offered bDMARD treatment (as per NICE recommendations for available biological and small molecule therapies, detailed below).[26, 38]

The following bDMARDs have been recommended in patients with active PsA (defined as at least three tender joints and at least three swollen joints), who have not responded to at least two csDMARDs:

- Tumour necrosis factor (TNF) inhibitors (TNFi): Adalimumab, Etanercept, Infliximab (TA199)[69]; Golimumab (TA220)[70]; Certolizumab pegol (TA445)[8] [after failure of one TNFi therapy]
- Phosphodiesterase (PDE)-4 inhibitor: Apremilast (TA433)[71]
- After failure of TNFi therapy or when TNFi therapies are contraindicated:
    - IL-17 modulators: Ixekizumab (TA537)[9]; Secukinumab (TA445)[8]
    - Janus kinase (JAK) inhibitor: Tofacitinib (TA543)[10]; Upadacitinib (TA768)[72]
    - IL-12/23 inhibitor: Ustekinumab (TA340)[41]
- For patients with moderate-to-severe psoriasis AND who have had two conventional DMARDs and at least one bDMARD:
    - IL-23 inhibitor: Guselkumab (TA711)[2]

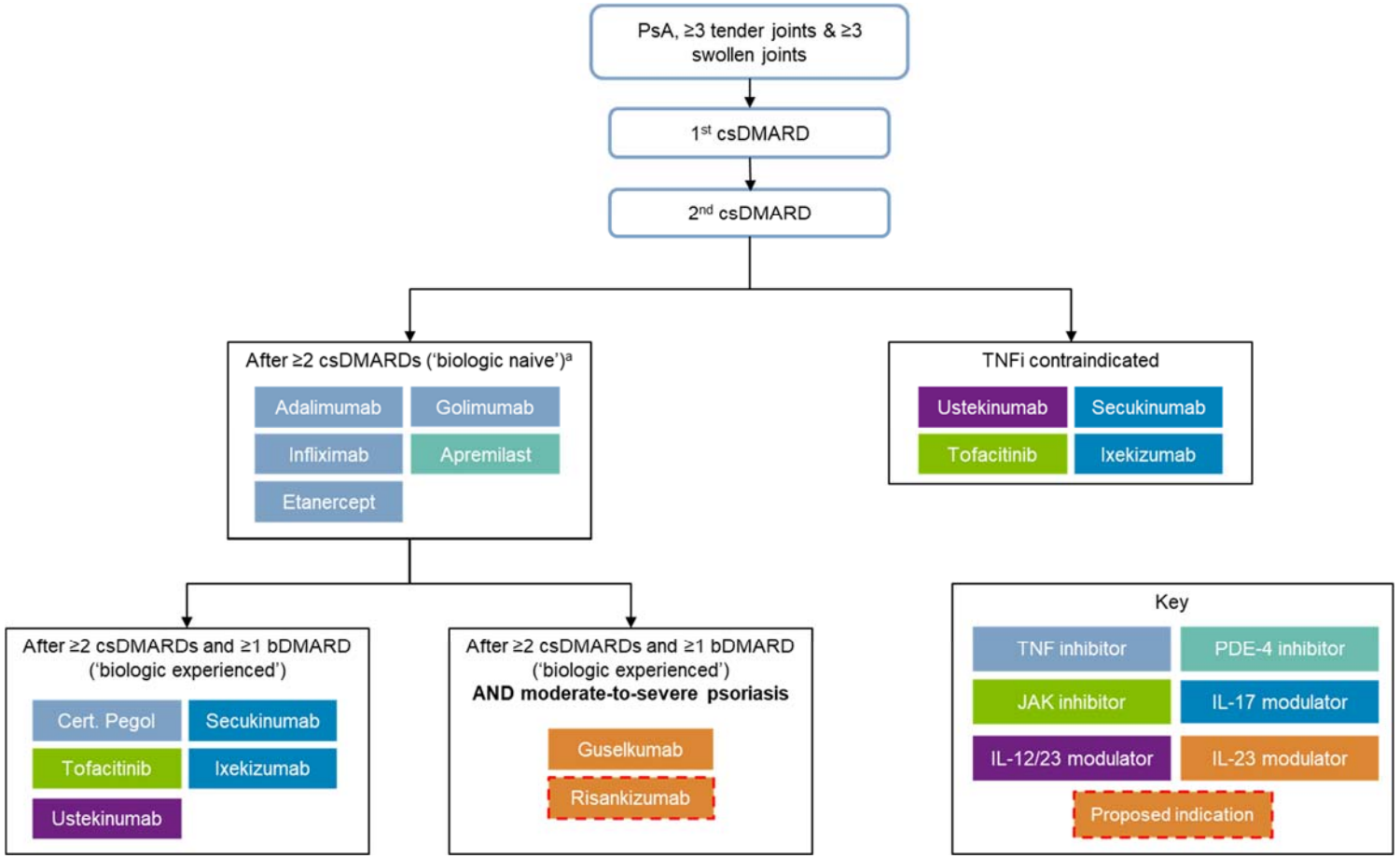
Note that in this conventional terminology apremilast and tofacitinib are described as bDMARDs. Both can be more correctly described as targeted synthetic DMARDs, however, for ease of reference and consistency with prior NICE technology appraisals, they will be grouped with bDMARDs.

The Technology Appraisal Guidance (TAG) for upadactinib for treating active PsA after inadequate response to DMARDs was only recently published on 2nd February 2022.[73] Therefore, upadactinib is not considered to be established in the current treatment pathway. The established UK treatment pathway from prescription of first csDMARD is presented in Figure 4, based on the subpopulations described within the final scope issued by NICE for this appraisal and published NICE technology appraisals.

Figure 4 also shows the proposed positioning of risankizumab in the treatment pathway. The population of relevance for this submission aligns with the specific population for which guselkumab has received a positive recommendation from NICE (patients with PsA who have had two csDMARDs and at least one bDMARD and who also have moderate-to-severe psoriasis),[2] as risankizumab and guselkumab share a therapeutic class and have similar costs and health benefits. Risankizumab is expected to be used as an alternative to guselkumab in clinical practice.

Risankizumab would provide an additional treatment option for patients with PsA who are biologic-experienced. These patients have often experienced multiple treatment discontinuations due to AEs or lack/loss of treatment effectiveness over time. Risankizumab offers an additional treatment option that effectively sustains skin clearance and addresses joint symptoms, with a favorable safety profile, predictable and convenient dosing regimen, and minimal budget impact.

Figure 4: UK PsA treatment pathway showing proposed position of risankizumab



Showing technologies established in current UK practice as per NICE published technology appraisal guidance.
[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.
Abbreviations: bDMARD: biological disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; IL: Interleukin; JAK: Janus kinase; PASI: Psoriasis Area and Severity Index; PDE: phosphodiesterase; PsA: psoriatic arthritis; TNFi: tumour necrosis factor inhibitor.

Unmet treatment needs in PsA

PsA is lifelong, chronic, progressive disease with a heterogenous course and presentation. The diverse clinical manifestations of PsA require treatments that combat both articular and extra-articular disease, including skin disease. In addition, due to significant metabolic and cardiovascular comorbidities associated with PsA, there is no “one size fits all” in terms of which treatment will work, for how long and with manageable side effects. For example, IL-17 inhibitors are contraindicated in patients with co-existing IBD such as Crohn’s disease and ulcerative colitis, whereas TNF inhibitors are contraindicated for patients who have moderate-to-severe heart failure.[74]

Patients with PsA often experience lack and loss of efficacy of bDMARDs, resulting in the reappearance of signs and symptoms of PsA. For example, out of 1,436 patients starting TNF inhibitor agents in a nationwide observational study, 432 (30%) switched to a second TNF inhibitor and 137 (10%) to a third TNF inhibitor.[39] The main reason for switching was lack of response (56%).[39] Thus, there is a requirement for biologic treatment options with alternative mechanism of action to TNF inhibition.

Differing mode of actions of bDMARD treatments are associated with differing AE profiles.[39] For example, TNFis may be associated with neurological, haematological or cardiac side effects, and IL-17 inhibitors are associated with candidiasis development and exacerbation of IBD which may lead to treatment discontinuation.

Despite current treatments, there remains unmet need for patients with PsA. The MAPP study included perspectives from dermatologists (n = 391) and rheumatologists (n = 390) in North America and Europe (France, Germany, Italy, Spain and UK). Over a quarter of rheumatologists (27.7%) reported feeling as though patients were leaving their clinic due to dissatisfaction or frustration with treatments, whilst 13.3% of rheumatologists stated that PsA treatments can be worse than the condition itself.[75] In the same survey, 54% of PsA patients reported that they found injectable biologic therapy for PsA to be burdensome. The most common reasons patients with PsA found biologic therapy burdensome were side effects (25.8%), fear of injections (22.7%), and inconvenience (9.1%).[30] The most common treatments used in this study were adalimumab and etanercept (TNF inhibitors) which are associated with more frequent dosing schedules compared to interleukin inhibitors.[30] Furthermore, 64% of patients in the survey expressed concern about the health risks of long-term therapy, and 90% of patients with PsA felt there was a need for better therapies.[30, 37]

In summary, in active PsA, patients’ treatment options are limited by contraindications, comorbidities, toxicities and previous treatment history. As PsA is a lifelong, relapse-remitting disease, multiple therapies are needed to provide patients and clinicians with a range of effective treatment options.[30, 36] The introduction of a new therapy that provides rapid, durable efficacy for the treatment of skin manifestations alongside joint symptoms whilst maintaining a simple dosing regimen would therefore help combat the burden of disease.[30, 36]

Risankizumab would provide an additional treatment option for patients with PsA who are biologic-experienced. These patients have often experienced multiple treatment discontinuations due to AEs or lack/loss of treatment effectiveness over time. Risankizumab has demonstrated dual improvement in both joint and skin symptoms in this patient population (see Section B.3.6.1). This is critically important for combatting the compounding functional and psychological burdens of PsA.[51]

Moreover, risankizumab is associated with a more convenient maintenance dosing schedule than guselkumab. Risankizumab is given every 12 weeks, while guselkumab is given every four or eight weeks.[16, 76] Thus, risankizumab will be the only IL-23 inhibitor licensed in PsA with 12 weekly maintenance dosing regimen (i.e. just four injections per year).

B.1.4 Equality considerations

It is not anticipated that the provision (or non-provision) of risankizumab would exclude from consideration any people protected by equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Nine NICE technology appraisals relating to biologic treatments specified in the NICE final scope for active PsA have had final guidance published following the NICE Single Technology Appraisal (STA) or Multiple Technology Appraisal (MTA) approaches. Upadactinib has not been considered further in this submission as the Technology Appraisal Guidance (TAG) was only recently been published on 2nd February 2022, therefore upadactinib is not considered to represent established clinical practice.[73] The eight remaining appraisals are listed below, with the main comparator related to this appraisal in bold.

- Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (MTA; TA199)[69]
- Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (MTA; TA445)[8]
- Ustekinumab for treating active psoriatic arthritis (STA; TA340)[41]
- Golimumab for the treatment of psoriatic arthritis (STA; TA220)[70]
- Apremilast for treating active psoriatic arthritis (STA; TA433)[71]
- Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs (STA; TA543)[10]
- Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs (STA; TA537)[9]
- **Guselkumab for treatment active psoriatic arthritis after inadequate response to DMARDs (STA; TA711)**[2]

In the appraisals mentioned above, three key measures of clinical effectiveness were used in all appraisals: PsARC response, PASI75 and HAQ-DI conditional on PsARC response. In the first technology appraisal in this indication (TA199), the economic assessment conducted by the University of York Assessment Group utilised PsARC response and PASI 75 to define responders and non-responders to treatment and used PASI75 and HAQ-DI conditional on PsARC response scores to assess the benefit of treatment on the psoriatic and rheumatic

components of the disease, respectively. As part of this model, the York assessment group also developed a utility algorithm that resulted in HAQ-DI having a greater effect on utility than PASI response. This approach was considered to be appropriate by the committee. In TA445, this structure was updated so that only PsARC response was used to determine continuation on treatment. In all subsequent appraisals, PsARC, PASI75 and HAQ-DI were included as relevant measures of response, using the York algorithm to map HAQ-DI and PASI to a utility score.

In all technology appraisals, a treatment waning effect was applied; for patients on-treatment, the PsARC response, HAQ-DI improvement, and PASI response were maintained, but for patients off-treatment, PsARC response is lost, and HAQ-DI and PASI scores revert to baseline. If patient discontinues active treatment and goes on to receive BSC, HAQ-DI worsens over time in line with natural history progression.

The timepoint of assessment for PsARC response has varied between prior appraisals and is dependent on the assessment time in the summary of product characteristics for each treatment. In TA711, the committee noted that, in addition to the primary response timepoint of 24 weeks, clinicians would value the option of assessing response to guselkumab at Week 16.[2] Whilst the primary outcome of the KEEPsAKE-2 trial was assessed at Week 24, a Week 16 timepoint for assessing response is also recommended for risankizumab in the SmPC, and thus a scenario analysis has been performed at this timepoint (see Section B.3.8.1.).

Other key clinical outcomes: Adverse events and discontinuation rates

In addition to clinical response, the incidence of adverse events (AEs) and the discontinuation rate have been discussed during committee meetings. Typically, the relevant NICE appraisals have not included a disutility associated with AEs; AEs were only considered in terms of the effects on initial response (responders could stop treatment because of adverse events) and on the long-term discontinuation and withdrawal rates from each treatment option. Given that the incidence tends to be similar across biologic therapies, it has been accepted that the inclusion of AEs would have limited impact on the cost-effectiveness analysis.

With regard to treatment discontinuation, a 16.5% annual probability of discontinuation of biologic treatment has been used in the majority of prior appraisals. This probability is derived from a meta-analysis of registry data from multiple countries for the cost-effectiveness analysis of etanercept, infliximab and adalimumab for active PsA.[77] In the more recent appraisal for guselkumab (TA711), different discontinuation rates were applied for each treatment based on one-year discontinuation rates from key clinical trials for each treatment and this was a key driver of cost-effectiveness. The committee concluded that a 16.5% discontinuation rate should be used for all treatments in the economic model, in line with the previous appraisals (TA220, TA433, TA537).

The clinical outcomes and measures used in the cost-effectiveness models are described in Table 3 below.

Table 3: Clinical outcomes and measures appraised in published NICE guidance for the comparators included in the NICE final scope

	Outcomes	Used in cost-effectiveness modelling	Committee's preferred assumptions	Uncertainties (if applicable)
NICE TA199 (etanercept, infliximab and adalimumab)[69]	Efficacy	In the assessment Group's model, patients were modelled as responders or non-responders using PsARC response rate. The benefit of treatment on the rheumatic component of the condition was captured using HAQ-DI score and on the psoriatic component of the condition using PASI score.	The committee accepted that the Assessment Group's approach to deriving utility values, which resulted in HAQ-DI response having a greater effect on utility than PASI, represented the best means of estimating utility for the purposes of the economic analysis given the available data.	The committee noted that the model was most sensitive to assumptions around the cost of treating uncontrolled psoriasis, differences in the relative HAQ score and the cost of infliximab (depending on the average number of vials required to treat people with psoriatic arthritis).
	Discontinuation	A 12-week probability of withdrawal of 3.96% was applied.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	-
NICE TA445 (certolizumab pegol and secukinumab)[8]	Efficacy	In the Certolizumab pegol cost-effectiveness model: • Patients were modelled as responders or non-responders using PsARC and PASI75 at 3 months • HAQ-DI and PASI scores were used to capture treatment effect at 12 and 16 week timepoints, assumed to remain constant from 6 months In the secukinumab cost-effectiveness model:	The committee did not discuss this.	-

		• Patients were modelled as responders or non-responders using PsARC at 24 weeks • HAQ-DI and PASI scores used to capture treatment effect • In the assessment Group's model, patients were modelled as responders or non-responders using PsARC response rate.		
	Discontinuation	16.5% withdrawal rate was assumed.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	-
NICE TA340 (ustekinumab)[41]	Efficacy	The model captured health-related quality of life through joint symptoms, disability and skin symptoms (PsARC response, HAQ-DI score and PASI score). People who had a PsARC or PASI response were assumed to have a fixed improvement in HAQ-DI or PASI score respectively.	The committee concluded that uncertainty remains as to how well the HAQ-DI assumptions apply to ustekinumab, but considered that the assumptions in the model were a sufficient basis on which to make a decision.	Data on patients who disease was TNF inhibitor refractory were scarce.
	Discontinuation	16.5% withdrawal rate was assumed.	The committee did not discuss this.	-
	Adverse events	Costs and disutility associated with adverse events were not included in the model.	The committee did not discuss this.	-
NICE TA220 (golimumab)[70]	Efficacy	Patients were modelled as responders or non-responders	The HAQ score response had a greater effect on utility than the PASI response did, indicating	-

		using PsARC response rate at Week 12. The benefit of treatment on the rheumatic component of the condition was captured using HAQ-DI score and on the psoriatic component of the condition using PASI score.	that the calculated utility benefit was driven more by the reduction in joint symptoms than the reduction in skin disease. The committee concluded that this assumption was appropriate.	
	Discontinuation	16.5% withdrawal rate was assumed.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	The committee noted that there was uncertainty around the long-term safety profile of golimumab.
NICE TA433 (apremilast)[71]	Efficacy	Patients were modelled as responders or non-responders using PsARC response rate at 16 weeks. The benefit of treatment on the rheumatic component of the condition was captured using HAQ-DI score and on the psoriatic component of the condition using PASI score.	The committee concluded that the modelled response to treatment was imperfect, but appropriate for decision-making.	Uncertainties about the results from the apremilast trials because they were not blinded after 24 weeks and there were no stopping rules, which was likely to have influenced the HAQ-DI results.
	Discontinuation	16.5% withdrawal rate was assumed.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	-
NICE TA543 (tofacitinib)[10]	Efficacy	PsARC (and PASI) response criteria were used to assess short-term efficacy at Week 12 post-treatment initiation, and HAQ-DI to capture longer-term outcomes.	The committee agreed with the manufacturer's approach to modelling disease progression, whereby HAQ-DI scores would remain stable during treatment with bDMARDs, and would rebound and progress in line	Tofacitinib might have additional benefits in treating fatigue, and that improvements in this domain might not be captured adequately by the HAQ-DI assessment and therefore the QALY.

			with best supportive care for patients who stopped treatment.	
	Discontinuation	A 12-week probability of withdrawal of 3.96% was applied, estimated from a meta-analysis of registry data from several countries obtained from the York model reported in TA199.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	-
NICE TA537 (ixekizumab)[9]	Efficacy	Patients were modelled as responders or non-responders using PsARC response rate at Week 16. The benefit of treatment on the rheumatic component of the condition was captured using HAQ-DI score and on the psoriatic component of the condition using PASI score.	The committee concluded that PsARC response should be assessed at 16 weeks to decide if ixekizumab treatment should continue, because this is in line with the Summary of Product Characteristics.	-
	Discontinuation	16.5% withdrawal rate was assumed.	The committee did not discuss this.	-
	Adverse events	AEs were only considered in terms of effect on initial response.	The committee did not discuss this.	-
NICE TA711 (guselkumab)[2]	Efficacy	Patients were modelled as responders or non-responders using PsARC response rate at 24 weeks. The benefit of treatment on the rheumatic component of the condition was captured using HAQ-DI score and on the	The committee noted that 24 weeks was the assessment time in the summary of product characteristics. The committee concluded, however, that clinicians would value the option of assessing response at 16 weeks.	-

		psoriatic component of the condition using PASI score.		
	Discontinuation	Discontinuation rates were based on one-year rates from key clinical trials for each treatment, ranging from 6.0% for guselkumab Q4W to 26.5% for apremilast.	The committee concluded that a 16.5% discontinuation rate should be used for all treatments in the economic model.	The heterogeneity across the trials in terms of study design and baseline characteristics, which suggested patients in the participating trials had limited access to the range of treatments available in the NHS. The committee concluded there were uncertainties in the evidence base supporting the use of treatment-specific discontinuation rates.
	Adverse events	Disutility associated with serious AEs was included in the manufacturer's base case.	The committee's preferred assumption was to exclude adverse events from the cost-effectiveness model.	-

Abbreviations: AE: Adverse event; HAQ-DI: Health assessment questionnaire disability index; PsA: Psoriatic Arthritis; TA: Technology appraisal.

In all of the appraisals outlined above, scenario and sensitivity analyses were conducted to identify key drivers of cost-effectiveness. Assumptions associated with the HAQ-DI were identified as the key drivers of cost-effectiveness in a number of appraisals (for example, the HAQ-DI coefficient for the utility algorithm, costs associated with HAQ-DI and progression of HAQ-DI on and off treatment). PsARC response rates, the proportion of people who had a PsARC response and HAQ-DI change associated with PsARC response were also identified as drivers of cost-effectiveness results.

B.2.2 Resource use assumptions

In one of the most recent appraisals in this disease area (TA711), most scenario analyses did not alter the conclusions from the reference case analysis in terms of the cost effectiveness of the treatment. The scenario analyses with the largest effect on the incremental cost-effectiveness ratio (ICER) were using the HAQ-DI rebound to natural history assumption, using ACR 20 response as an alternative response definition, and using the DISCOVER-2 algorithm as the source of utilities.[2] DISCOVER-1 and -2 were multicentre, placebo-controlled, double-blind phase III RCTs comparing guselkumab to placebo. DISCOVER-1 recruited biologic-experienced or biologic-naïve patients with active PsA and DISCOVER-2 recruited only biologic-naïve patients.[78,79]

Resource use assumptions

Resource use considered in the relevant NICE technology appraisals listed in Section B.2.1 followed the approach taken in the York Assessment Group PsA model in TA199 and TA445 and include:

- Drug acquisition
- Treatment administration
- Disease-related costs
    - Costs for uncontrolled and controlled psoriasis, based on achievement of PASI75
    - Costs for rheumatic symptoms, based on HAQ-DI scores using the Kobelt *et al.* (2002) algorithm
- Monitoring costs
    - This includes both routine laboratory monitoring tests and outpatient visits
- Best supportive care

Only one appraisal (TA711) included costs associated with adverse events, however the ERG concluded the approach was unlikely to reflect the safety profile of the different treatments and was not consistent with prior appraisals. Adverse events were subsequently removed from the company's cost-effectiveness model.

There appeared to be consensus that these were the standard resources used in the treatment of adult patients with PsA.

However, the only resource use relevant to this appraisal is drug acquisition costs, the reasons for which are outlined in Section B.4.2.3.

B.3 Clinical effectiveness

Clinical evidence

- The efficacy and safety of risankizumab has been demonstrated in KEEPsAKE-1 and KEEPsAKE-2, two ongoing, Phase III, international, randomised, double-blind, placebo-controlled trials.[80, 81]
- This submission targets the biologic-experienced population. Therefore, the primary source of evidence for this appraisal is KEEPsAKE-2 (in which 46.5% of patients were biologic-experienced), with KEEPsAKE-1 providing supportive evidence in biologic-naïve patients.

Efficacy

- KEEPsAKE-2 met its primary endpoint, a significantly greater proportion of patients achieved 20% improvement per American College of Rheumatology criteria (ACR20) at Week 24 treated with risankizumab versus placebo (51.3% versus 26.5%, p<0.001).[80]
- All secondary endpoints, including ACR 50, ACR 70, Health Assessment Questionnaire-Disability Index (HAQ-DI), PASI90 and MDA, were met.[80]
- The durability of treatment response was demonstrated in the open-label phase of the KEEPsAKE-2 study, which showed a consistent treatment effect with risankizumab up to 52 weeks.[82]
- Patients treated with risankizumab demonstrated efficacy with significant improvements in signs and symptoms of PsA compared with placebo in both the biologic-naïve and biologic-experienced (BIO-IR) subgroups:
  - At Week 24, more patients achieved ACR20 with risankizumab compared to placebo in the BIO-IR subgroup, (45.7% versus 14.9%).[83]
  - Improvements were also observed for the BIO-IR subgroup in ACR 50, ACR 70 and ACR 90 at Week 24.[83]

Indirect treatment comparisons

- A series of NMAs were conducted under a Bayesian framework for PsARC, PASI 50/70/90, HAQ-DI change from baseline, HAQ-DI change from baseline conditional on PsARC response and ACR 20/50/70 at Week 24. Considering the only comparator relevant to this appraisal, guselkumab, [redacted] between risankizumab and guselkumab. The differences in point estimates between risankizumab and guselkumab were considered to be clinically insignificant, based on input from UK clinical experts. Together, these results suggest clinical equivalence between risankizumab and guselkumab.
- Similar results were observed in a scenario analysis conducted using data from Week 16
- NMA results for safety outcomes of the proportion of patients experiencing any AE or a serious adverse event (SAE) demonstrates that risankizumab provides a comparable safety profile to guselkumab.
- The efficacy results for risankizumab from the NMA are used to inform the cost-comparison model presented in Section B.4.

Adverse reactions

- With regards to safety and tolerability, risankizumab was consistent with the known safety profile and there were no new safety signals of concern.
- Similar proportions of patients in the risankizumab and placebo arms experienced serious TEAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug.

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify clinical evidence on the efficacy and safety of risankizumab for patients with moderate-to-severe PsA. The scope of the SLR was broad and also included treatments commonly used across multiple jurisdictions for the treatment of moderate-to-severe PsA for the purposes of allowing a potential indirect treatment comparison with risankizumab. The original review was conducted in May 2020, with the latest update completed in December 2021. Across the original SLR and subsequent updates, a total of 62 unique trials from 726 publications were identified. Three of these trials (KEEPsAKE-1, KEEPsAKE-2 and NCT02719171) included patients receiving risankizumab.[84-86] Full details of the SLR, including search strategy, study selection process and detailed results, can be found in Appendix D.

B.3.2 List of relevant clinical effectiveness evidence

Three separate randomised controlled trials (RCTs) were identified in the SLR that provide evidence for the efficacy and safety of risankizumab in patients with moderate-to-severe PsA:

- KEEPsAKE-1 (NCT03675308) is a Phase III, international, randomised, double-blind, placebo-controlled trial assessing the efficacy and safety of risankizumab in patients with moderate-to-severe PsA who have experienced an inadequate response or intolerance to ≥1 conventional synthetic DMARD therapy (csDMARD-IR).[85] Data from KEEPsAKE-1 have been published in the Annals of the Rheumatic Diseases by Kristensen et al.[81] Additional data from KEEPsAKE-1 is provided in the clinical study report (CSR) located in the reference pack accompanying this submission
- KEEPsAKE-2 (NCT03675308) is a Phase III, international, randomised, double-blind, placebo-controlled trial assessing the efficacy and safety of risankizumab in patients with moderate-to-severe PsA who have experienced an inadequate response or intolerance to 1 or 2 biologic therapies (BIO-IR) and/or csDMARD-IR.[86] Data from KEEPsAKE-2 have been published in the Annals of the Rheumatic Diseases by Östör et al.[80] Additional data from KEEPsAKE-2 is provided in the CSR located in the reference pack accompanying this submission
- The NCT02719171 trial was a Phase II, randomised, double-blind, placebo-controlled, proof-of-concept, dose-ranging study of risankizumab in patients with active PsA.[84] The overall purpose of the trial was to assess clinical efficacy and safety of different subcutaneous doses of risankizumab in adult patients with PsA in order to select doses for further clinical trials

As the population relevant for this submission is the biologic-experienced population, the primary source of evidence for this appraisal is KEEPsAKE-2, in which 46.5% of patients were biologic-experienced. The two other trials identified are not considered to be the primary source of evidence for risankizumab in this indication. KEEPsAKE-1 only includes biologic-naïve patients and therefore provides supportive evidence for this appraisal. The smaller, Phase II NCT02719171 trial is not considered as a primary source of evidence for risankizumab in this submission given the availability of evidence from the pivotal, Phase III KEEPsAKE trials. However, this trial is included in the NMA discussed in Section B.3.8.1. A summary of the clinical effectiveness evidence from KEEPsAKE-1, KEEPsAKE-2 and NCT02719171 trials is presented in Table 4. Full details of KEEPsAKE-1 are provided in Appendix I.

Table 4: Summary of clinical effectiveness evidence

Study	KEEPsAKE-1	KEEPsAKE-2	NCT02719171
Study design	Phase III, multi-centre, randomised, double-blind, placebo-controlled trial consisting of a 24-week randomised period followed by an open-label extension period		Phase II, randomised, double-blind, placebo-controlled, proof-of-concept, dose-ranging trial
Population	Adults (≥18 years) with active PsA who have experienced an inadequate response or intolerance to ≥1 conventional synthetic DMARD therapy (csDMARD-IR)	Adults (≥18 years) with active PsA who have experienced inadequate response or intolerance to 1 or 2 biologic therapies (BIO-IR) and/or are csDMARD-IR	Adults (≥18 years) with active PsA
Number of participants	964	443	185
Intervention(s)	Period 1 (randomised period): risankizumab 150 mg, administered at Week 0, 4, and 16 Period 2 (open-label extension): risankizumab 150 mg Q12W for study duration		Arm 1: 150 mg risankizumab Q4W for 16 weeks Arm 2: 150 mg risankizumab at Weeks 0, 4 and 16 Arm 3: 150 mg risankizumab at Weeks 0 and 12 Arm 4: 75 mg risankizumab at Week 0
Comparator(s)	Period 1 (randomised period): placebo for 24 weeks Period 2 (open-label extension): N/A		Placebo comparator: Q4W weeks for 16 weeks
Indicate if trial supports application for marketing authorisation (yes/no)	Yes	Yes	No
Reported outcomes specified in the NICE Final Scope	• Disease activity (assessed using PASI, MDA, PsARC and ACR response) • Functional Capacity (HAQ-DI) • Periarticular disease (enthesitis and dactylitis resolution) • Treatment-emergent adverse effects (TEAEs) • Health-related quality of life (SF-36 and FACIT-Fatigue)		• Disease activity (assessed by ACR response, TJC and SJC) • Functional Capacity (HAQ-DI) • Health-related quality of life (SF-36 and FACIT-Fatigue) • Periarticular disease (enthesitis and dactylitis assessment)
	• Periarticular (nail) disease • Radiographic progression	N/A	• Periarticular (nail) disease

All other outcomes reported in this submission	N/A	N/A

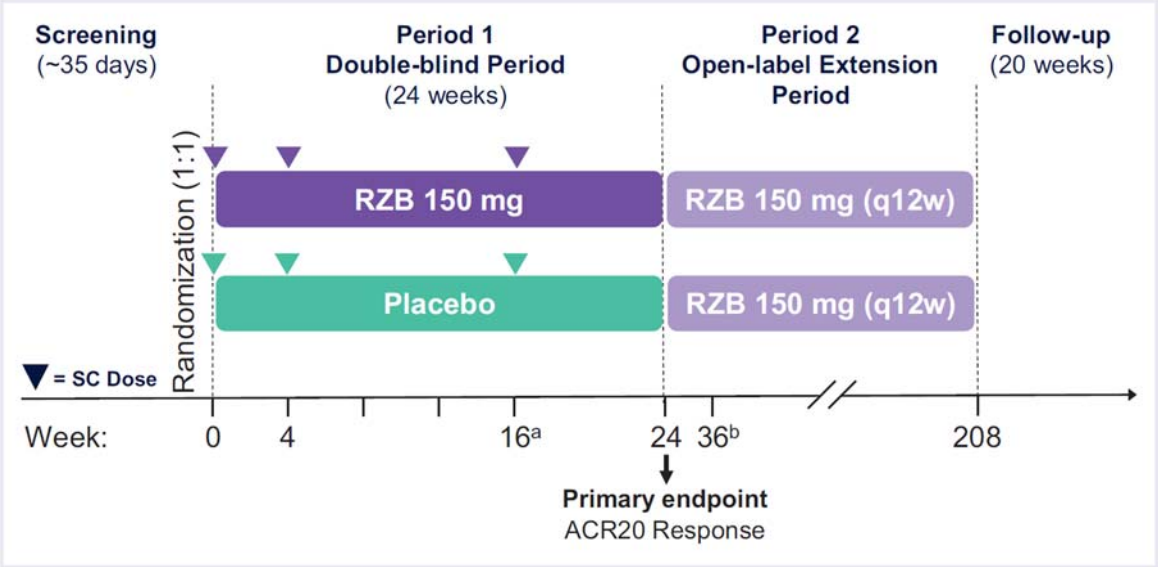
Abbreviations: ACR: American College of Rheumatology; ASDAI: Ankylosing Spondylitis Disease Activity Score; csDMARD: Conventional synthetic disease-modifying antirheumatic drug – inadequate/ FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy Fatigue Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; MDA: minimal disease activity; PASI: Psoriasis Area Severity Index; QXW: every X weeks; SF-36: 36-Item Short Form Health Survey Physical Component Summary; TJC: Tender Joint Count; SJC Swollen Joint Count; TEAE: Treatment-Emergent Adverse Event.
Sources: AbbVie Data on File KEEPsAKE-1 CSR;[14] AbbVie Data on File KEEPsAKE-2 CSR;[15] ClinicalTrials.gov: NCT02719171[84].

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Trial design and methodology

A summary of the trial design for KEEPsAKE-2 is presented in Figure 5 and a summary of the methodology is presented in Table 5.

Figure 5: KEEPsAKE-2 study design



[a]At Week 16, non-responders (patients not achieving ≥20% improvement from baseline in TJC and/or SJC at both Week 12 and Week 16) were eligible to add or modify rescue concomitant medications/therapy.
[b]Starting at Week 36, non-responders were discontinued from study drug.
Abbreviations: ACR20: ≥20% improvement in American College of Rheumatology score; q12w: every 12 weeks; RZB: risankizumab; SC: subcutaneous.
Source: Östör et al. (2021).[82]

During a screening period of approximately 35 days, patients were 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), then randomised using an interactive response technology system. Patients were randomised in a 1:1 ratio to receive double-blind treatment with risankizumab 150 mg or matched placebo for 24 weeks, administered via SC injection at weeks 0, 4 and 16 during Period 1. The last patient completed their Week 24 visit on 22nd June 2020.

Period 2 began at Week 24. To maintain blinding to the original treatment allocation, treatment at the Week 24 visit was blinded; patients randomised to placebo in Period 1 receive a blinded dose of risankizumab and patients randomised to risankizumab treatment in Period 1 receive a blinded dose of placebo. At Week 28 and for the remaining dosing visits (to Week 208), all patients receive open-label risankizumab 150 mg Q12W. Patients remain blinded to the original randomisation allocation for the duration of the study. The total study duration is 228 weeks including a telephone call 20 weeks after last dose of study drug. Efficacy and safety have been assessed up to Week 52 of the trial.

Table 5: Summary of trial methodology for KEEPsAKE-2

Study	KEEPsAKE-2
Location	99 sites in Argentina, Australia, Belgium, Brazil, Canada, Denmark, Estonia, France, Germany, Greece, Hungary, Israel, Italy, New Zealand, Poland, Portugal, South Africa, Spain, Sweden, the **UK**, and the US including Puerto Rico
Trial design	Phase III, multi-centre, randomised, double-blind, placebo-controlled trial consisting of a 24-week randomised period followed by an open-label extension period
Eligibility criteria for participants	Adults (age ≥18 years) who were able to provide informed consent. In terms of disease activity, patients had: • Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfilment of the CASPAR criteria at Screening Visit • Active disease defined as ≥5 tender joints (based on 68 joint counts) and ≥5 swollen joints (based on 66 joint counts) at both the Screening Visit and Baseline • Diagnosis of active plaque psoriasis with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis at Screening Visit In terms of therapeutic history the patient must have demonstrated: • **BIO-IR population:** Inadequate response (lack of efficacy after minimum 12-week duration of therapy) or intolerance to treatment with 1 or 2 biologic therapies intended to treat PsA OR • **csDMARD-IR population:** Inadequate response (lack of efficacy after minimum 12-week duration of therapy) or intolerance to previous or current treatment with at least 1 csDMARD at maximally tolerated dose (methotrexate, sulfasalazine, leflunomide, apremilast, bucillamine and iguratimod, or ciclosporin A)
Method of study drug administration	Risankizumab 150 mg or matching placebo dose subcutaneously
Permitted and disallowed concomitant medication	Disallowed: • Prior exposure to any IL-23, IL-12/23 or anti-IL-17 antagonist • Patients must have discontinued all biologic therapy prior to first dose of study drug Permitted: • Stable treatment with ≤2 concomitant csDMARDs at study entry was permitted if treatment was started ≥ 12 weeks before baseline at protocol-approved doses • Patients could remain taking stable doses of concomitant NSAIDs, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day) and other analgesics if they were started ≥ 1 week before baseline • Patients previously treated with biologic agents, except for IL-23, IL-12/23 or IL-17 antagonists, were eligible for enrolment. However discontinuation was required for prespecified durations before the first study treatment
Primary outcome	Proportion of patients achieving American College of Rheumatology (ACR) 20 Response (ACR20) at Week 24

Ranked secondary endpoints with multiplicity adjustment	1. Change from Baseline (CFB) in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24 2. Proportion of patients achieving Psoriasis Area Severity Index (PASI) 90 response at Week 24 (in the subset of patients with a body surface area (BSA) ≥3% at Baseline) 3. % patients achieving ACR20 at Week 16 4. % patients achieving Minimal Disease Activity (MDA) at Week 24 5. Change from Baseline in 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS) at Week 24 6. CFB in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) Questionnaire at Week 24
Other secondary endpoints without multiplicity adjustment	1. % patients achieving ACR50 response at Week 24 2. % patients achieving ACR70 response at Week 24 3. % patients with resolution of enthesitis (LEI=0) at Week 24 in patients with enthesitis at Baseline 4. % patients with resolution of dactylitis (LDI=0) at Week 24 in patients with dactylitis at Baseline
Exploratory endpoints (relevant to the submission)	% patients achieving PsARC response at Week 24
Pre-planned subgroup analyses	Subgroup factor and categories: • Age: <65 years, ≥65 years, ≥65 and <75 years, ≥75 years • Sex: Male vs. Female • BMI: <25, ≥25 and <30, ≥30 kg/m^2 • Race: White vs. Non-white • Geographic Region: North America, South/Central America, Western Europe, Eastern Europe, Asia, Other • Number of prior csDMARDs: ≤1 vs. >1 • Number of prior biologic therapies: 0 vs. ≥1 • Number of prior anti-TNFs: 0 vs. ≥1 • hsCRP at Baseline: <3 vs ≥3 mg/L • Extent of psoriasis at Baseline: ≥3% BSA vs <3% BSA • Duration of PsA: ≤5, >5 and ≤10, >10 years • Concomitant csDMARD at baseline: o Any csDMARD ▪ MTX (and another csDMARD) ▪ csDMARD other than MTX o None
Duration of study and follow-up	The total study duration is 228 weeks including Period 1 (24 weeks), Period 2 (184 weeks) and a telephone call 20 weeks after last dose of study drug

Abbreviations: ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; BMI: Body mass index; BSA: Body Surface Area; CASPAR: CFB: Change from baseline; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; –IR: –inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAQ-DI: health assessment questionnaire disability index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesis Index; MDA: minimal disease activity; MTX: Methotrexate; PASI: Psoriasis Area Severity Index; PsA: Psoriatic Arthritis; PsARC: Psoriatic Arthritis Response Criteria; SF-36 PCS: short form-36 physical component summary.
Source: AbbVie Data on File KEEPsAKE-2 CSR.[15]

Definition of outcome measures

The definitions of the efficacy outcomes used in KEEPsAKE-2 are presented in Table 6.

Table 6: Outcome definitions used in KEEPsAKE-2

Outcome Measure	Definition
ACR20/50/70	A measure for arthritis symptoms. Response criteria are as follows: • At least 20/50/70% improvement in swollen count joint compared to baseline AND • At least 20/50/70% improvement in tender joint count compared to baseline AND • At least 20/50/70% improvement in at least three out of the following five variables: o Patient's assessment of pain on VAS o Patient's global assessment of the disease on VAS o Investigator's global assessment of the disease on VAS o Patient's assessment of disability on HAQ-DI o Acute phase reactant (serum CRP)
PASI90	A measure of psoriasis severity. Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration, and desquamation using a five-point scale. Based on the extent of lesions in a given anatomic site, the area affected is assigned a numerical value. A higher score indicates more severe psoriasis. PASI90 indicates ≥90% improvement in PASI score.
MDA	A composite measure which signifies the achievement of a state of low disease activity. A patient is classified as achieving MDA when at least five of the seven following criteria are met: • Tender joint count ≤1 • Swollen joint count ≤1 • PASI ≤ 1 or BSA ≤3% • Patient Assessment of Pain-VAS ≤15 • Patient Global Assessment of Disease Activity VAS ≤20 • HAQ-DI ≤0.5 • Tender entheseal points ≤1
LDI	A validated tool for assessing dactylitis in all 20 of the patient's digits. The evaluation involves visual inspection of the hands and feet, measurement of circumference and tenderness assessment. A minimum difference of 10% is used to define a dactylitic digit. The ratio of circumference (affected digit: digit on the opposite hand or foot) is multiplied by a tenderness score.
LEI	A validated enthesitis index that uses six sites for evaluation of enthesitis: lateral epicondyle humerus left and right, Achilles tendon insertion left and right, and medial condyle femur left and right.
HAQ-DI	A self-reported assessment of how the patient's illness affects their ability to function in their daily life over the past week. The HAQ-DI for a patient is calculated as the mean of the following eight category scores: Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. A lower score demonstrates less disability.
SF-36 PCS	A 36-item survey of patient health consisted of eight scaled scores, which are weighted sums of the questions in their section. The eight sections are physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. A higher score

	indicates a more favourable health state. The PCS is an aggregate summary of the eight scale scores.
FACIT-Fatigue	A 13-item questionnaire that evaluates fatigue/tiredness and its impact on daily activities and functioning in chronic diseases. This instrument includes items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (e.g., sleeping, and social activities). A lower score indicates less negative impact on daily activities.
PsARC	A patient is defined as a PsARC responder if they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors: • Patient global assessment of disease activity (0 – 100 mm VAS scale, improvement defined as decrease of ≥ 20 mm) • Physician global assessment of disease activity (0 – 100 mm VAS scale, improvement defined as decrease ≥ 20 mm) • Tender 68-joint count (improvement defined as decrease of ≥ 30%) • Swollen 66-joint count (improvement defined as decrease of ≥ 30%)

Abbreviations: ACR: American college of Rheumatology; BSA: body surface area; CRP: C-reactive protein; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAQ-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesis Index; PASI: Psoriasis Area Severity Index; PsARC: Psoriatic Arthritis Response Criteria; SF-36 PCS: short form-36 physical component summary; VAS: visual analogue scale.
Source: KEEPsAKE-2 CSR.[15]

Safety outcomes

Safety evaluations included AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (haematology, chemistry) as a measure of safety and tolerability for the entire study duration.

B.3.3.2 Baseline characteristics

Table 7 demonstrates that demographics and baseline disease characteristics were generally balanced between treatment and placebo groups.

The population in KEEPsAKE-2 is broadly comparable to the patient population expected to receive risankizumab in the UK, based on the input from expert clinicians. Across both arms, the median age (range) was 53 (23–84) years and 55.1% were female. In general, KEEPsAKE-2 enrolled patients with a poor prognosis, considered to be representative of the target patient cohort. EULAR treatment guidelines consider the following to be prognostic factors: ≥5 active joints, radiographic damage, elevated acute-phase reactants, and extra-articular manifestations and all patients in KEEPsAKE-2 had at least one of these prognostic factors (i.e., ≥5 active joints).

As discussed in section B.3.6, exposure to prior biologics was a stratification factor in KEEPsAKE-2. In line with the patient eligibility criteria, nearly half of patients across both arms in KEEPsAKE-2 were biologic-experienced: 206 (46.5%) patients had failed ≥ 1 biologic DMARD (biologic-experienced; BIO-IR). Just over half of patients (53.5%) were biologic-naïve and of these, the majority (56.7%) of patients had received at least two prior csDMARDs. UK clinical experts highlighted that the efficacy of risankizumab in the BIO-IR population can be considered to be generalisable to the specific subgroup relevant to this appraisal (adult patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD).

Table 7: Baseline characteristics

Baseline characteristics	Risankizumab 150 mg (N=224)	Placebo (N=219)	Total (N=443)
Female, n (%)	124 (55.4)	120 (54.8)	244 (55.1)
Age (years), median (range)	53 (23–84)	52 (24–83)	53 (23–84)
Race, n (%)			
White	218 (97.3)	210 (95.9)	428 (96.6)
Black or African–American	2 (0.9)	3 (1.4)	5 (1.1)
Asian	2 (0.9)	3 (1.4)	5 (1.1)
Other	2 (0.9)	3 (1.4)	5 (1.1)
BMI (kg/m2), mean (SD)	31.5 (8.0)	31.2 (6.8)	31.4 (7.4)
PsA duration (years), mean (SD)	8.2 (8.2)	8.2 (8.3)	8.2 (8.3)
Swollen joint count,[a] mean (SD)	13.0 (8.7)	13.6 (9.0)	13.3 (8.9)
Tender joint count,[b] mean (SD)	22.8 (14.9)	22.3 (13.8)	22.6 (14.4)
HAQ-DI, mean (SD)	1.10 (0.62)	1.13 (0.63)	1.12 (0.62)
hsCRP (mg/L),[d] mean (SD)	7.5 (10.9)	8.2 (17.1)	7.8 (14.3)
Presence of psoriasis affecting ≥3% BSA, n (%)	123 (54.9)	119 (54.3)	242 (54.6)
BSA (%), mean (SD)	12.5 (15.4)	11.7 (14.9)	12.1 (15.1)
PASI, mean (SD)	7.7 (6.7)	8.4 (9.9)	8.04 (8.4)
MDA, n (%)	5 (2.2)	5 (2.3)	10 (2.3)
Presence of enthesitis,[e] n (%)	147 (65.6)	158 (72.1)	305 (68.8)
LEI, mean (SD)	3.0 (1.5)	3.0 (1.6)	3.0 (1.6)
Presence of dactylitis,[f] n (%)	40 (17.9)	57 (26.3)	97 (22.0)
LDI, mean (SD)	78.9 (98.4)	109.8 (155.3)	97.09 (135.1)
SF-36 PCS score, mean (SD)	35.6 (8.8)	35.2 (9.1)	35.39 (8.9)
FACIT-Fatigue score, mean (SD)	28.2 (11.5)	27.7 (12.7)	28.0 (12.1)
Prior csDMARDs, n (%)			
0	12 (5.4)	11 (5.0)	23 (5.2)
1	88 (39.3)	81 (37.0)	169 (38.1)
2	60 (26.8)	60 (27.4)	120 (27.1)
≥3	64 (28.6)	67 (30.6)	131 (29.6)
Any prior biologic, n (%)	105 (46.9)	101 (46.1)	206 (46.5)
Prior failed biologics, n (%)			
0	137 (61.2)	132 (60.3)	269 (60.7)
1	72 (32.1)	64 (29.2)	136 (30.7)
≥2	15 (6.7)	23 (10.5)	38 (8.6)
Prior TNF antagonist, n (%)	103 (46.0)	100 (45.7)	203 (45.8)
Concomitant medication at baseline, n (%)			
MTX[g]	110 (49.1)	99 (45.2)	209 (47.2)
csDMARD other than MTX	31 (13.8)	30 (13.7)	61 (13.8)

MTX and another csDMARD	8 (3.6)	10 (4.6)	18 (4.1)
Oral corticosteroids	28 (12.5)	22 (10.0)	50 (11.3)
NSAIDs	141 (62.9)	145 (66.2)	286 (64.6)

[a]Based on 66 joints. [b]Based on 68 joints. [c]Scored as millimetres on a 100 mm horizontal visual analogue scale. [d]Reference range: 0–10 mg/dL. [e]LEI >0. [f]LDI >0. [g]As monotherapy or in combination with another csMARD.
Abbreviations: BMI: body mass index; BSA: Body Surface Area; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI: Health Assessment Questionnaire–Disability Index; hsCRP: high-sensitivity C-reactive protein; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; SF-36 PCS: 36-Item Short Form Health Survey Physical Component Summary; PGA: physician's global assessment; PsA: psoriatic arthritis; PtGA: patient's global assessment; TNF: tumour necrosis factor.
Source: KEEPsAKE-2 CSR;[15] Östör et al (2021).[80]

B.3.3.3 Participant flow

A total of 444 patients at 99 sites were randomised to receive risankizumab (n=224) or placebo (n=220); of these patients, 215 (96.0%) and 199 (90.9%), respectively, completed the Week 24 study visit (Figure 6). One patient was randomised but never received the study drug and was excluded from the efficacy analyses; therefore, 443 patients were included in the full analysis set (FAS). No patients discontinued from the study because of COVID-19 infection during the double-blind period; however, one patient discontinued because of COVID-19-related logistical restrictions. A similar percentage of patients in each treatment arm discontinued due to AEs (risankizumab: n=2 [0.9%], placebo: n=3 [1.4%]) and due to lack of efficacy (risankizumab: n=2 [0.9%], placebo: n=7 [3.2%]). The reasons for study discontinuation are summarised in Figure 6.

Figure 6: KEEPsAKE-2 participant flow diagram

*One patient was randomised but never received study drug and was therefore excluded from the efficacy analyses, resulting in 219 patients included in the PBO group in the full analysis set.
Abbreviations: PBO: placebo; RZB: risankizumab.
Sources: Östör et al (2021).[80]

B.3.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Trial populations

The FAS includes all randomised patients who received at least one dose of study drug (N=443; 224 in the risankizumab arm and 219 in the placebo arm). The FAS was used for all efficacy and baseline analyses. Patients were included in the analysis according to the treatment groups that they were randomised to.

The Safety Analysis Set (SAS) consists of all patients who received at least one dose of study drug (N=443; 224 in the risankizumab arm and 219 in the placebo arm). Patients were included in the analysis according to the study drug that they actually received. The SAS was used for all safety analysis.

Primary efficacy analysis

The primary efficacy analysis was conducted after all patients completed Week 24 and the Week 24 database lock occurred (June 2020). Full details of the statistical methods for the primary efficacy analysis of the KEEPsAKE-2 trial are presented in Table 8.

Table 8: Statistical methods for the primary efficacy analysis of KEEPsAKE-2

Statistical methods	KEEPsAKE-2
Hypothesis objective	The primary objective was to compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of PsA in the study population during the double-blind Period 1. The secondary objectives are the following: • Period 1 Double-Blind: To compare the safety and tolerability of risankizumab 150 mg vs. placebo in the study population • Period 2 Open-Label: To evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in patients who have completed Period 1
Statistical analysis	• The comparisons between the risankizumab and placebo treatment groups for the primary efficacy endpoint (ACR20 at Week 24) were performed using the Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors (concomitant csDMARD at Baseline, prior biologic use, and extent of psoriasis), with a two-sided alpha of 0.05 • For continuous efficacy endpoints, the treatment comparisons were conducted using a Mixed-Effect Model Repeated Measures (MMRM) method as primary inference purpose, with a two-sided alpha of 0.05 • Categorical efficacy variables were analysed using the CMH test controlling for stratification variables • Long-term efficacy by time point is summarised using descriptive statistics • A fixed sequence testing procedure is used to control the overall type I error rate at 2-sided alpha = 0.05 for the primary endpoint and ranked secondary endpoints
Sample size, power calculation	• It was estimated that 210 patients per treatment group would have a 90% power to detect a mean difference of 0.24 for the changes from baseline in HAQ-DI between risankizumab and placebo, assuming a common SD of 0.72. This sample size would also ensure that analyses would have at least a 90% power to detect a 20% treatment difference in ACR20 at Week

	24, with an assumed placebo response rate of 35%, using a two-sided test at a significance level of 0.05 and accounting for a 10% dropout rate
Data management, patient withdrawals	• For categorical efficacy endpoints, missing data were handled by non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) • Missing data unrelated to COVID-19 were handled by non-responder imputation, and missing data due to COVID-19 (infection or logistical restrictions) were handled by multiple imputation • Patients were considered non-responders after the initiation of rescue therapy or concomitant medications for PsA that could have meaningfully impacted efficacy assessments • For continuous efficacy endpoints, observations after the initiation of rescue therapy or concomitant medications for PsA that could have meaningfully impacted efficacy assessments were considered as missing and were excluded from the model

Abbreviations: ACR20: ≥20% improvement in American College of Rheumatology score; CMH: Cochran-Mantel-Haenszel; csDMARD: Conventional synthetic disease modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire–Disability Index; MMRM: Mixed-Effect Model Repeated Measures; PsA: Psoriatic arthritis; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; SD: standard deviation.
Sources: AbbVie Data on File KEEPsAKE-2 CSR.[15]

B.3.4 Quality assessment of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment can be found in Appendix D.

A quality assessment of KEEPsAKE-2 was performed using the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs (as per recommendations in the NICE user guide) and is presented in Appendix D.[87] Overall, KEEPsAKE-2 is considered to be of high quality with low risk of bias.

B.3.5 Clinical effectiveness results of the relevant trials

A summary of key clinical outcomes from the KEEPsAKE-2 trial for both the overall trial population and the BIO-IR and csDMARD-IR subgroups are presented in Table 9.

KEEPsAKE-2 met its primary endpoint, a significantly greater proportion of patients achieved 20% improvement in ACR criteria at Week 24 treated with risankizumab versus placebo ($p<0.001$).[80] All ranked secondary endpoints, including ACR 50, ACR 70, Health Assessment Questionnaire-Disability Index (HAQ-DI), PASI90 and MDA, were met.[80]

Table 9: Overview of KEEPsAKE-2 efficacy results (FAS)

Efficacy endpoint	Overall population				BIO-IR				csDMARD-IR			
	Risankizumab 150 mg (N=224)		Placebo (N=219)		Risankizumab 150 mg (N=105)		Placebo (N=101)		Risankizumab 150 mg (N=119)		Placebo (N=118)	
	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI	PE	95% CI
Primary endpoint												
ACR20 at Week 24, %	51.3***	[redacted]	26.5	[redacted]	45.7	[redacted]	14.9	[redacted]	56.3	[redacted]	36.6	[redacted]
Ranked secondary endpoints												
Change in HAQ-DI, LS-Mean	-0.22***	-0.28, -0.15	-0.05	-0.12, 0.02	-0.19	[redacted]	0.04	[redacted]	-0.24	[redacted]	-0.12	[redacted]
PASI 90 at Week 24,† %	55.0***	[redacted]	10.2	[redacted]	53.4	[redacted]	8.8	[redacted]	56.5	[redacted]	11.5	[redacted]
ACR20 at Week 16, %	48.3***	[redacted]	25.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MDA at Week 24, %	25.6***	[redacted]	11.4	[redacted]	19.0	[redacted]	5.9	[redacted]	31.4	[redacted]	16.1	[redacted]
CfB in SF-36 PCS score at Week 24, LS-Mean	5.87***	4.86, 6.88	2.01	0.94, 3.08	5.58	[redacted]	0.51	[redacted]	6.09	[redacted]	3.04	[redacted]
CfB in FACIT-Fatigue score at Week 24, LS-Mean	4.9**	3.7, 6.0	2.6	1.4, 3.9	4.1	[redacted]	1.0	[redacted]	5.8	[redacted]	4.1	[redacted]
Non-ranked secondary endpoints												
ACR50 at Week 24, %	26.3###	[redacted]	9.3	[redacted]	18.5	[redacted]	5.0	[redacted]	33.1	[redacted]	13.1	[redacted]
ACR70 at Week 24, %	12.0#	[redacted]	5.9	[redacted]	5.7	[redacted]	3.0	[redacted]	17.6	[redacted]	8.3	[redacted]
Resolution of enthesitis at Week 24‡, %	42.9##	[redacted]	30.4	[redacted]	45.3	[redacted]	26.4	[redacted]	40.3	[redacted]	33.7	[redacted]
Resolution of dactylitis at Week 24§, %	72.5###	[redacted]	42.1	[redacted]	69.6	[redacted]	37.9	[redacted]	76.5	[redacted]	46.4	[redacted]

***p<0.001; **p<0.01; ###nominal p<0.001; ##p<0.01; #nominal p<0.05. †Among patients with ≥3% BSA affected by psoriasis at baseline (risankizumab, n=123; placebo, n=119). ‡Defined as LEI=0 among patients with LEI >0 at baseline (risankizumab, n=147; placebo, n=158). §Defined as LDI=0 among patients with LDI>0 at baseline (risankizumab, n=40; placebo, n=57).

Abbreviations: ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CI: confidence interval; CfB: change from baseline; csDMARD-IR: conventional synthetic disease modifying anti-rheumatic drug – inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAQ-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PE: point estimate; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Source: AbbVie Data on File KEEPsAKE-2 CSR, Tables 8–13 and Table 14.2__3.11.[15] Östör *et al.* (2021),[80] and Lidar *et al.* (2021).[83]

B.3.5.1 Primary efficacy endpoint

Proportion of patients achieving ACR20 response at Week 24

At Week 24, a statistically significantly greater proportion of patients achieved ACR20 in the risankizumab arm compared with the placebo arm (51.3% versus 26.5%, respectively; p<0.001) (Figure 7).[80] Joint pain and swelling cause physical dysfunction and immobility, representing one of the largest contributing factors to self-perceived disease severity and key drivers of reduced HRQoL in patients with PsA.[30] Improvement in the number of tender and swollen joints as measured by ACR20 is therefore an important outcome in the treatment of moderate-to-severe PsA.

Figure 7: ACR20 response at Week 24 (NRI-C, FAS)

95% CI for response rate is calculated based on normal approximation to the binomial distribution. Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively. *** P-value <0.001.
Abbreviations: ACR20: American College of Rheumatology 20% improvement criteria; CI: confidence interval; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 8.[15]

B.3.5.2 Secondary efficacy endpoints

Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24

At Week 24, a statistically significantly greater mean change from baseline in HAQ-DI was observed in the risankizumab arm compared with the placebo arm (-0.22 versus –0.05, respectively; p<0.001) (Figure 8). The HAQ-DI is a measure of patients' physical function and scores generally worsen (i.e. increase) as the number of inflamed joints and disease activity increases, reducing both the capacity to carry out daily activities and HRQoL.[54] Change from baseline in HAQ-DI is therefore a very important outcome to assess if treatments improve patients' ability to function in their daily lives.

Figure 8: Change from Baseline in HAQ-DI Score at Week 24 (NRIC-C, MMRM, FAS)

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; HAQ-DI: Health assessment questionnaire disability index; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Proportion of patients achieving PASI90 response at Week 24 (in the subset of patients with a BSA ≥ 3% at Baseline)

At Week 24, a statistically significantly greater proportion of patients achieved PASI90 in the risankizumab arm compared with the placebo arm (55.0% versus 10.2%, respectively; p<0.001) (Figure 9). An estimated 80% of PsA patients have skin psoriasis, characterised by erythematous, flaking, scaling skin,[23] which can severely affect patients' HRQoL.[35] Improvement in psoriatic skin disease, as measured by PASI90, is therefore important to consider for improving symptom burden for PsA patients.

Figure 9: Proportion of patients achieving PASI90 at Week 24 (NRIC-C, MMRM, FAS)

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; PASI: Psoriasis Area Severity Index; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Proportion of patient achieving ACR20 at Week 16

At Week 16, a statistically significantly greater proportion of patients achieved ACR20 in the risankizumab arm compared with the placebo arm ([redacted]% versus [redacted]%, respectively; [redacted]) (Figure 10). This demonstrates an early and sustained improvement in arthritis symptoms with risankizumab.

Figure 10: ACR20 response at Week 16 (NRI-C, MMRM, FAS)

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation; MDA: minimal disease activity.
incorporating multiple imputation to handle missing data due to COVID-19.
Source: AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Proportion of patients achieving Minimal Disease Activity (MDA) at Week 24

A significantly greater proportion of patients achieved MDA in the risankizumab arm compared with the placebo arm (25.6% versus 11.4%, respectively; p<0.001) (Figure 11).[80] MDA defines a state of low disease activity across multiple domains, thus capturing the heterogeneity of PsA. Patients achieving MDA have reduced joint and skin symptoms, pain, self-perceived disease activity and functional disability. MDA responders are more likely to achieve minimal clinically important improvements in HRQoL, disability and productivity.[88]

Figure 11: MDA at Week 24

Data for ▌patients in the risankizumab arm were missing due to COVID-19.
*** P-value <0.001.
Abbreviations: ACR20: American College of Rheumatology 20% improvement criteria; CI: confidence interval; FAS: Full Analysis Set; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Change from Baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24

KEEPsAKE-2 demonstrated clear improvements in HRQoL with risankizumab treatment. The change from baseline in SF-36 PCS was significantly greater with risankizumab versus placebo (5.87 versus 2.01, respectively; p<0.001) (Figure 12).[80] This indicates that patients who received risankizumab had a more favourable self-perceived health state (including reduced bodily pain, disability and fatigue and better emotional health and social health).

Figure 12: Change from Baseline in SF-36 PCS Score at Week 24

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; SF-36 PCS: 36-Item Short Form Health Survey Physical Component Score.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT Fatigue) questionnaire at Week 24

At Week 24, patients in the risankizumab versus placebo arm demonstrated greater improvements in change from Baseline in FACIT-Fatigue score (4.9 versus 2.6, respectively; p<0.01) (Figure 13). Fatigue/tiredness is a common symptom in PsA which is detrimental to HRQoL, mental health and daily functioning.[51, 56] A greater reduction in level of fatigue would substantially improve HRQoL for patients.

Figure 13: Change from Baseline in FACIT-Fatigue

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; MMRM: mixed model for repeated measures; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; FACIT = Functional Assessment of Chronic Illness Therapy.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

Secondary endpoints without multiplicity adjustment

Proportion of patients achieving ACR50 and ACR70 response at Week 24

With risankizumab, 26.3% of patients achieved ≥50% improvement in ACR score and 12.0% achieved ≥70% improvement in ACR score (compared with 9.3% and 5.9% in the placebo arm, respectively). For ACR50, nominal p<0.001 and for ACR70, nominal p<0.05 (Figure 14). Thus, more patients experience substantial improvement in arthritis symptoms with risankizumab, compared with placebo.

Figure 14: ACR50 and ACR70 response at Week 24 (NRI-C, FAS)

ACR50: Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively. ACR70: Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
p<0.001; # p<0.05.
Abbreviations: ACR50: American College of Rheumatology 50% improvement criteria; ACR70: American College of Rheumatology 70% improvement criteria; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 13.[15]

Proportion of patients with resolution of enthesitis (LEI=0) at Week 24 in patients with enthesitis at Baseline

Among the subset of patients with enthesitis at baseline (n=305), a larger percentage of patients in the risankizumab arm achieved resolution of enthesitis (LEI=0) at Week 24 compared with the placebo arm (42.9% versus 30.4%; nominal p<0.01) (Figure 15). Enthesitis is inflammation at the attachment site of tendon/ligament and bone, and is a major source of pain and disability in PsA.[30] Enthesitis is observed in 30–50% of patients with PsA in clinical practice.[26] A higher number of enthesitis locations is associated with worse QoL scores.[89] Resolution of enthesitis is therefore an important outcome to patients.[30]

Figure 15: Resolution of enthesitis (LEI=0) at Week 24 (For patients with baseline presence of enthesitis) (NRI-C, FAS)

Data for [redacted] and [redacted] patients were missing due to COVID-19 in the risankizumab and placebo arms, respectively.
p<0.01.
Abbreviations: FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; LEI: Leeds Enthesitis Index.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 13.[15]

Proportion of patients with resolution of dactylitis (LDI=0) at Week 24 in patients with dactylitis at Baseline

Among the subset of patients with dactylitis at Baseline (n = 97), a larger percentage of patients in the risankizumab arm achieved resolution of dactylitis (LDI=0) at Week 24 (compared with the patients in the placebo arm (72.5% versus 42.1%; nominal p<0.001). Dactylitis is observed in 30–50% of patients with PsA in clinical practice, is a marker of disease severity and predicts radiographic damage.[26] For patients, dactylitis causes significant symptom burden.

Figure 16: Resolution of dactylitis (LDI=0) at Week 24 (For patients with baseline presence of dactylitis) (NRI-C, FAS)

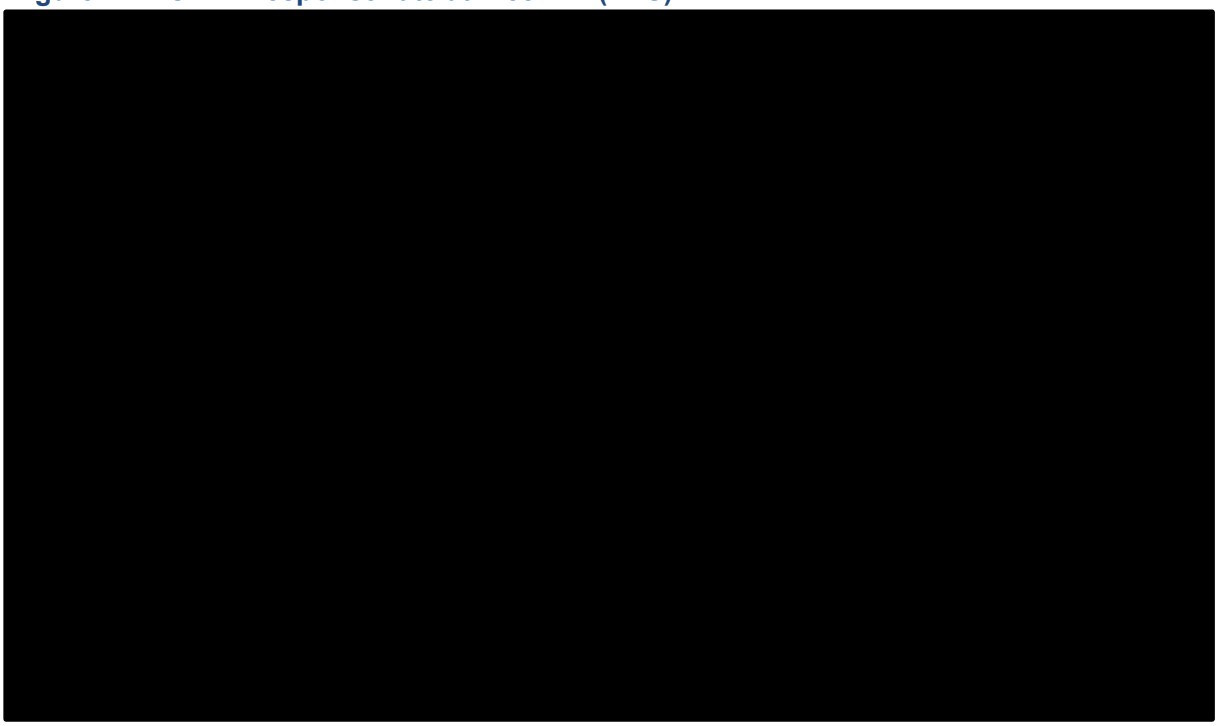
p<0.001.
Abbreviations: FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; LDI: Leeds Dactylitis Index.
Source: Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 13.[15]

Additional Efficacy Endpoints

Proportion of patients who achieved a PsARC response at Week 24

KEEPsAKE-2 demonstrated clear improvements in PsARC with risankizumab treatment. The percentage of patients who achieved a PsARC response was [redacted] versus [redacted], respectively; p<[redacted]) (Figure 17).[15] PsARC is composite measure of disease encompassing joint disease and patient and physician global assessment. Patients achieving PsARC have reduced joint symptoms.

Figure 17: PsARC response rate at Week 24 (FAS)



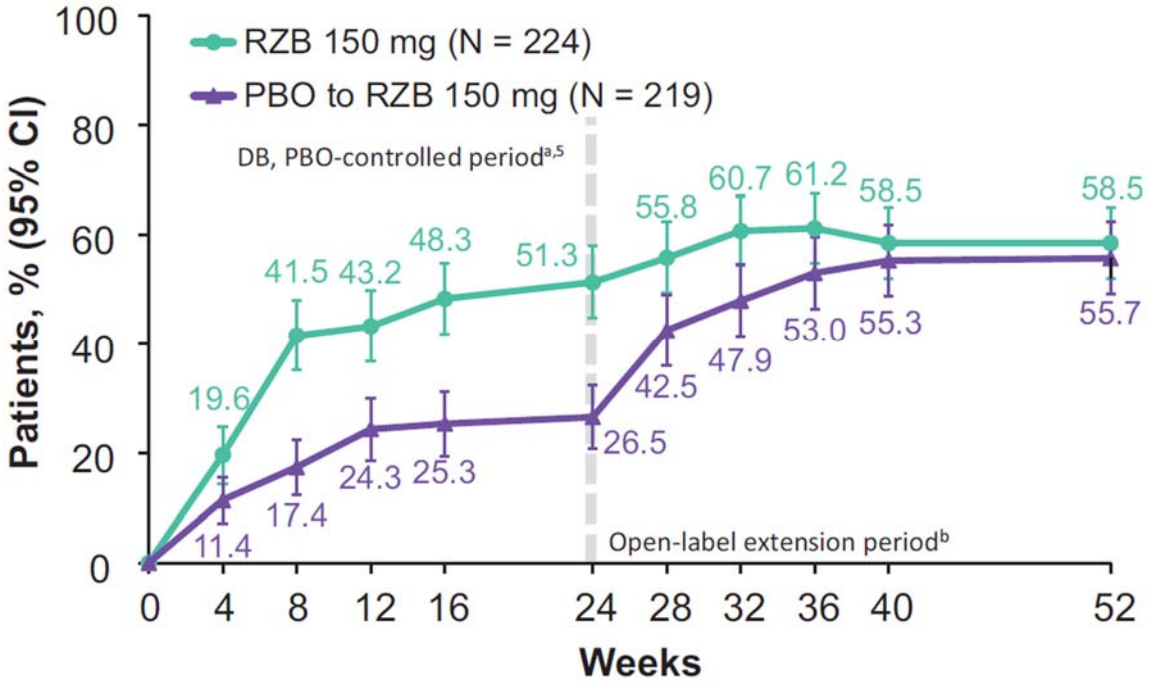
*** P-value <0.001.
Abbreviations: CI: confidence interval; FAS: Full Analysis Set; PsARC: Psoriatic Arthritis Response Criteria.
Source: AbbVie Data on File KEEPsAKE-2 CSR, Table 10.[15]

3.5.2.1 Long-term outcomes

ACR20/50/70 responses over time

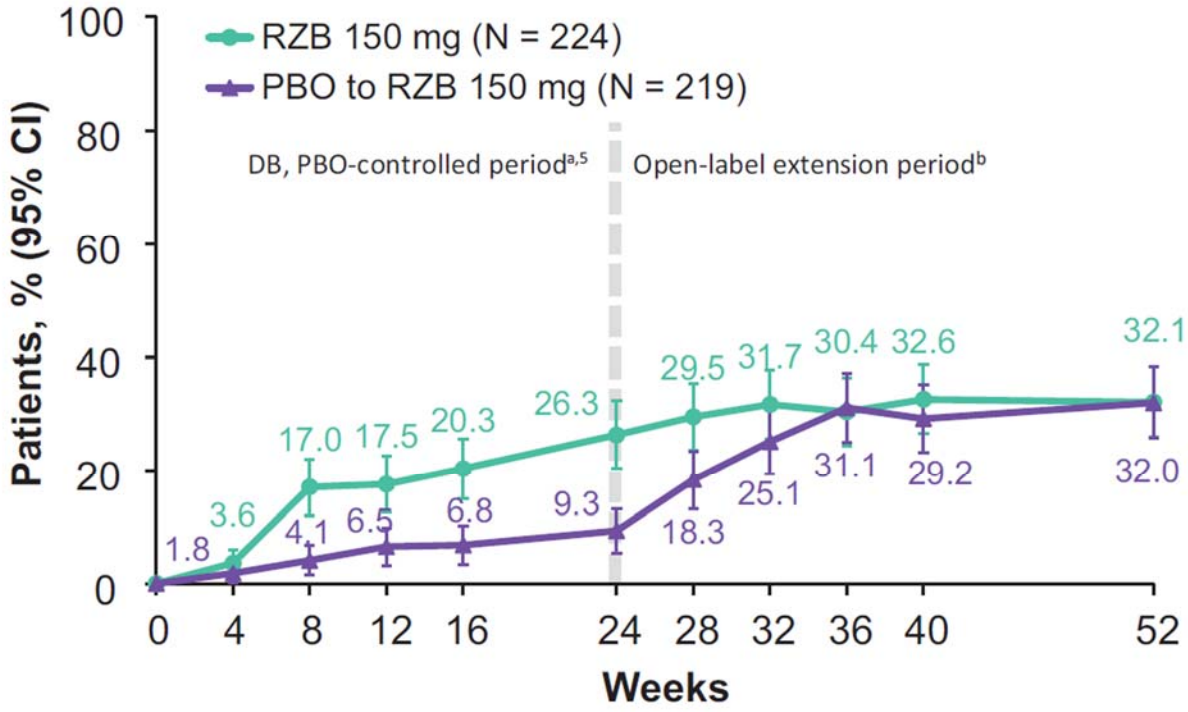
ACR20 response was maintained at Week 52; 58.5% of patients who were originally randomised to receive risankizumab and 55.7% of patients who were originally randomised to receive placebo and switch to risankizumab at Week 24 achieved ACR20 (Figure 18). Maintenance of response at Week 52 was also observed for ACR50 and ACR70 (Figure 19; Figure 20).

Figure 18: ACR20 by visit – Period 1 and Long-term



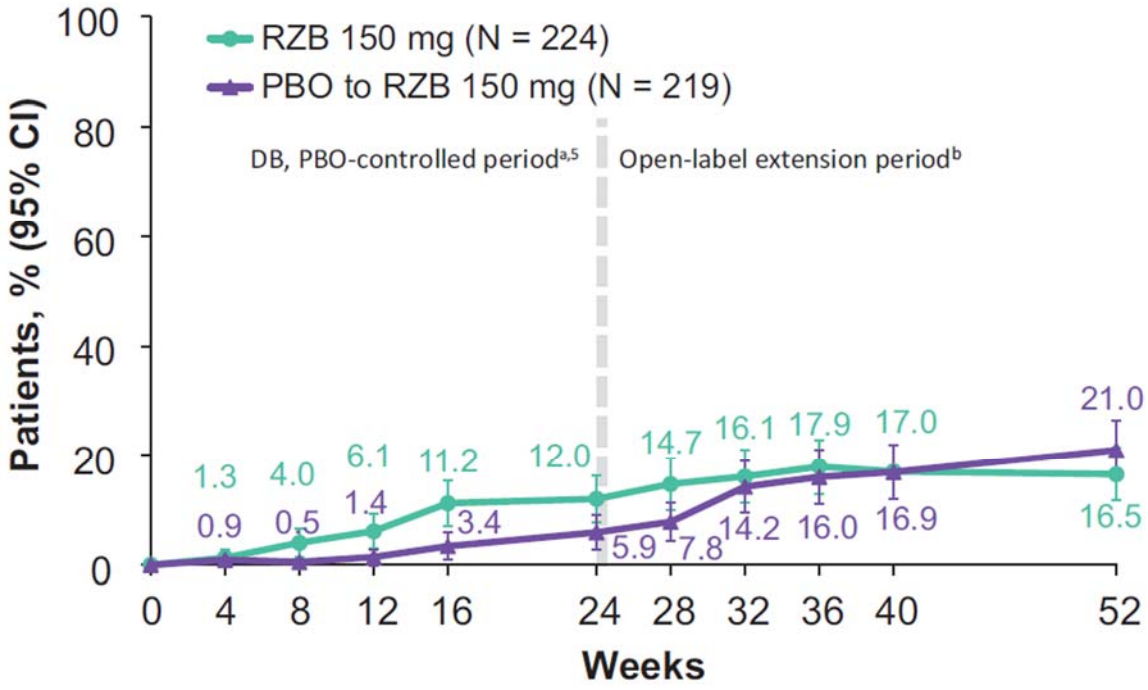
[a]Based on full analysis set, NRI-C. [b]Based on full analysis set, NRI (as observed with imputation) was used for missing data.
Abbreviations: ACR20, ≥20% improvement in American College of Rheumatology score; DB, double-blind; NRI, non-responder imputation; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
Source: Ostor et al. (2021).[82]

Figure 19: ACR50 by visit – Period 1 and Long-term



[a]Based on full analysis set, NRI-C. [b]Based on full analysis set, NRI (as observed with imputation) was used for missing data.
Abbreviations: ACR50, ≥50% improvement in American College of Rheumatology score; DB, double-blind; NRI, non-responder imputation; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.
Source: Ostor et al. (2021).[82]

Figure 20: ACR70 by visit – Period 1 and Long-term

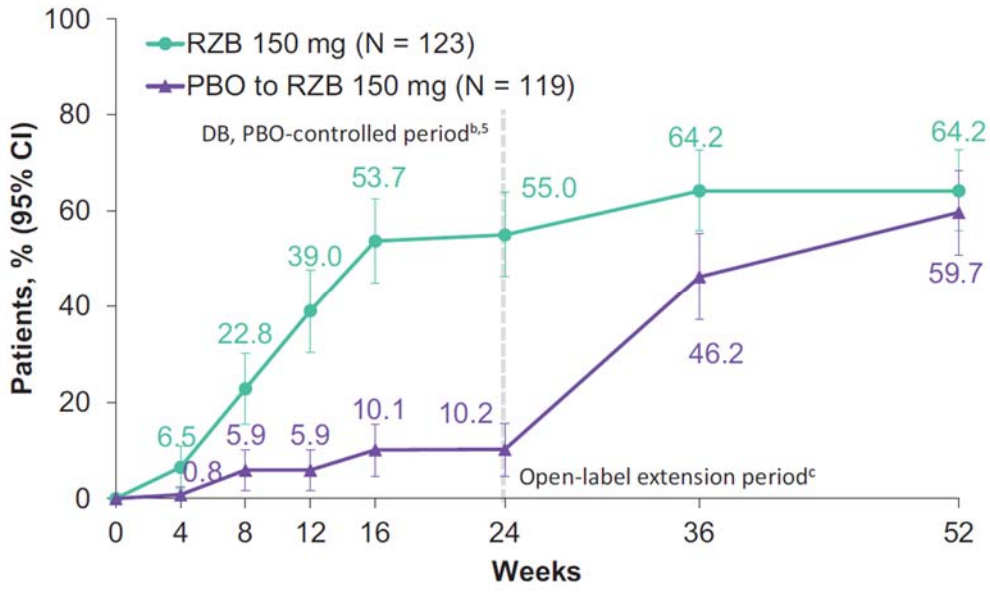


[a]Based on full analysis set, NRI-C. [b]Based on full analysis set, NRI (as observed with imputation) was used for missing data.
Abbreviations: ACR70, ≥70% improvement in American College of Rheumatology score; DB: double-blind; NRI: non-responder imputation; NRI-C: non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO: placebo; RZB: risankizumab.
Source: Ostor et al. (2021).[82]

PASI 90 response over time

PASI 90 response was maintained at Week 52; 64.2% of patients who were originally randomised to receive risankizumab and 59.7% who were originally randomised to receive placebo and switch to risankizumab at Week 24 achieved PASI 90 at Week 52 (Figure 24).

Figure 21: PASI 90 response Over Time[a]



[a]Among patients with ≥3% body surface area affected by psoriasis at baseline.
[b]Based on full analysis set, NRI-C.
[c]Based on full analysis set, NRI (as observed with imputation) was used for missing data.
Abbreviations: DB: double-blind; PASI 90: ≥90% reduction in Psoriasis Area and Severity Index; NRI: non-responder imputation; NRI-C: non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO: placebo; RZB: risankizumab.
Source: Ostor et al. (2021).[82]

B.3.6 Subgroup analysis

B.3.6.1 Prior biologic therapies

Exposure to prior biologics was a stratification factor in KEEPsAKE-2 (Section B.3.3.1). Subgroup analyses were performed on primary and key secondary endpoints in the csDMARD-IR and BIO-IR populations at Week 24. The results demonstrate simillar efficacy between the csDMARD and BIO-IR populations. The treatment effect of risankizumab in the BIO-IR population is considered to be generalisable to the specific subgroup relevant to this appraisal (adult patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD), based on input from UK clinical experts.

Proportion of patients achieving ACR20 response at Week 24

In line with the overall population, at Week 24, more patients achieved ACR20 with risankizumab compared to placebo in both the csDMARD-IR subgroup (56.3% versus 36.6%; Figure 22) and the BIO-IR subgroup (45.7% versus 14.9%). A greater improvement compared with placebo was observed in the BIO-IR subgroup compared to the csDMARD-IR subgroup (30.8% versus 19.7%). As described in Section B.1.3, improvement in joint symptoms as measured by ACR20 is important given these symptoms are key drivers of reduced HRQoL in patients with PsA.[30] Whilst the trial was not powered to detect differences between risankizumab and placebo within these subgroups, the results provide evidence for the clinical effectiveness of risankizumab in both these subgroups.

Figure 22: ACR20 response at Week 24, by number of prior biologics (NRI-C, FAS)

95% CI for response rate is calculated based on normal approximation to the binomial distribution. Data for [redacted] and [redacted] patients in the csDMARD-IR subgroup were missing due to COVID-19 in the risankizumab and placebo arms, respectively. No data were missing in the BIO-IR subgroup.
Abbreviations: ACR20: American College of Rheumatology 20% improvement criteria; CI: confidence interval; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Lidar *et al.* (2021),[83] AbbVie Data on File KEEPsAKE-2 CSR, Table 9.[15]

Secondary efficacy endpoints

Proportion of patients achieving ACR50 at Week 24

At Week 24, more patients achieved ACR50 with risankizumab compared to placebo in both the csDMARD-IR subgroup (33.1% versus 13.1%; Figure 23) and the BIO-IR subgroup, (18.5% versus 5.0%).

Figure 23: ACR50 response at Week 24, by number of prior biologics (NRI-C, FAS)

95% CI for response rate is calculated based on normal approximation to the binomial distribution. Data for [redacted] and [redacted] patients in the csDMARD-IR subgroup were missing due to COVID-19 in the risankizumab and placebo arms, respectively. Data for [redacted] patient in the BIO-IR subgroup in the risankizumab arm was missing.
Abbreviations: ACR50: American College of Rheumatology 50% improvement criteria; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Lidar *et al.* (2021),[83] AbbVie Data on File KEEPsAKE-2 CSR, Table 14.2__3.11.[15]

Proportion of patients achieving ACR70 at Week 24

At Week 24, more patients achieved ACR70 with risankizumab compared to placebo in both the csDMARD-IR subgroup (17.6% versus 8.3%; Figure 24) and the BIO-IR subgroup, (5.7% versus 3.0%).

Figure 24: ACR70 response at Week 24, by number of prior biologics (NRI-C, FAS)

95% CI for response rate is calculated based on normal approximation to the binomial distribution. Data for [redacted] and [redacted] patients in the csDMARD-IR subgroup were missing due to COVID-19 in the risankizumab and placebo arms, respectively. No data for the BIO-IR subgroup was missing.
Abbreviations: ACR50: American College of Rheumatology 50% improvement criteria; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: Lidar *et al.* (2021),[83] AbbVie Data on File KEEPsAKE-2 CSR, Table 14.2__3.11.[15]

Proportion of patients achieving PASI 90 at Week 24

At Week 24, more patients achieved PASI 90 with risankizumab compared to placebo in the csDMARD-IR subgroup (56.5% versus 11.5%; Figure 25) and a similar improvement was observed in the BIO-IR subgroup, (53.4% versus 8.8%).

Figure 25: PASI90 response at Week 24, by number of prior biologics (NRI-C, FAS)

95% CI for response rate is calculated based on normal approximation to the binomial distribution. Data for [redacted] and [redacted] patient in the csDMARD-IR subgroup were missing due to COVID-19 in the risankizumab and placebo arms, respectively. No data were missing in the BIO-IR subgroup.
Abbreviations: FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PASI 90: ≥90% reduction in Psoriasis Area and Severity Index.
Source: Lidar *et al.* (2021),[83] AbbVie Data on File KEEPsAKE-2 CSR, Table 12.[15]

B.3.6.2 Other pre-planned subgroup analyses

To identify any variation in the efficacy of risankizumab, the primary endpoint was analysed by several demographic (age, sex, BMI, race and geographic region) and disease characteristic (prior csDMARDs, prior biologic therapies, prior anti-TNF inhibitors, hsCRP at baseline, extent of psoriasis, duration of PsA and concomitant therapies) subgroups. Results are shown in Figure 26 and Figure 27. Across the majority of demographic and disease characteristic subgroups, treatment with risankizumab showed a greater proportion of patients achieving ACR20 compared with the placebo arm.

Figure 26: Forest Plot of ACR20 Response Rate at Week 24 by Demographic Subgroups (NRI-C) (FAS)

Rate difference and 95% CI are determined using Cochran-Mantel-Haenszel test adjusting for the stratification factors of current use of csDMARD (0 vs ≥1), number of prior biologic therapies (0 vs ≥1), and extent of psoriasis (>= 3% BSA or < 3% BSA) at baseline.*Placebo and risankizumab 150 mg represents n/N (%). #"Other" geographic region contains South Africa, Australia, New Zealand.
Abbreviations: ACR20: American College of Rheumatology 20% improvement criteria; BMI: body mass index; CI: confidence interval; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: AbbVie Data on File KEEPsAKE-2 CSR, Figure 14.2_6.11.[15]

Figure 27: Forest Plot of ACR20 Response Rate at Week 24 by Disease Characteristic Subgroups (NRI-C) (FAS)

Rate difference and 95% CI are determined using Cochran-Mantel-Haenszel test adjusting for the stratification factors of current use of csDMARD (0 vs ≥1), number of prior biologic therapies (0 vs ≥1), and extent of psoriasis (>= 3% BSA or < 3% BSA) at baseline.*Placebo and risankizumab 150 mg represents n/N (%). #"Other" geographic region contains South Africa, Australia, New Zealand.
Abbreviations: ACR20: American College of Rheumatology 20% improvement criteria; BMI: body mass index; CI: confidence interval; FAS: Full Analysis Set; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
Source: AbbVie Data on File KEEPsAKE-2 CSR, Figure 14.2_6.11.[15]

B.3.7 Meta-analysis

KEEPsAKE-2 was a large, multicentre Phase III RCT in biologic-naïve and biologic-experienced patients and represents one of the pivotal trials for risankizumab in this indication.[15] Additional trials (KEEPsAKE-1 and NCT02719171) were identified in the SLR that also investigated the efficacy of risankizumab versus placebo in patients with active PsA. KEEPsAKE-1 was conducted in a biologic-naïve population and NCT02719171 was a Phase II RCT, therefore these trials only provide supporting evidence for risankizumab in this indication.[81, 84] Given the lack of head-to-head RCT data for risankizumab versus guselkumab in UK clinical practice, a network meta-analysis (NMA) was performed, as presented in Section B.3.8.

B.3.8 Indirect and mixed treatment comparisons

For reasons detailed in Section B.1.1, guselkumab has been selected as the reference comparator for the cost-comparison analysis. Risankizumab and guselkumab have not been studied in head-to-head RCTs, however pivotal trials of each treatment shared the common comparator treatment, placebo. Three analysis were explored to compare risankizumab to guselkumab: an NMA with a broad range of comparators at Week 24 ('primary analysis'), a similar NMA at Week 16 ('scenario analysis') and an anchored MAIC ('additional analysis'). These are introduced in the following sections.

Primary analysis

An NMA at Week 24 was explored to compare risankizumab to guselkumab via a connected network. The results from the NMA are used to inform the cost-comparison model presented in Section B.4. AbbVie initially conducted broad NMAs in both the biologic-naïve and biologic-experienced populations including licenced therapies that are used in most countries. As a result, the eligibility criteria for the SLR included biologic-naïve and biologic-experienced populations and a wide range of treatments. The treatment effect of risankizumab in the biologic-experienced population is considered to be generalisable to the specific subgroup relevant to this appraisal (moderate-to-severe psoriasis [a body surface area of at least 3% affected by plaque psoriasis and a PASI score greater than 10] and received two csDMARDs), based on input from UK clinical experts. This assumption was accepted in the previous appraisal for guselkumab, where the same efficacy and safety data for the biologic-experienced population were used in the cost-effectiveness model regardless of psoriasis severity. This model subsequently formed the basis from which the Committee made their recommendation for guselkumab in patients with moderate-to-severe psoriasis.[2]

The NMA is discussed in more detail below, with results focusing on the comparison between risankizumab and guselkumab in the biologic-experienced population, the only relevant comparator and population in this appraisal (see Section B.1.1). Guselkumab is the only other IL-23 inhibitor that is recommended by NICE for treatment of PsA and psoriasis. Response at Week 24 is considered to be the primary analysis, as both the KEEPsAKE-2 and DISCOVER-1 trials included response at Week 24 as the primary outcome. In addition, the SmPC for risankizumab notes some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.[16]

However, the NMA includes other interleukin inhibitors (secukinumab and ixekizumab) and the results are confirmatory of the main committee and ERG conclusions in the recent guselkumab

NICE appraisal (TA711) – that "*guselkumab appeared to be very similar in effectiveness to other interleukin inhibitors (secukinumab and ixekizumab)".*[2] Results for all comparators included in the networks are presented in Appendix D.

Scenario analysis

An additional NMA was also conducted as a scenario analysis, whereby response was measured at Week 16. This analysis was performed because, although the primary outcome of KEEPsAKE-2 was assessed at Week 24, the SmPC for risankizumab recommends that a response assessment be conducted at Week 16. Furthermore, in TA711, the Committee noted that clinicians would value the option of assessing response at Week 16.[2] and the NICE recommendation for guselkumab recommends response asessment at 16 weeks.

The statistical methods used for this scenario analysis are in line with the methods used in the primary analysis at Week 24, which is discussed in more detail below.

Additional analysis

As an additional supportive analysis, an anchored Matching-Adjusted Indirect Comparison (MAIC) was performed to compare risankizumab to guselkumab using only KEEPsAKE-2 and DISCOVER-1, with placebo as the common comparator. This approach utilises a propensity score weighting approach (PSW) to adjust for observed differences in the baseline characteristics between the two cohorts. The methodology and results of the MAIC is reported in Appendix D.

B.3.8.1 NMA

Identification and selection of relevant studies

As reported in Section B.3.1 and in line with the NICE methods guide, an SLR was conducted in May 2020 and updated in December 2021 to identify efficacy data of treatments for moderate-to-severe PsA. Across the original SLR and subsequent updates, a total of 62 unique trials from 726 publications were identified. Full details of the SLR methodology and studies included in the NMA are provided in Appendix D.

Eligibility for the NMA

Studies considered for inclusion in the NMA were informed by the clinical SLR. The clinical SLR captured data from all potentially relevant studies from a global perspective, and thus a number of studies were not eligible for inclusion in the NMA (e.g. those not reporting relevant outcomes, or those investigating treatments that are not licenced for the treatment of moderate-to-severe PsA). The full eligibility criteria for the NMA and a summary of the included trials is presented in Appendix D. The NMA comparisons were stratified by patients with prior biologics use (biologic-experienced) and without prior biologics use (biologic-naïve) to account for its potential modification of the treatment effects. The population of relevance for this submission includes only 'biologic-experienced' patients, in line with the population for which guselkumab has received a positive recommendation from NICE.[2] A total of 10 trials were included in the biologic-experienced NMAs.

Aside from the KEEPsAKE-2 and NCT02719171 trials discussed in Section B.3.1, the SLR identified the following trials providing evidence for guselkumab, the key comparator in this appraisal, in biologic-experienced patients:

- **Deodhar 2018** – Multicentre, placebo-controlled, phase II RCT comparing guselkumab to placebo in biologic-experienced or biologic-naïve patients with active PsA[90]
- **DISCOVER-1** – Multicentre, placebo-controlled, double-blind phase III RCT comparing guselkumab to placebo in biologic-experienced or biologic-naïve patients with active PsA[78]
- **COSMOS** – Multicentre, placebo-controlled, double-blind phase IIIb RCT comparing guselkumab to placebo in biologic-experienced active PsA[91]

All risankizumab and guselkumab trials reported data separately for biologic-experienced populations, which were subsequently included in the NMAs.

Network of evidence

A series of NMAs were performed using a Bayesian framework deriving comparisons between interventions for each efficacy endpoint (PsARC, PASI 50/70/90, HAQ-DI change from baseline, HAQ-DI change from baseline conditional on PsARC response and ACR 20/50/70) and safety (AEs and SAEs) outcomes. The network diagrams for all outcomes for both the Week 16 and Week 24 analyses are presented in Appendix D.

Heterogeneity of trials included

Of the 10 trials included in the biologic-experienced NMAs, two were Phase II trials, seven were Phase III trials, and one was a Phase IIIb trial. All trials were placebo controlled, and all assessed outcomes at Week 24, which was consistent with the timepoint for the assessment of the primary endpoint in the KEEPsAKE-2 trial. Details of the differences in key aspects of study design, outcomes and patient characteristics are discussed below.

Study Design

Eligibility criteria

Different criteria were applied across trials for the inclusion of biologic-experienced patients. The COSMOS and SPIRIT-P2 trials included only biologic-experienced patients. The biologic-experienced patients in the SPIRIT-P2, COSMOS, and FUTURE trials had inadequate response or intolerance to anti-TNFs.[92-96] The biologic-experienced patients in the KEEPsAKE-2 trial had inadequate response or intolerance with bDMARDs.[80]

The trials also applied mixed standards for the permitted numbers of prior anti-TNFs. Only the COSMOS and SPIRIT-P2 trials included biologic-experienced patients with inadequate response or intolerance to one to two TNF inhibitors.[91, 92] The biologic-experienced patients in the DISCOVER-1, PSUMMIT 2, NCT02719171, and Deodhar 2018 trials were permitted to have prior TNF inhibitor use, including both patients with TNF inhibitor failure and exposure.[78, 84, 90, 97] The trials applied mixed standards for the permitted number of prior biologics, ranging from a maximum of one TNF inhibitor in Deodhar 2018 to a maximum of three TNF inhibitors in the FUTURE-2, -3 and -5 trials.[90, 95, 96, 98]

Concomitant medication

All the included trials permitted the concomitant use of csDMARDs during the trial period, however, different criteria were applied. The Deodhar 2018, FUTURE 2-5, PSUMMIT 2, and NCT02719171 trials permitted concomitant use of methotrexate whereas the DISCOVER-1, KEEPsAKE-2, COSMOS, and SPIRIT-P2 trials permitted concomitant use of one or at least one csDMARD (including but not limited to methotrexate).[78, 84, 90, 92-97]

Treatment switching, rescue therapy and imputation

Seven of the 10 trials included in the NMA implemented treatment crossover or early escape design prior to Week 24. In these trials, early escape for non-responders occurred at Week 16 and there was heterogeneity in the criteria used to define non-responders, ranging from <5% to <20% change in swollen and tender joint counts. The use of imputation differed between these trials. The PSUMMIT trial used last observation carried forward (LOCF) from Week 16 to impute data at Week 24 whereas the FUTURE 2, 3 and 5 trials, SPIRIT-P2 and COSMOS trials all applied non-responder imputation (NRI) to patients escaping early.[91, 92 94-97] The Deodhar 2018 trial applied NRI for ACR and LOCF for PASI among patients who escaped early.[90] The use of NRI and LOCF, however, does not necessarily reproduce the counterfactual outcomes had the early escapers been treated with the randomised treatment (e.g., placebo) through to Week 24. For example, the application of NRI may disproportionally underestimate the response rate for the placebo arm, therefore potentially overestimating the treatment contrast between active treatment and placebo.

Rescue therapy was only permitted in the DISCOVER-1, COSMOS, SPIRIT-P2, KEEPsAKE-2 and NCT02719171 trials at Week 16.[78, 80, 84, 91, 92] The rescue therapy permitted and criteria for non-responder differed slighty between these trials. In the guselkumab trials (DISCOVER-1 and COSMOS), patients with <5% improvement in swollen and tender joint counts at Week 16 were considered as non-responders.[78, 91] In the DISCOVER-1 trial, investigator could initiate or increase the dose of NSAIDs or other analgesics, oral corticosteroids, or non-biologic DMARDs for these patients. However, the non-responders at Week 16 were assumed to be non-responders at Week 24 in DISCOVER-1, which likely disproportionally underestimated the response rate for the placebo arm and exaggerated the treatment contrast between guselkumab and placebo. In the COSMOS trial, early escapers could initiate or increase the dose of one permitted concomitant medication up to the maximum allowed dose at the physician's discretion.

In the KEEPsAKE-2 trial, patients with < 20% improvement in either or both swollen joint counts and tender joint counts at both Week 12 and Week 16 were considered as non-responders. The non-responders could add or modify background therapy (e.g., NSAIDs, analgesics, corticosteroid injection, csDMARD). NRI was applied for those who received rescue therapy.[80] In the NCT02719171 trial, patients with < 20% improvement in both tender and swollen joint counts at Week 16 were considered as non-responders.[84] The non-responders could alter concomitant PsA treatment or start additional treatment except biologics.

Outcome definitions

As PsARC, PASI, ACR, and HAQ-DI are commonly adopted, standardised outcomes, their definitions were generally consistent across the included trials.

Baseline characteristics

A comparison of patient demographics and baseline characteristics between trials indicated that patients with wide ranging demographics and disease durations and prior treatments were included across trials.

The mean/median age ranged from 44.2 years in the placebo arm of the Deodhar 2018 trial to 54.1 years in the placebo arm of the SELECT-PsA 2 trial.[90, 99] Relative to other trials, the SPIRIT-P2, KEEPsAKE-2, NCT02719171, and FUTURE 3 trials included older patients. Most trials had a generally balanced gender distribution. The percentage of female patients ranged from 45% in the secukinumab 150 mg arm of the FUTURE 2 trial to 60.2% in the placebo arm of the FUTURE 2 trial. Trials that reported race distributions enrolled predominantly white patients, with the percentage of white patients ranging from 80.9% in the secukinumab 150 mg with loading dose arm in the FUTURE 5 trial to 100% in the guselkumab Q8W and placebo arms of the Deodhar 2018 trial.[90, 95]

The mean duration of PsA, thought to be a treatment effect modifier, varied substantially across trials, from 4.5 years in the ustekinumab 90 mg arm of the PSUMMIT 2 trial to 11.0 years in the ixekizumab Q4W arm of the SPIRIT-P2 trial.[90, 95] In addition, there was also heterogeneity in baseline plaque psoriasis, also thought to be a treatment effect modifier. The percentage of patients with at least 3% body surface area (BSA) affected by psoriasis ranged from 41.0% in the secukinumab 300 mg arm of the FUTURE-2 trial to 100% in the Deodhar 2018 trial.[90, 98]

Placebo response rates also varied between trials, with more recent trials such as KEEPsAKE-2 and SPIRIT-P2 having higher placebo response rates compared with earlier trials. This trend was observed for PsARC and PASI 75 outcomes but no clear time trend was observed across all other outcomes due to the small number of trials included in the networks. The time trends of the outcomes among placebo patients is presented in Appendix D.

Summary

In summary, there was some heterogeneity in trial design and patient characteristics across the studies included in the NMA. Further details of the studies, patient and disease characteristics are presented in Appendix D. While the heterogeneities in the aspects discussed above may modify the treatment contrasts, the small number of trials included in the NMAs made it difficult to evaluate the impact of such potential effect modifications. Where possible, multiple models (including fixed- and random-effects models) were fitted to account for heterogeneity in the NMAs. Furthermore, to explore the impact of adjusting for treatment effect modifiers, a supportive MAIC was conducted to compare risankizumab to guselkumab using only KEEPsAKE-2 and DISCOVER-1 and adjusting for differences in baseline characteristics. The methodology and results of the MAIC are reported in Appendix D.

Methodology

The statistical methods followed the recommended methods in the NICE Decision Support Unit Technical Support Document 2 and 3, with the NMAs conducted under a Bayesian generalised linear model framework.[100, 101] The outcomes followed or were assumed to follow a given distribution and a link function was applied for the relationship between the distribution of the outcome and the linear predictors. Specifically:

- PsARC follows a binomial distribution. Logistic regressions were used to model PsARC.
- PASI 50/75/90/100 follow multinomial distributions. Probit regressions were used to jointly model PASI 50/75/90/100.
- HAQ-DI change from baseline was assumed to follow a normal distribution. Linear regressions were used to model unconditional HAQ-DI change, HAQ-DI change among PsARC responders, and HAQ-DI change among PsARC non-responders, respectively.
- ACR 20/50/70 follow multinomial distributions. Probit regressions were used to jointly model ACR 20/50/70.
- Adverse events (AE), serious AE and AE leading to treatment discontinuation

The following models in Table 10 were implemented for each outcome in each network. In the networks for PsARC, HAQ-DI change, and HAQ-DI change conditional on PsARC, one edge was connected by two trials and all other edges were connected by only one trial. In the network for PASI, two edges were connected by two trials and all other edges were connected by only one trial. These networks contained an insufficient number of trials to (a) accurately estimate the cross-trial heterogeneity parameter in a random-effects model or (b) accommodate adjustment for covariates in a meta-regression. Therefore, a fixed-effects model was selected as the primary model for these networks. Nonetheless, a random-effects model was further fitted to demonstrate the insufficient number of trials for accommodating the random effects, which was used to further justify the application of a fixed-effects model to these networks. The results from the random-effects model are presented in Appendix D.

For networks with a rich set of included trials, multiple models were fitted and compared for these networks, given the large variations in placebo response rates across trials.

Table 10. NMA models used in the analysis

Analysis	Primary analysis
PsARC	Fixed-effects model (primary) Random-effects binary model
PASI 50/75/90/100	Fixed-effects model (primary) Random-effects binary model
HAQ-DI change	Fixed-effects model (primary) Random-effects binary model
HAQ-DI change conditional on PsARC response	Fixed-effects model (primary) Random-effects binary model
ACR 20/50/70	Random-effects model; selected from four candidate models
AEs and serious AEs	Fixed-effects model

Abbreviations: ACR: American college of Rheumatology; AE: adverse event; HAQ-DI: health assessment questionnaire-disability index; PASI: psoriasis area severity index; PsARC: Psoriatic arthritis Response Criteria.

Model selection was based on model fit as measured by deviance information criterion (DIC), consideration of cross-trial heterogeneity and the association between treatment effect and placebo response. Full details of the models used and justifications are provided in Appendix D.

Results

Biologic-experienced population at Week 24

Key efficacy and safety results in the biologic-experienced population at Week 24 are presented in the following sections and are focused on comparisons of risankizumab and guselkumab. For reasons detailed in Section B.1.1, guselkumab has been selected as the reference comparator for the cost-comparison analysis. Results against all comparators included in the NMA are presented in Appendix D.

Table 11 lists the Odds Ratios (OR) and 95% credible intervals (CrIs) for each endpoint at Week 24 where comparison versus guselkumab was possible. ORs <1 favour guselkumab and ORs >1 favour risankizumab. Importantly, [redacted] between risankizumab and guselkumab across all endpoints assessed. Whilst the point estimates of the ORs do slightly favour guselkumab, the estimates are close to one for all outcomes suggesting a similar treatment effect between risankizumab and guselkumab. Furthermore, the differences in point estimates of the response rates between risankizumab and guselkumab are considered to be clinically insignificant, based on input from UK clinical experts. Together, these results suggest clinical equivalence between risankizumab and guselkumab. Table 12 lists the estimated HAQ-DI Change from Baseline [Posterior Median (95% CrI)] at Week 24. A difference >0 favours guselkumab, [redacted] Comparison versus guselkumab was not possible for HAQ-DI change from baseline conditional on PsARC response as data for the treatment effect of guselkumab was not available for this outcome.

Table 11: Risankizumab 150 mg vs guselkumab 100 mg Q8W: Summary results from the biologic-experienced efficacy NMA (Week 24)

Endpoint[a]	Response rates % (95% CI)		OR (95% CrI) for risankizumab versus guselkumab[b]
	Risankizumab	Guselkumab	
PsARC response	[redacted]	[redacted][c]	[redacted][c]
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]

[a]Results presented vs guselkumab Q8W, given a dose of Q4W is only recommended for patients at high risk for joint damage according to clinical judgement. [b]Fixed-effects model were selected for PsARC and PASI 50/75/90/100. A random-effects model was selected for ACR 20/50/70. [c]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; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area Severity Index.

Table 12: Risankizumab 150 mg vs guselkumab 100 mg Q8W: HAQ-DI Change from Baseline from the biologic-experienced efficacy NMA (Week 24)

Endpoint[a]	Posterior Median (95% CrI)	

	Risankizumab	Guselkumab	Estimated Differences [Posterior Median (95% CrI)]
HAQ-DI CFB	[redacted]	[redacted]	[redacted]

A fixed-effects continuous NMA was implemented.
Abbreviations: CFB: change from baseline; CrI: credible interval; HAQ-DI: health assessment questionnaire-disability index; NMA: Network Meta Analysis; Q8W: once every 8 weeks.

Biologic-experienced population at Week 16

Table 13 lists the ORs and 95% CrIs for each endpoint at Week 16 where comparison versus guselkumab was possible. ORs <1 favour guselkumab and ORs >1 favour risankizumab. [redacted] between risankizumab and guselkumab across all endpoints assessed at Week 16.

Table 13: Risankizumab 150 mg vs guselkumab 100 mg Q8W: Summary results from the biologic-experienced efficacy NMA (Week 16)

Endpoint[a]	Response rates % (95% CI)		OR (95% CrI) for risankizumab versus guselkumab[b]
	Risankizumab	Guselkumab	
PsARC response	[redacted]	[redacted][c]	[redacted][c]
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]

[a]Results presented vs guselkumab Q8W, given a dose of Q4W is only recommended for patients at high risk for joint damage according to clinical judgement. [b]Fixed-effects model were selected for PsARC and PASI 50/75/90/100. A random-effects model was selected for ACR 20/50/70. [c]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; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area Severity Index.

Safety outcomes

Table 14 lists the OR and 95% CrIs for each safety endpoint; an OR value >1 favours guselkumab. [redacted] in safety endpoints, suggesting that the two agents have similar safety outcomes.

Table 14: Risankizumab 150 mg vs guselkumab 100 mg Q8W: Summary results from the safety NMA (Week 24)

Endpoint	Rate % (95 CI)		OR (95% CrI) for risankizumab versus guselkumab
	Risankizumab	Guselkumab	

AE	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; CrI: credible interval; OR: odds ratio; SAE: serious adverse event.

Conclusions

Overall, the NMA demonstrates that risankizumab has comparable clinical efficacy and similar tolerability compared to guselkumab, thus justifying the use of the cost-comparison analysis where the intervention demonstrates similar health benefits to technologies already recommended by NICE in technology appraisal guidance. The results suggest that risankizumab and guselkumab can be considered clinically equivalent in biologic-experienced patients with moderate-to-severe active PsA.

The NMA results against all comparators (see Appendix D) provide evidence to show that risankizumab broadly compares with other interleukin inhibitor treatments in this disease area, but should not be considered as a robust ranking of the treatments. The results for guselkumab and other interleukin inhibitor treatments are in line with the NMA submitted in the previous NICE appraisal for guselkumab (TA711).[2]

B.3.8.2 Limitations of the indirect and mixed treatment

The KEEPsAKE-2 and DISCOVER-1 trials are key trials in the network, influencing the effect estimates of risankizumab and guselkumab respectively in the biologic-experienced population. Due to the sparsity of most Week 24 biologic-experienced networks in the NMA, which prevented the derivation of a heterogeneity parameter, a simple comparison of baseline characteristics of these two trials was undertaken to see if there might be significant differences. Heterogeneity across studies is common in this disease area and previous NMAs and NICE appraisals have accepted that trials in PsA are heterogenous.[8-10]

Nonetheless, there were significant differences in baseline age, swollen joint counts, body surface area (BSA) affected, HAQ-DI, C-reactive protein (CRP, a marker of inflammation), DMARD use at baseline and PASI (see Appendix D) between the KEEPsAKE-2 and DISCOVER-1 trials. These differences in baseline characteristics are clinically relevant and can be considered as treatment effect modifiers, based on input from UK clinical experts. The risankizumab patients included in the KEEPsAKE-2 trial were considered to be a harder-to-treat population compared to the guselkumab patients included in DISCOVER-1, based on the disease duration, PASI, and CRP levels at baseline.

Despite this, the OR and 95% CrIs for all efficacy and safety outcomes in the NMA indicate comparable clinical efficacy and similar tolerability between risankizumab and guselkumab, and the overall NMA indicates a ‘class effect’ of interleukin inhibitors in line with conclusions from previous appraisals. To explore the impact of the differences in baseline characteristics between KEEPsAKE-2 and DISCOVER-1, a MAIC was conducted and is included in Appendix D, for completeness. The results of the MAIC also demonstrated [redacted].

Given the conclusions of the NMA and MAIC were similar, the NMA results were used to inform the cost-comparison model presented in Section B.4, since the NMA was informed by a larger evidence base than the MAIC.

B.3.9 Adverse reactions

All treatment-emergent AEs were summarised using Medical Dictionary for Regulatory Activities (MedDRA®, version 23.1). The number and proportion of patients with reported treatment-emergent AEs were summarised by MedDRA® primary system organ class (SOC) and preferred term (PT). Treatment-emergent AEs (TEAEs) are defined as those with an onset date that is after the first dose of study drug, and no more than 140 days after the last dose of study drug. A patient with more than 1 AE reported for the same PT is counted only once for that term. All AEs presented in this section were treatment-emergent, unless otherwise noted.

Safety analysis for Period 1 was performed on safety data up to Week 24. This is a study in patients with PsA as the underlying disease. In presentations of AE data, PTs suggestive of underlying disease, e.g., "psoriatic arthropathy," refer to a worsening of the underlying disease.

B.3.9.1 Summary of adverse events

Risankizumab was generally well-tolerated by patients with PsA, consistent with the known safety profile in psoriasis.[16] A total of 124 patients (55.4%) in the risankizumab group and 120 patients (54.8%) in the placebo group reported at least one TEAE during Period 1. Furthermore, similar proportions of patients in the risankizumab and placebo arms experienced serious TEAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug.

Among all patients who received risankizumab during Period 1, 9 patients (4.0%) had reported serious adverse events (SAEs); this frequency was comparable to the placebo arm (5.5%). Patients experienced [redacted] SAEs with any risankizumab exposure through the open-label extension period. A total of [redacted] patients with any risankizumab exposure had SAEs considered to have a reasonable possibility of being related to study drug.

During Period 1, the proportion of patients with AEs leading to discontinuation of study drug in the risankizumab arm (0.9%) was lower than the placebo arm (2.3%). Two patients with any risankizumab exposure experienced AEs leading to discontinuation (both due to psoriatic arthropathy) and was considered to have no reasonable possibility of being related to study drug by the investigator. The rate of AEs leading to discontinuation of study drug remained stable in patients with any risankizumab exposure through the open-label extension period.

Table 15 provides a summary of TEAEs and deaths during Period 1 and the open-label extension.

Table 15: Overview of TEAEs and Deaths (Safety Analysis Set)

Patients with:	Period 1					Long Term
	Placebo (n=219; PYs=101.3)		Risankizumab 150 mg (n=224; PYs=104.3)		Between Groups Comparison (Risankizumab 150 mg – Placebo)[a]	Any Risankizumab 150 mg (n=419; PYs=509.7)
	n (%)	Events (E/100 PYs)	n (%)	Events (E/100 PYs)	Rate Difference (%) [95% CI]	Events (E/100 PYs)
Any TEAEs	120 (54.8)	[redacted]	124 (55.4)	286 (274.2)	[redacted]	939 (184.2)
Any COVID-19 related TEAEs	0	0	1 (0.4)	1 (1.0)	[redacted]	38 (7.5)
Any TEAE related to study drug according to the investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any serious TEAE	12 (5.5)	[redacted]	9 (4.0)	14 (13.4)	[redacted]	48 (9.4)
Any severe TEAE	7 (3.2)	[redacted]	6 (2.7)	[redacted]	[redacted]	NR
Any TEAE leading to discontinuation of study drug	5 (2.3)	[redacted]	2 (0.9)	2 (1.9)	[redacted]	8 (1.6)
Any TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
All Deaths	0	0	0	0	0.0	0

[a]The rate difference and 95% CI are based on normal approximation to binomial distribution.Treatment-emergent AE for Period 1 safety analysis is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 140 days after the last dose of study drug if subject discontinued study drug prematurely before Week 24 dosing. Treatment-emergent AE for long-term safety analysis is defined as an AE with an onset date that is on or after the first dose of risankizumab and up to 140 days after the last dose of risankizumab if patient discontinued study drug prematurely. The any risankizumab 150 mg group includes all patients who received risankizumab 150 mg, including those who started on risankizumab 150 mg at randomisation and who switched from placebo to risankizumab 150 mg.
Abbreviations: CI: confidence interval; E: Events; NR: not reported; PY: patient year; TEAE: treatment-emergent adverse event.

B.3.9.2 Source: Östör *et al.* (2021),[82] Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 18.[15] Analysis of adverse events

The proportions of patients during Period 1 who experienced AEs assessed by a study investigator as having a reasonable possibility of being related to study drug were comparable between the risankizumab and placebo arms. The most frequently reported AEs in the risankizumab arm that were determined to have a reasonable possibility of being related to the study drug were upper respiratory tract infections (17 events) and hypertension ([redacted]).

While hypertension is the second most frequently reported AE in the risankizumab arm, [redacted]% of the patients in the risankizumab arm had a baseline medical history of hypertension. The organ

class with the most frequently reported AEs with any risankizumab exposure was infections and infestations ([redacted]). Table 16 shows AEs reported during Period 1.

Table 16: Adverse Events Reported in ≥ 1 % of Patients by Decreasing Frequency in the Risankizumab Arm-Period 1 (Safety Analysis Set)

MedDRA 23.1 Preferred Term	Placebo (n=219) n (%)	Risankizumab 150 mg (n=224) n (%)
Upper respiratory tract infection	12 (5.5)	17 (7.6)
Hypertension	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]

Treatment-emergent AE is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 140 days after the last dose of study drug if patient discontinued study drug prematurely before Week 24 dosing.
Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term.
Source: AbbVie Data on File KEEPsAKE-2 CSR, Table 19.[15]

The majority of AEs observed in the risankizumab arm during Period 1 were classed as mild to moderate in severity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 or 2) and this was consistent with the placebo arm. Most AEs observed in patients with any risankizumab exposure through the open-label extension period were also mild to moderate in severity.

Table 17 presents AEs in Areas of Safety Interest occurring during the study. During Period 1, AEs in ASIs were low overall, and rates were comparable between risankizumab and placebo arms. Similar trends were observed when assessing AEs in ASIs by number of prior biologic therapies (0 versus ≥ 1). No patient in any treatment arm had treatment-emergent active tuberculosis (TB), serious anaphylactic reactions, and adjudicated anaphylactic reactions.

Table 17: Overview of Areas of Safety Interest (Safety Analysis Set)

Outcome	Period 1				Long Term
	Placebo (n=219; PYs = 101.3)		Risankizumab 150 mg (n=224; PYs = 104.3)		Any Risankizumab 150 mg (n=419; PYs = 509.7)
	n (%)	Events (E/100 PYs)	n (%)	Events (E/100 PYs)	Events (E/100 PYs)
Any MACE	[redacted]	[redacted]	[redacted]	1 (1.0)	3 (0.6)
Any extended MACE	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any serious infections	[redacted]	[redacted]	[redacted]	3 (2.9)	10 (2.0)
Any active tuberculosis	[redacted]	[redacted]	[redacted]	0	0
Any opportunistic infection excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]	0	1 (0.2)
Any herpes zoster	[redacted]	[redacted]	[redacted]	0	3 (0.6)
Any malignant tumours	[redacted]	[redacted]	[redacted]	[redacted]	11 (2.2)
Any non-melanoma skin cancer (NMSC)	[redacted]	[redacted]	[redacted]	1 (1.0)	9 (NR)
Any malignant tumours excluding NMSC	[redacted]	[redacted]	[redacted]	0	2 (0.4)
Any hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any serious anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any adjudicated anaphylactic reactions	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any hepatic events	[redacted]	[redacted]	[redacted]	[redacted]	NR
Any injection site reactions	[redacted]	[redacted]	[redacted]	[redacted]	NR

[a]The rate difference and 95% CI are based on normal approximation to binomial distribution. TEAEs for Period 1 and the long term safety analysis is defined as an AE with an onset date that is on or after the first dose of study drug in Period 1 and prior to the Week 24 dose date, or up to 140 days after the last dose of study drug if patient discontinued study drug prematurely before Week 24 dosing. MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Extended MACE is defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina, and coronary revascularization procedures.
Abbreviations: AE: Adverse event; E: Event; NMSC: non-melanoma skin cancer; MACE: Major adverse cardiac event; TB: Tuberculosis.
Source: Östör *et al.* (2021),[82] Östör *et al.* (2021),[80] AbbVie Data on File KEEPsAKE-2 CSR, Table 20.[15]

B.3.10 Conclusions about comparable health benefits and safety

Risankizumab is indicated alone or in combination with methotrexate for the treatment of active PsA in adults who have had an inadequate response or who have been intolerant to one or more DMARDs.[1] The submission focuses on a subgroup of the technology's anticipated marketing authorisation, in order to align to the population for which guselkumab has received a positive recommendation from NICE. This population is adult patients with PsA who have[3]:

- 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 Psoriasis Area and Severity Index [PASI] score greater than 10), and
- had 2 conventional (synthetic) DMARDs and ≥1 biological DMARD.

Full details of treatment pathway, proposed positioning and corresponding decision problem can be found in Section B.1.3.3 above.

The KEEPsAKE-2 trial enrolled patients who were either biologic-naïve or biologic-experienced and did not restrict based on BSA and PASI score. In addition, patients were eligible for enrolment provided they had received at least one prior csDMARD. As a result, 43.3% of patients had not received at least two csDMARDs, which is the target population for this appraisal.[80] The population enrolled in the KEEPsAKE-2 trial is therefore a broader population compared to the population specified in the decision problem. However, this was likely due to the differences in treatment pathways between the UK and other settings. Despite not receiving at least two csDMARDs, these patients are still considered broadly representative of the target population for this appraisal, based on input from UK clinical experts, as they have received at least one bDMARD. This broader biologic-experienced population is consistent with the clinical data provided in the previous appraisal for guselkumab, which formed the evidence base from which NICE made their recommendation (TA711).[3] The treatment effect of risankizumab has also been demonstrated irrespective of the number of prior csDMARDs (see Section B.3.6.2).

The evidence base provides data across patients who have previously been exposed to biologic treatments. In UK practice, it is likely that adult patients with active PsA will go through a sequence of treatments that is specific for each patient and may switch to another biologic treatment, after inadequate response to their current therapy. Importantly, pre-specified subgroup analyses confirm a benefit in favour of risankizumab across baseline characteristics including BMI, disease severity and treatment history, essentially meaning that patients will benefit from treatment with risankizumab across all subgroups (see Section B.3.6.2).

Risankizumab demonstrated superior efficacy across the primary endpoint (ACR20) and ranked secondary endpoints (ACR 50, ACR 70, HAQ-DI, PASI90 and MDA) compared to placebo across 24 weeks. The durability of treatment response was demonstrated in the open-label phase of the KEEPsAKE-2 study, which showed a consistent treatment effect with risankizumab through to 52 weeks. Risankizumab and guselkumab have not been studied in head-to-head RCTs, indirect treatment comparison methods were therefore conducted for this comparison. A series of NMAs were conducted under a Bayesian framework for PsARC, PASI 50/70/90, HAQ-DI change from baseline, HAQ-DI change from baseline conditional on PsARC response and ACR 20/50/70. Considering the only comparator relevant to this appraisal, guselkumab, [redacted]

[redacted] between risankizumab and guselkumab. While the [redacted], imbalances in treatment effect modifiers between these trials may bias these results. An anchored MAIC between KEEPsAKE-2 and DISCOVER-1 was therefore also conducted to adjust for these imbalances. The results of the MAIC demonstrate, across all outcomes assessed, there is [redacted] and the [redacted] compared to the NMA for most outcomes in the relevant BIO-IR subgroup.

With regards to safety and tolerability, risankizumab was consistent with the known safety profile from 4.5 years risankizumab treatment in psoriasis and there were no new safety signals of concern. Similar proportions of patients in the risankizumab and placebo arms experienced serious TEAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug. This safety profile is further supported by the NMA results for safety outcomes. The proportion of patients experiencing any AE or a serious adverse event (SAEs) was comparable between risankizumab and guselkumab.

Risankizumab has demonstrated statistically significant improvements versus placebo in signs and symptoms of joint disease, as well as significant improvements in plaque psoriasis, physical function, and HRQoL, all of which are key areas of importance to patients. ITC results suggest that risankizumab has comparable clinical efficacy and tolerability compared to guselkumab, the alternative biologic recommended by NICE in the patient population relevant to this appraisal.

B.3.11 Ongoing studies

Other than KEEPsAKE-1 and -2, there are no ongoing studies relevant to this appraisal.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Risankizumab is not anticipated to require any changes to current service provision and management. Risankizumab is a subcutaneous injection that is administered at weeks 0 and 4, and every 12 weeks thereafter if patients are eligible for maintenance therapy. Patients can self-inject at home if this is deemed appropriate by a physician. Should a patient require self-administartion support at home, the cost of supervision will be covered by AbbVie.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost-comparison analysis was conducted to evaluate the cost to the NHS of using risankizumab versus guselkumab for treating adults with active psoriatic arthritis (PsA) in patients who have failed prior treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs). This population are referred to as biologic-experienced PsA patients in the model. A simple economic model was developed in Microsoft Excel to facilitate the comparison. The treatment effect of risankizumab in the biologic-experienced population is considered to be

generalisable to the specific subgroup relevant to this appraisal (moderate-to-severe psoriasis [a body surface area of at least 3% affected by plaque psoriasis and a PASI score greater than 10] and received two csDMARDs), based on input from UK clinical experts.

As introduced in Section B.1, guselkumab was selected as the appropriate comparator because:

- Guselkumab is one of the most recent biologic therapy for PsA to enter the UK market with published technology appraisal guidance, and thus has recently been judged to be a cost-effective treatment option for this patient population. Guselkumab can therefore be assumed to be broadly representative of, or superior to, the full group of treatment comparators in terms of cost-effectiveness.
- Guselkumab is the only technology recommended specifically in patients with PsA and moderate-to-severe psoriasis who have had two conventional DMARDs and at least one biological DMARD, and the patient population addressed in the submission has been exactly aligned with this restricted population.
- As guselkumab is relatively new to the UK market for PsA, it is not expected that guselkumab has a significant market share in the overall PsA population at present. However, increasing market share can be observed for guselkumab in PsA in countries where guselkumab launched earlier than the UK.[5] It is expected that the market share in the UK will increase within the subgroup of patients with moderate-to-severe psoriasis and who are 'biologic-experienced', as guselkumab is the only technology currently recommended for this population specifically. The criteria of increasing market share was endorsed by the committee in the appraisal of risankizumab in moderate-to-severe plaque psoriasis (TA596), which was informed by a cost-comparison analysis.[4] Therefore, guselkumab represents the most relevant comparator used in clinical practice in this population which should form the basis for decision making.
- Guselkumab is an IL-23 inhibitor and shares a therapeutic class with risankizumab

A 10-year time horizon was adopted in the analysis, with a shorter 5-year time horizon tested in scenario analyses. A 10-year time horizon was adopted to align with ERG and Committee preferences in previous appraisals that employed cost-comparison analyses (TA596, TA521 and TA723) in moderate-to-severe plaque psoriasis (in the absence of cost-comparison precedence in PsA).[4, 11, 12] A 4-week cycle length was applied in the model to accurately capture the dosing schedule of each therapy. Costs were not discounted in the base case analysis in line with the user guide for cost-comparison for fast track appraisal.[3]

Figure 28: Model structure diagram

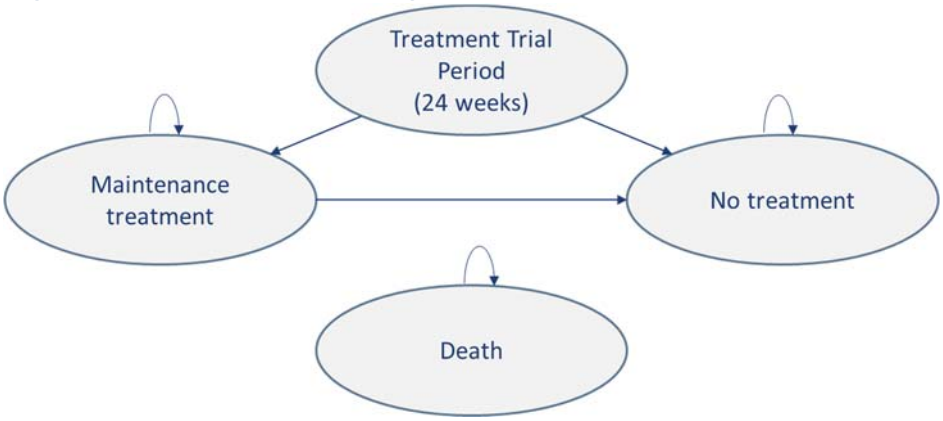


Figure 28 outlines the model structure. All patients are assumed to begin in the Treatment Trial Period, with 100% of patients assumed to receive therapy in this period with no discontinuation of treatment. Response at Week 24 is considered to be the primary analysis, as both the KEEPsAKE-2 and DISCOVER-1 trials included response at Week 24 as the primary outcome. Furthermore, for guselkumab, the period of initial treatment before assessment of response is 24 weeks, in line with the SPCs. Patients who have not responded adequately to treatment at 24 weeks are assumed to stop therapy immediately and transition to the No Treatment state in the model. A Week 16 timepoint for assessing response is also recommended for risankizumab in the SmPC; a scenario analysis is therefore presented in B.4.4 whereby response is assessed at 16 weeks.

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. A result versus guselkumab for the PsARC outcome was not available in the biologic-experienced NMA, presented in Section B.3.8.1, due to the lack of published data for guselkumab for this outcome. The NMA does, however, demonstrate [redacted] between risankizumab and guselkumab across the other outcomes included. In TA711, the probability of PsARC response for guselkumab was 0.6630 (from the unadjusted fixed-effects model) which is in line with the probability of [redacted] for risankizumab based on the NMA (from the fixed-effects model).[2] Therefore, in this cost-comparison model, patients were assumed to have the same probability of responding to treatment at 24 weeks for both therapies ([redacted]).

Patients who have responded adequately to treatment receive subsequent maintenance therapy. Patients treated with risankizumab are assumed to receive 150 mg in Week 0, Week 4, and every 12 weeks thereafter, whereas patients treated with guselkumab receive 100 mg in Week 0, Week 4, and thereafter every 8 weeks, in line with the summary of product characteristics.[2, 16, 76] Both are administered as subcutaneous injections. Guselkumab is also licenced with a dosing schedule of every 4 weeks only for patients at high risk for joint damage according to clinical judgement. In TA711, the ERG and committee concluded that the Q8W and Q4W dosing have the same treatment effect.[2] Therefore, a comparison against only the Q8W dosing schedule is a conservative approach that potentially underestimates the costs for guselkumab in clinical practice, as a proportion of patients treated in the UK will be receiving the Q4W dosing schedule that is associated with higher costs.

Patients who discontinue treatment upon assessment of response are assumed to incur no further cost within the model. In practice, upon failure of biological therapy with risankizumab or guselkumab, patients will likely receive an alternative treatment. However, 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. Therefore, we have excluded any further costs associated with subsequent treatment from the base case cost-comparison. Patients who continue biological treatment with risankizumab or guselkumab have a probability of discontinuing treatment each week. In the base case, the probability of discontinuing treatment is set at an annual probability of 16.5%. This figure was informed by Rodgers *et al.* (2011)[77], and has been used in prior appraisals in this disease area (TA445, TA340, TA220, TA433 and TA537; see Section B.2.1).[8, 9, 41, 70, 71] An annual probability of 16.5% discontinuation equates to a 4-weekly probability of discontinuing treatment of 1.37%. In the absence of an alternative input for discontinuation rates in PsA and in order to investigate the sensitivity of the model to this input, scenario analysis have been conducted using an alternative discontinuation rate applied a prior psoriasas appraisal (TA511; see Section B.4.4).[102]

The model also accounted for mortality, based on UK life tables.[2] The model does not include excess mortality associated with PsA. Prior appraisals using cost-utility analysis have included a standarised mortality rate for PsA of 1.05, however 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.[4, 11, 12] This assumption is expected to have minimal impact on the results, and has been validated by clinicians.

B.4.2.2 Intervention and comparators' acquisition costs

Table 18 presents a summary of the acquisition costs included for risankizumab and guselkumab. Table 18: Acquisition costs of the intervention and comparator technologies

	Risankizumab	Guselkumab
Pharmaceutical formulation	Risankizumab is available as 150 mg/1 ml solution for injection in a pre-filled pen or syringe[22]	100 mg solution for subcutaneous injection in a pre-filled syringe (1mL).
(Anticipated) care setting	Primary care	
Acquisition cost (excluding VAT) *	List price of £3,326.09 per 150 mg dose[22] PAS price of [redacted] per 150 mg dose	List price of £2,250.00 per 100 mg dose[103]
Method of administration	Subcutaneous injection	
Doses	150 mg dose per administration	100 mg dose per injection
Dosing frequency	Risankizumab is administered in Week 0, Week 4, and every 12 weeks[16]	Guselkumab is administered in Week 0, Week 4, and thereafter every 8 weeks[76]
Dose adjustments	N/A	N/A
Average length of a course of treatment	The model estimates an average time on treatment of [redacted] years over a 10-year time horizon for both risankizumab and guselkumab	
Average cost of a course of treatment (acquisition costs only)	[redacted] (list price), based on the average length of a course of treatment reported above	[redacted] (list price), based on the average length of a course of treatment reported above
(Anticipated) average interval between courses of treatment	N/A – continuous treatment	
(Anticipated) number of repeat courses of treatment	N/A	

Abbreviations: N/A: not applicable; VAT: Value-added tax.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Risankizumab and guselkumab are administered via subcutaneous injection. Patients may self-inject after training if deemed appropriate by a physician. AbbVie funds a homecare service to facilitate these administrations, so no administration costs were included in the analysis. It is understood that administration of guselkumab will follow similar scenario, with homecare service provided by the manufacturer; therefore no administration cost was applied in the comparator arm. This approach has been validated by UK clinical experts. Scenario analysis is presented assuming that a cost of £42 is applied for each administration of treatment, where treatment is administered by a professional in the treatment trial period only.[104]

Risankizumab and guselkumab require monitoring in the form of rheumatologist visits, full blood counts and other healthcare resource use. No monitoring costs were included in the analysis due to the similarity in healthcare resource use between the two treatments, confirmed by clinical experts; however a scenario analysis including monitoring costs was carried out, assuming the healthcare resource use and costs presented in Table 19. Healthcare resource differs between the treatment trial period and the maintenance treatment period. Concomitant medication use was assumed to be equal between risankizumab and guselkumab and therefore was not included in the model. This assumption was confirmed by clinical experts.

Table 19: Monitoring costs for the intervention and comparator technologies

Monitoring required	Monitoring frequency		Unit Cost	Source
	Contacts for trial period	Maintenance contacts per year		
Rheumatologist visit	2	2	£149.14	NHS Reference Cost 2019-2020, WF01A (410) (Rheumatology) [105]
Full blood count	2	2	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology) [105]
Liver function test	2	2	£1.20	NHS Reference Cost 2019-2020, DAPS04 (Clinical biochemistry)[105]
Urea & electrolyte	2	2	£1.20	NHS Reference Cost 2019-2020, DAPS04 (Clinical biochemistry)[105]
ESR	2	2	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology) [105]
Chest X-ray	1	0	£32.73	NHS Reference Cost 2019-2020, DAPF (Direct Access Plain Film) [105]
TB Heaf Test	1	0	£10.59	Rodgers et al. (2011); inflation-adjusted price[77]
ANA test	1	0	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology) [105]
ds DNA Test	1	0	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology) [105]

Abbreviations: ANA: antinuclear antibody; ds DNA: double stranded DNA; ESR: erythrocyte sedimentation rate; TB: tuberculosis
Sources: Monitoring frequencies were in line with estimates from the previous NICE submission for guselkumab in PsA (TA711) Unit costs (excluding TB heaf testing) were informed by NHS reference costs 2019–2020.[105] Unit cost for TB Heaf Test was unformed by data from Rodgers et al. (2011), inflation-adjusted to 2019/2020 prices.[77]

B.4.2.4 Adverse reaction unit costs and resource use

As reported in Section B.3.8.1, results of the NMA analyses for AEs indicated that the incidence of AEs associated with the use of risankizumab and guselkumab are similar. Therefore, as in NICE submissions for risankizumab and guselkumab in psoriasis (TA596 and TA521),[4, 11] it is assumed that the costs associated with treating AEs would be similar for both therapies, and any difference would be negligible, thus, AE costs were omitted from the analysis. This assumption was validated by clinicians.

B.4.2.5 Miscellaneous unit costs and resource use

No other costs have been included in the model.

B.4.2.6 Clinical expert validation

The model method was designed to align with NICE's preferred methods. All of the parameters and assumptions applied in the cost-comparison model were validated by clinicians. Quality-control procedures were undertaken to ensure the programming and physical implementation of the conceptual model was completed correctly. Once the model was finalised, it was validated by internal modellers. A programmer (different to the programmer who built the model) reviewed all formulae and labelling in the model, to ensure accuracy.

B.4.2.7 Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis are summarised in Table 20 and all of the key assumptions are presented in Table 21.

Table 20: Summary of model inputs

Input	Parameter value	Source
Time horizon (years)	10	NICE TA521[11]
Discount rate	0%	NICE FTA Guidelines[3]
Average age (years)	53	KEEPsAKE-2[14]
Percent female	55.1	KEEPsAKE-2[14]
Time until response assessment (weeks)	24	KEEPsAKE-2[14]
Discontinuation rate (annual)	16.5%	Rodgers et al. (2011)[77], in line with prior appraisals conducted in PsA (TA445, TA340, TA220, TA433 and TA537)
Efficacy (risankizumab and guselkumab)		

Input	Parameter value	Source
PsARC	[redacted]	Risankizumab PsARC outcome from network meta-analysis (NMA)
Costs		
List price: Cost per pack (risankizumab)	£3,326.09	BNF[22]
PAS price: Cost per pack (risankizumab)	[redacted]	-
List price: Cost per pack (guselkumab)	£2,250.00	BNF[103]
Cost per treatment administration, where treatment is administered by a professional	£42	Curtis et al. (2020)[104]
Unit cost per rheumatologist visit	£149.14	NHS Reference Cost 2019-2020, WF01A (410) (Rheumatology)[105]
Unit cost per full blood count	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology)[105]
Unit cost per liver function test	£1.20	NHS Reference Cost 2019-2020, DAPS04 (Clinical biochemistry)[105]
Unit cost per urea & electrolyte	£1.20	NHS Reference Cost 2019-2020, DAPS04 (Clinical biochemistry)[105]
Unit cost per ESR	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology)[105]
Unit cost per chest X-Ray	£32.73	NHS Reference Cost 2019-2020, DAPF (Direct Access Plain Film)[105]
Unit cost per TB Heaf Test	£10.59	Rodgers et al. (2011); inflation-adjusted price[77]
Unit cost per ANA Test	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology)[105]
Unit cost per ds DNA Test	£2.53	NHS Reference Cost 2019-2020, DAPS05 (Haematology)[105]
Healthcare Resource Use		
Administrations (treatment trial period)	3	SmPC for risankizuamb[16] SmPC for guselkumab[76]
Rheumatologist Visit (treatment trial period)	2.00	NICE submission for guselkumab in PsA (TA711)[2]
Full blood count (treatment trial period)	2.00	
Liver function test (treatment trial period)	2.00	
Urea & Electrolyte (treatment trial period)	2.00	
ESR (treatment trial period)	2.00	
Chest X-Ray (treatment trial period)	1.00	
TB Heaf Test (treatment trial period)	1.00	
ANA Test (treatment trial period)	1.00	
ds DNA Test (treatment trial period)	1.00	
Rheumatologist Visit (maintenance period, contacts per year)	2.00	

Input	Parameter value	Source
Full blood count (maintenance period, contacts per year)	2.00	
Liver function test (maintenance period, contacts per year)	2.00	
Urea & Electrolyte (maintenance period, contacts per year)	2.00	
ESR (maintenance period, contacts per year)	2.00	
Chest X-Ray (maintenance period, contacts per year)	0.00	
TB Heaf Test (maintenance period, contacts per year)	0.00	
ANA Test (maintenance period, contacts per year)	0.00	
ds DNA Test (maintenance period, contacts per year)	0.00	

Abbreviations: ANA: antinuclear antibody; ds DNA: double strand DNA; ESR: erythrocyte sedimentation rate; FTA: fast track appraisal; NMA: network meta-analysis; PsA: psoriatic arthritis; PsARC: Psoriatic Arthritis Response Criteria; SmPC: summary of product characteristics; TB: tuberculosis.

Table 21: Key assumptions of the analysis

Assumption	Rationale for assumption	Relevant sensitivity analysis
Patients are assumed to remain on initial biological treatment until assessment of response.	This assumption is aligned with published NICE technology appraisals for moderate-to-severe plaque psoriasis (TA199, TA445, TA340, TA220, TA433, TA543, TA537 and TA711)[2, 8, 10, 41, 69, 71]	-
Response to treatment with risankizumab and guselkumab is assessed at 24 weeks.	Based on the SmPCs for both interventions, treatment should be stopped in people whose psoriasis has not responded adequately by 24 weeks after starting treatment.	A scenario analysis has been undertaken, whereby response is assessed at 16 weeks
The probability of responding to treatment is identical for risankizumab and guselkumab.	Given the results of the NMA, risankizumab is associated with a similar relative efficacy compared with guselkumab.	-
The annual probability of discontinuation after the initial assessment of response is 16.5% for each treatment.	This value is sourced from Rodgers *et al.* (2011),[77] in line with prior appraisals conducted in PsA (TA445, TA340, TA220, TA433 and TA537)	A sensitivity analysis was carried out in which discontinuation data from alternative sources were explored.
Adverse events are equivalent between risankizumab and guselkumab.	NMA data for adverse events indicate that adverse event incidence is similar in patients	-

Assumption	Rationale for assumption	Relevant sensitivity analysis
	treated with risankizumab or guselkumab, therefore AE costs were omitted from the analysis	
Monitoring and administration costs are equivalent between risankizumab and guselkumab.	Given the results of the NMA, for safety and efficacy, and the equivalent treatment trial period, the healthcare resource use for treatment administration and monitoring patients is expected to be similar with risankizumab or guselkumab.	A scenario analysis was carried out in which administration and monitoring costs are included.
Vial wastage is not considered within the analysis.	Risankizumab and guselkumab are available in sizes that are appropriate for administration. Consequently, vial sharing is not possible, and estimates of vial wastage are not necessary.	-

Abbreviations: NICE: National Institute for Health and Care Excellence; NMA, network meta-analysis; PsA: psoriatic arthritis; TA: technology appraisal.

B.4.3 Base-case results

Table 22 and Table 23 presents the base case results for a 10-year time horizon with risankizumab at list price and PAS price, respectively.

Table 22: Base case results for a 10-year time horizon at list price

Technologies	Acquisition costs	Administration costs	Monitoring costs	Total costs
Risankizumab	£46,646	N/A	N/A	£46,646
Guselkumab	£45,733	N/A	N/A	£45,733
Difference	£914	N/A	N/A	£914

Table 23: Base case results for a 10-year time horizon at risankizumab PAS price

Technologies	Acquisition costs	Administration costs	Monitoring costs	Total costs
Risankizumab	[redacted]	N/A	N/A	[redacted]
Guselkumab	[redacted]	N/A	N/A	[redacted]
Difference	[redacted]	N/A	N/A	[redacted]

B.4.4 Sensitivity and scenario analyses

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model results to individual inputs, holding all else constant. The lower and upper bounds for the PsARC

response rates were set based on the credible intervals estimated from the NMA, with confidence intervals being used for other parameters where available. However, when such information was not available, the upper and lower bounds were assumed to be within ± 20% of the base case value. For discounting a value of 3.5% was utilised as the upper bound. Figure 29 presents a tornado diagram with parameters shown in descending order of cost difference sensitivity. These results demonstrate that the model is relatively insensitive to the majority of parameters, with the analysis being most sensitive to the PsARC response, discontinuation rate and discount rate. Table 24 and Table 25 present the scenarios explored in the analysis and their results; in particular, the inclusion of administration and monitoring costs leads to little change in the overall cost for either risankizumab or guselkumab. This suggests that the omission of administration and monitoring costs from inclusion in the model is justified.

Figure 29: Results of the one-way sensitivity analysis

Abbreviations: PsA: psoriatic arthritis; PsARC: Psoriatic arthritis Response Criteria

Table 24: Scenario analysis results (risankizumab and guselkumab at list price)

Model assumption	Scenario	Overall cost for risankizumab	Overall cost for guselkumab	Difference in cost
Base case		**£46,646**	**£45,733**	**£914**
Time horizon	5 years	£35,231.32	£34,444.00	£787
Treatment discontinuation	Based on value used in TA511[102]	£43,522.55	£42,599.07	£923
Mortality	Exclude mortality	£47,277.04	£46,364.22	£913
Administration costs	Include drug administration costs	£46,772.33	£45,858.66	£914
Monitoring costs	Include monitoring costs	£48,426.84	£47,513.17	£914

PsARC response rate and assessment time	Based on Week 16 PsARC response rate from NMA ([redacted]) and assessment at 16 weeks	£30,995.16	£28,537.85	£2,457
PsARC response rate	Based on value used in TA711 (0.6630)[2]	£53,391.56	£52,489.95	£902

Table 25: Scenario analysis results (risankizumab PAS price and guselkumab at list price)

Model assumption	Scenario	Overall cost for risankizumab	Overall cost for guselkumab	Difference in cost
Base case		[redacted]	[redacted]	[redacted]
Time horizon	5 years	[redacted]	[redacted]	[redacted]
Treatment discontinuation	Based on value used in TA511[102]	[redacted]	[redacted]	[redacted]
Mortality	Exclude mortality	[redacted]	[redacted]	[redacted]
Administration costs	Include drug administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	Include monitoring costs	[redacted]	[redacted]	[redacted]
PsARC response rate and assessment time	Based on Week 16 PsARC response rate from NMA ([redacted]) and assessment at 16 weeks	[redacted]	[redacted]	[redacted]
PsARC response rate	Based on value used in TA711 (0.6630)[2]	[redacted]	[redacted]	[redacted]

B.4.5 Subgroup analysis

No subgroup analyses were conducted.

B.4.6 Interpretation and conclusions of economic evidence

The cost-comparison analysis demonstrates that, when equivalent clinical effectiveness is assumed, risankizumab is cost-neutral when compared to guselkumab. As outlined in Section B.1.1, guselkumab was selected as the comparator for the cost-comparison analysis, because risankizumab is being positioned in the same restricted sub-population that guselkumab was recommended by NICE in TA711 (biologic-experienced PsA patients with concomitant moderate-to-severe psoriasis). Other biological therapies are recommended in broader populations.[2] Furthermore, guselkumab is one of the most recent biologic therapies for PsA to enter the UK market with published technology appraisal guidance, and is expected to have an increasing market share in the UK, in line with the market share for guselkumab in PsA in countries where guselkumab launched earlier than the UK.[5] Furthermore, guselkumab is an IL-23 inhibitor and shares therauptic

class with risankizumab. Guselkumab therefore represents the most relevant comparator used in clinical practice in this restricted population, which should form the basis for decision making. In the analysis, only relevant costs, those associated with drug acquisition, were included. Risankizumab was not associated with any additional resource use as detailed above and, in line with previous cost-comparison analyses submitted as part of the NICE appraisals for risankizumab and guselkumab in moderate-to-severe plaque psoriasis, treatment sequencing was excluded.[4, 11] A series of sensitivity and scenario analyses all confirmed the base case analysis of risankizumab as a cost-neutral option.

Risankizumab offers a well-tolerated and efficacious alternative to guselkumab in patients with PsA . These patients have often experienced multiple treatment discontinuations due to AEs or lack/loss of treatment effectiveness over time. Risankizumab has demonstrated dual improvement in both joint and skin symptoms in this patient population (see Section B.3.5), which is critically important for combatting the compounding functional and psychological burdens of PsA.[51] The results of the NMA and MAIC (Section B.3.8.1 and Appendix D) suggest that risankizumab has comparable clinical efficacy and tolerability compared to guselkumab. Moreover, risankizumab is associated with a more convenient maintenance dosing schedule than guselkumab, with a 12 weekly maintenance dosing regimen (i.e. just four injections per year). The results of the cost-comparison analysis demonstrate that risankizumab would provide PsA patients with a valuable new treatment option, whilst offering budget neutrality to the NHS.

References

1. European Medicines Agency (EMA). Human Medicine European Public Assessment Report: Skyrizi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi. [Last accessed: 01/11/2021]. 2019.
2. National Institute for Health and Care Excellence (NICE). TA711: Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta711 [Last accessed: 31/01/2022], 2021.
3. National Institute for Health and Care Excellence (NICE). User guide for company evidence submission template: Fast track appraisal cost-comparison case. Available from: https://www.nice.org.uk/process/pmg32/resources/user-guide-for-the-cost-comparison-company-evidence-submission-template-pdf-72286772526277. [Last accessed: 12/11/2021], 2017.
4. National Institute for Health and Care Excellence (NICE). TA596: Risankizumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta596. [Last accessed: 10/11/2021], 2019.
5. AbbVie. Data on File: PsA and Psoriasis Market Development - Germany 2021.
6. Lee YH, Song GG. Overall and sex-specific mortality in psoriatic arthritis and ankylosing spondylitis: a meta-analysis. Journal of Rheumatic Diseases 2018;25:197.
7. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700–712.
8. National Institute for Health and Care Excellence (NICE). TA445: Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta445 [Last accessed: 31/01/2022]. 2017.
9. National Institute for Health and Care Excellence (NICE). TA537: Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta537 [Last accessed: 31/01/2022]. 2018.
10. National Institute for Health and Care Excellence (NICE). TA543: Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta543 [Last accessed: 31/01/2022]. 2018.
11. National Institute for Health and Care Excellence (NICE). TA521: Guselkumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta521 [Last accessed: 31/01/2022], 2018.
12. National Institute for Health and Care Excellence (NICE). TA723: Bimekizumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta723 [Last accessed: 12/01/2022]. 2021.
13. National Institute for Health and Care Excellence (NICE). Final scope for the appraisal of risankizumab for previously treated active psoriatic arthritis. Available from: https://www.nice.org.uk/guidance/gid-ta10819/documents/final-scope [Last accessed: 11/01/2021]. 2021.
14. AbbVie. Data on File: Clinical Study Report (CSR) for KEEPsAKE-1.
15. AbbVie. Data on File: Clinical Study Report (CSR) for KEEPsAKE-2.
16. Electronic Medicines Compendium (EMC). Risankizumab (Skyrizi) summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/12625/smpc. [Last accessed: 03/02/2022], 2022.
17. Fitch E, Harper E, Skorcheva I, et al. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. Curr Rheumatol Rep 2007;9:461-7.
18. Schurich A, Raine C, Morris V, et al. The role of IL-12/23 in T cell-related chronic inflammation: implications of immunodeficiency and therapeutic blockade. Rheumatology (Oxford) 2018;57:246-254.
19. AbbVie. AbbVie Submits Regulatory Applications for SKYRIZI® (risankizumab) in Psoriatic Arthritis to FDA and EMA. Available at: https://news.abbvie.com/news/press-releases/abbvie-

submits-regulatory-applications-for-skyrizi-risankizumab-in-psoriatic-arthritis-to-fda-and-ema.htm [Accessed: 15/11/2021].
20. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) Positive Opinion for Skyrizi (risankizumab). Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/skyrizi-0. [Last accessed: 01/11/2021]. 2021.
21. AbbVie. AbbVie's SKYRIZI® Receives MHRA Approval For Use In Adults with Active Psoriatic Arthritis. Available from: https://news.cision.com/abbvie/r/abbvie-s-skyrizi-----risankizumab--receives-mhra-approval-for-use-in-adults-with-active-psoriatic-ar,c3459136. [Last accessed: 01/12/2021], 2021.
22. British National Formulary (BNF). Risankizumab Medicinal Forms. Available from: https://bnf.nice.org.uk/medicinal-forms/risankizumab.html. [Last accessed: 03/11/2021], 2020.
23. Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med (Lond) 2017;17:65–70.
24. Tintle SJ, Gottlieb AB. Psoriatic arthritis for the dermatologist. Dermatologic clinics 2015;33:127–148.
25. McGonagle D, Tan AL, Watad A, et al. Pathophysiology, assessment and treatment of psoriatic dactylitis. Nature Reviews Rheumatology 2019;15:113–122.
26. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957–970.
27. Coates LC, FitzGerald O, Helliwell PS, et al. Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same? Seminars in Arthritis and Rheumatism 2016;46:291-304.
28. Office for National Statistics. Population estimates (UK, mid-year 2020). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates [accessed: 10/11/2021].
29. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. Rheumatology (Oxford) 2013;52:568–575.
30. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. Rheumatology and therapy 2016;3:91–102.
31. Haroon M, FitzGerald O. Psoriatic arthritis: complexities, comorbidities and implications for the clinic. Expert Review of Clinical Immunology 2016;12:405–416.
32. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. Curr Opin Rheumatol 2015;27:118–126.
33. Shah K, Paris M, Mellars L, et al. Real-world burden of comorbidities in US patients with psoriatic arthritis. RMD open. Volume 3, 2017:e000588.
34. Gudu T, Gossec L. Quality of life in psoriatic arthritis. Expert Review of Clinical Immunology 2018;14.
35. Husni ME, Fernandez A, Hauber B, et al. Comparison of US patient, rheumatologist, and dermatologist perceptions of psoriatic disease symptoms: results from the DISCONNECT study. Arthritis research & therapy. Volume 20, 2018:102.
36. Lebwohl MG, Kavanaugh A, Armstrong AW, et al. US perspectives in the management of psoriasis and psoriatic arthritis: patient and physician results from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. Am J Clin Dermatol 2016;17:87–97.
37. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. Am J Clin Dermatol 2014;70:871–881.e30.
38. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology 2020;59:i37–i46.
39. Glintborg B, Østergaard M, Krogh NS, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149–1155.

40. Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. Drugs 2014;74:423–441.
41. National Institute for Health and Care Excellence (NICE). TA340: Ustekinumab for treating active psoriatic arthritis. Available from https://www.nice.org.uk/guidance/ta340 [Last accessed: 31/01/2022] 2017.
42. Kerschbaumer A, Fenzl K, Erlacher L, et al. An overview of psoriatic arthritis – epidemiology, clinical features, pathophysiology and novel treatment targets. Wiener klinische Wochenschrift 2016;128.
43. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. The Lancet 2018;391:2273–2284.
44. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–2673.
45. Psoriatic Arthritis. How Is Psoriatic Arthritis Severity Determined? Available at https://psoriatic-arthritis.com/psa-basics/severity [accessed 10/11/2021]. 2016.
46. Littlewood S, MacPhie E. 247. Evaluation of a Psoriatic Arthritis Response Criteria Standardization Training Session for Clinicians. Rheumatology 2014;53:i152–i152.
47. Haddad A, Saliba W, Lavi I, et al. The association of psoriatic arthritis with all-cause mortality and leading causes of death in psoriatic arthritis. Available at: https://pubmed.ncbi.nlm.nih.gov/34266988/ [Last accessed: 31/01/2022]. J Rheumatol 2021.
48. Buckley C, Cavill C, Taylor G, et al. Mortality in psoriatic arthritis–a single-center study from the UK. The Journal of rheumatology 2010;37:2141–2144.
49. Ali Y, Tom BD, Schentag CT, et al. Improved survival in psoriatic arthritis with calendar time. Arthritis Rheum 2007;56:2708–2714.
50. Ogdie A, Maliha SG, Shin DB, et al. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology 2017;56:90W 911.
51. Husni ME, Merola JF, Davin S. The psychosocial burden of psoriatic arthritis. Semin Arthritis Rheum 2017;47:351–360.
52. Alten R, Strand V, Conaghan PG, et al. 2770: Psoriatic arthritis limits patients' abilities to undertake activities crucial for normal daily life and impacts happiness, results from a multinational real-world sample. Arthritis Rheumatol 2016;68 (suppl 10).
53. Merola JF, Shrom D, Eaton J, et al. Patient Perspective on the Burden of Skin and Joint Symptoms of Psoriatic Arthritis: Results of a Multi-National Patient Survey. Rheumatology and therapy 2019;6:33-45.
54. Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. Pharmacy and Therapeutics 2010;35:680–689.
55. Strand V, Sharp V, Koenig AS, et al. Comparison of health-related quality of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept treatment. Ann Rheum Dis 2012;71:1143-50.
56. Sumpton D, Kelly A, Tunnicliffe DJ, et al. Patients' Perspectives and Experience of Psoriasis and Psoriatic Arthritis: A Systematic Review and Thematic Synthesis of Qualitative Studies. Arthritis Care Res (Hoboken) 2020;72:711–722.
57. Kamalaraj N, El-Haddad C, Hay P, et al. Systematic review of depression and anxiety in psoriatic arthritis. International journal of rheumatic diseases 2019;22:967–973.
58. Cortesi PA, Scalone L, D'Angiolella L, et al. Systematic literature review on economic implications and pharmacoeconomic issues of psoriatic arthritis. Clin Exp Rheumatol 2012;30:S126–131.
59. Poole CD, Lebmeier M, Ara R, et al. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. Rheumatology 2010;49:1949–1956.
60. Tillett W, Shaddick G, Askari A, et al. Factors influencing work disability in psoriatic arthritis: first results from a large UK multicentre study. Rheumatology 2015;54:157–162.
61. Tillett W, Shaddick G, Jobling A, et al. Work disability after initiation of anti-TNF and DMARD treatment in psoriatic arthritis; investigator led, UK, multicentre observational cohort study (lopas II). Ann Rheum Dis 2015;2):64.

62. Conaghan PG AR, Strand V, Deodhar AA, Sullivan E, Blackburn S, Tian H, Gandhi K, Jugl S. The relationship between physical functioning and work for people with psoriatic arthritis: results from a large real-world study in 16 countries. Arthritis Rheumatol 2016;68 (suppl 10).
63. Coates LC, Soriano E, Corp N, et al. OP0229 The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations 2021. Ann of the Rheum Dis 2021;80:139–140.
64. Kavanaugh A, Coates LC, van der Windt DA, et al. GRAPPA Treatment Recommendations: Updates and Methods. The Journal of Rheumatology 2020;96:41–45.
65. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060–1071.
66. Elmamoun M, Fitzgerald O. Treatment of psoriatic arthritis. Handbook of Psoriasis and Psoriatic Arthritis 2016:85.
67. Coates LC, Tillett W, Chandler D, et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology 2013;52:1754–1757.
68. Warren R, Menter A. Handbook of Psoriasis and Psoriatic Arthritis. Springer, 2016.
69. National Institute for Health and Care Excellence (NICE). TA199: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Available from: https://www.nice.org.uk/Guidance/TA199 [Last accessed: 31/01/2022]. 2010.
70. National Institute for Health and Care Excellence (NICE). TA220: Golimumab for the treatment of psoriatic arthritis. Available from: https://www.nice.org.uk/Guidance/TA220 [Last accessed: 31/01/2022]. 2011.
71. National Institute for Health and Care Excellence (NICE). TA433: Apremilast for treating active psoriatic arthritis. Available from: https://www.nice.org.uk/guidance/ta433 [Last accessed: 31/01/2022]. 2017.
72. National Institute for Health and Care Excellence (NICE). TA768: Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta768 [Last accessed: 03/02/2022]. 2022.
73. National Institute for Health and Care Excellence (NICE). TA768: Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Availavle from: https://www.nice.org.uk/guidance/ta768 [Last accessed: 03/02/2022]. 2022.
74. Fraenkel L, Bathon JM, England BR, et al. American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2021;73:924–939.
75. van de Kerkhof PC, Reich K, Kavanaugh A, et al. Physician perspectives in the management of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. J Eur Acad Dermatol Venereol 2015;29:2002–2010.
76. Electronic Medicines Compendium (EMC). Guselkumab (Tremfya) summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/9587/smpc#AUTHDATE. [Last accessed: 03/02/2022], 2021.
77. Rodgers M, Epstein D, Bojke L, et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health technology assessment (Winchester, England) 2011;15:i–xxi, 1–329.
78. Deodhar A, Helliwell PS, Boehncke W-H, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. The Lancet 2020;395:1115–1125.
79. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. The Lancet 2020;395:1126–1136.
80. Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis 2021;Epub ahead of print.

81. Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis 2021:annrheumdis-2021-221019.
82. Östör A, Bosch FVd, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 52-week results from KEEPsAKE 2. Poster. Presented at the Fall Clinical Dermatology Conference (FC21), October 21–24, 2021., 2021.
83. Lidar M AJ, Tarr G, Papp K, Barcomb L, Soliman A, Lu W, Eldred A, Ostor A. Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 24-Week Results from the Phase 3, Randomized, Double-blind Clinical Trial for CsDMARD-IR and Bio-IR Patients [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). Available from: https://acrabstracts.org/abstract/efficacy-and-safety-of-risankizumab-for-active-psoriatic-arthritis-24-week-results-from-the-phase-3-randomized-double-blind-clinical-trial-for-csdmard-ir-and-bio-ir-patients/. [Accessed: 10/01/2022]. 2021.
84. ClinicalTrials.gov. NCT02719171. BI 655066/ABBV-066/Risankizumab Compared to Placebo in Patients With Active Psoriatic Arthritis 2016. Available at: https://clinicaltrials.gov/show/NCT02719171. Volume 2021.
85. ClinicalTrials.gov. A Study Comparing Risankizumab to Placebo in Participants With Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE-1). Available from: https://clinicaltrials.gov/ct2/show/NCT03675308 [Last accessed: 31/01/2022].
86. ClinicalTrials.gov. A Study Comparing Risankizumab to Placebo in Participants With Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(Ies) (KEEPsAKE-2). Available from: https://clinicaltrials.gov/ct2/show/NCT03671148 [Last accessed: 31/01/2022].
87. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template: Quality assessment of the relevant clinical effectiveness evidence. Available at: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-clinical-effectiveness-evidence. [accessed: 09/12/2021]. 2017.
88. Coates LC, Orbai A-M, Morita A, et al. Achieving minimal disease activity in psoriatic arthritis predicts meaningful improvements in patients' health-related quality of life and productivity. BMC Rheumatology 2018;2.
89. Wervers K, Luime JJ, Tchetverikov I, et al. Influence of disease manifestations on health-related quality of life in early psoriatic arthritis. The Journal of Rheumatology 2018;45:1526–1531.
90. Deodhar A, Gottlieb AB, Boehncke WH, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. The Lancet 2018;391:2213–2224.
91. Coates LC, Gossec L, Theander E, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIB, randomised, controlled study (COSMOS). Ann Rheum Dis 2021.
92. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. The Lancet 2017;389:2317–2327.
93. Coates LC, Gossec L, Theander E, et al. OP0230 Efficacy and saftey of guselkumab in patients with active PsA who demonstrated inadequate response to TNF inhibition: Week 24 results of a Phase IIIB, randomized, controlled study Annals of the Rheumatic Diseases 2021;80:140–141.
94. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2015;386:1137–1146.
95. Mease P, van der Heijde D, Landewe R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77:890–897.

96. Nash P, Mease PJ, McInnes IB, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther 2018;20:47.
97. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990–999.
98. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137–1146.
99. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Annals of the rheumatic diseases 2021;80:312–320.
100. Dias S, Welton N, Sutton A, et al. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD2-General-meta-analysis-corrected-15April2014.pdf [accessed: 27/04/2020]. 2011.
101. Dias S, Sutton A, Welton N, et al. NICE DSU technical support document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment. http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD3-Heterogeneity.final-report.08.05.12.pdf [accessed: 27/04/2020]. 2011.
102. National Institute for Health and Care Excellence (NICE). TA511: Brodalumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta511 [Last accessed: 03/02/2022], 2018.
103. British National Formulary (BNF). Guselkumab Medicinal Forms. Available from: https://bnf.nice.org.uk/medicinal-forms/guselkumab.html. [Last accessed: 03/11/2021], 2020.
104. Curtis LA, Burns A. Unit Costs of Health & Social Care 2020. Available at: https://www.pssru.ac.uk/pub/uc/uc2015/full.pdf: PSSRU, University of Kent, 2020.
105. NHS. National Schedule of Reference Costs: The Main Schedule, in NHS Reference Costs 2019–2020. Available at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ [last accessed 31/01/2022].

Appendices

Appendix I: Results from KEEPsAKE-1

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Clarification questions

March 2021

File name	Version	Contains confidential information	Date
ID1399_Risankizumab PsA_Company Response to Clarification Questions_ACIC	Final	Yes	17/03/2022

Section A: Clarification on effectiveness data

Decision problem and proposed positioning of risankizumab

A1. CS, Section B.1.1. Please clarify if the positioning intended by the company is for risankizumab alone, in combination with methotrexate or both (as per marketing authorisation for risankizumab in this indication approved by the EMA and MHRA.

The proposed positioning of risankizumab with respect to methotrexate is in line with the marketing authorisation for risankizumab in this indication approved by the EMA and MHRA. Risankizumab is indicated "alone or in combination with methotrexate, for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)".[1] Specifically, the submission focuses on a subgroup of the technology's marketing authorisation representing patients who are biologic-experienced, with skin symptoms. The proposed population is patients with active PsA who have previously received at least two conventional synthetic DMARDs (csDMARDs) and at least one biological DMARD (bDMARD) therapy and also have moderate-to-severe psoriasis.

A2. CS, Section B.1.3.3 Figure 4. Please clarify if the drugs in the "biologic experienced" population (left box) would be considered eligible treatment for "biologic experienced" and moderate-to-severe psoriasis patients.

The only relevant comparator for this appraisal, guselkumab, is the only technology recommended by NICE in the restricted subgroup of patients with PsA who are 'biologic-experienced' and have moderate-to-severe psoriasis (TA711), in which risankizumab is positioned for use.[3] Guselkumab, therefore, represents the most relevant comparator used in clinical practice in this specific population, with other bDMARDs (namely, certolizumab pegol, tofacitinib, ustekinumab, secukinumab and ixekizumab) recommended for broader patient populations that do not align to the positioning of risankizumab:

- Certolizumab pegol is recommended for treating active PsA in adults if their disease has stopped responding to a tumour necrosis factor (TNF)-alpha inhibitor after 12 weeks (TA445)[4]
- Secukinumab, tofacitinib and ixekizumab are recommended for treating active PsA in adults if their disease has not responded/stopped responding to a TNF-alpha inhibitor after 12 weeks, or if TNF-alpha inhibitors are contraindicated but would otherwise be considered (TA445, TA543, TA537)[5, 6]
- Ustekinumab is recommended for treating active PsA in adults if treatment with TNF-alpha inhibitors is contraindicated but would otherwise be considered, or the person has had treatment with 1 or more TNF-alpha inhibitors (TA340)[7]

Given these broader recommendations do not preclude use in 'biologic-experienced' patients with moderate-to-severe psoriasis, some patients in this restricted population may also be eligible for these alternative treatments. However, as specified in the NICE user guide for Fast Track Appraisal (FTA), an appropriate comparator can be selected in a cost-comparison if it fulfils the relevant criteria, as outlined in Section B.1.1 of Document B.

Importantly, guselkumab is one of the most recent technologies to be recommended by NICE for patients with PsA (June 2021); the cost-effectiveness of guselkumab has therefore been established by NICE when compared to all other treatments that could be considered established practice in this restricted population. The committee and ERG in TA711 also agreed that guselkumab appeared to be very similar in effectiveness to other interleukin inhibitors (secukinumab and ixekizumab).[3] Risankizumab provides similar health benefits at a similar or lower cost than guselkumab, which eliminates the need for comparisons to other treatments to be replicated in this appraisal and makes guselkumab the only relevant comparator.

In addition, given risankizumab and guselkumab share a similar mechanism of action, clinicians would likely consider them as equivalent treatment options. IL-23 inhibitors (risankizumab and guselkumab) are considered to be a preferred biologic treatment option for patients with moderate-to-severe psoriasis, compared with other treatments used in 'biologic-experienced' patients, due to superior improvement on skin symptoms. For example, risankizumab demonstrated superior efficacy versus the IL-17 inhibitor secukinumab in a head-to-head study in patients with moderate-to-severe psoriasis; at Week 52, 87% of patients treated with risankizumab achieved PASI 90 compared with 57% of patients treated with secukinumab (N=327, $p<0.001$).[8] Guselkumab and risankizumab are therefore likely to be preferentially considered in patients where managing the psoriasis component of the disease is important.

Guselkumab fulfils all of the criteria for the selection of an appropriate comparator in a cost-comparison, and thus is the most appropriate comparator for this appraisal. This is consistent with the selection of guselkumab as the only relevant comparator in appraisal of risankizumab in moderate-to-severe plaque psoriasis (TA596), which was informed by a cost-comparison analysis.[9]

Effectiveness data from the KEEPsAKE-2 trial

A3. CS, Section B.3.3.4. The CS states that non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19 for categorical efficacy endpoints in the KEEPsAKE-2. Please provide details of the multiple imputation method used. Please also provide details on the characteristics of the missing data such as the number and percentage of missing data in each treatment group for each of the endpoints analysed where multiple imputation was performed.

Non-responder imputation (NRI) incorporating multiple imputation (MI) was used to handle missing data due to COVID-19 (NRI-C) for binary variables as follows:[10]

- Missing data due to COVID-19 infection or logistical restriction related to COVID-19 pandemic were handled by MI.
- Patients who did not have evaluation during a specific visit window due to reasons other than COVID-19 infection or logistical restriction related to COVID-19 pandemic were handled by NRI for that visit. NRI considers a patient with missing evaluation as a non-responder with the exception for composite binary endpoints including ACR20, ACR50, ACR70, MDA and modified PsARC for which the missing components were imputed with last observation carry forward to derive composite score before imputing missing evaluations as a non-responder.
- Patients were considered as non-responders after initiation of rescue medication or initiation of concomitant medications for PsA that could meaningfully impact efficacy assessment; these medications were identified prior to database lock and unblinding.

For composite binary endpoints including ACR20, ACR50, ACR70, MDA and modified PsARC, the missing binary values due to COVID-19 infection or logistical restriction were imputed via MI with the logistic regression option. For other binary endpoints dichotomised from a continuous scale, the MI was applied to the original continuous scale and the dichotomised endpoint was derived from the imputed value for missing due to COVID-19 infection or logistical restriction.[10]

Full details of the imputation methods can be found in the Statistical Analysis Plan for KEEPsAKE-2, provided in the reference pack accompanying this response.

The numbers of patients in KEEPsAKE-2 with missing data and therefore imputed for clinical response data are presented in Table 1.

Table 1: Numbers of patients in KEEPsAKE-2 with missing data and therefore imputed for clinical response (FAS)

Endpoint	Risankizumab 150 mg		Placebo	
	N	n (%)	N	n (%)
ACR20 at Week 24	[redacted]	[redacted]	[redacted]	[redacted]
PASI90 at Week 24 (for patients with BSA >=3% at Baseline)	[redacted]	[redacted]	[redacted]	[redacted]
ACR20 at Week 16	[redacted]	[redacted]	[redacted]	[redacted]
MDA at Week 24	[redacted]	[redacted]	[redacted]	[redacted]

ACR50 at Week 24	[redacted]	[redacted]	[redacted]	[redacted]
ACR70 at Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Resolution of Enthesitis at Week 24 (for patients with Baseline LEI>0)	[redacted]	[redacted]	[redacted]	[redacted]
Resolution of Dactylitis at Week 24 (for patients with Baseline LDI>0)	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: N denotes total number of patients, n denotes number of patients with missing data.
Abbreviations: ACR: American college of Rheumatology; FAS: full analysis set; MDA: minimal disease activity; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index.

A4. PRIORITY. In the KEEPsAKE-2 trial BIO-IR subgroup, please provide for each of the treatment groups the number of patients (and the percentage) who:

A. have moderate-to-severe psoriasis (a body surface area of at least 3% affected by plaque psoriasis and a PASI score greater than 10) at baseline;
B. have had prior treatment with two csDMARD at baseline;
C. have moderate-to-severe psoriasis and have had prior treatment with 2 csDMARD at baseline; and
D. have moderate-to-severe psoriasis, have had at baseline prior treatment with 2 csDMARD, by type of concomitant medication (please include no concomitant treatment as one of the categories).

The number and proportion of patients in KEEPsAKE-2 with moderate-to-severe psoriasis, prior treatment with two csDMARDs, both, and by concomitant medication are presented in Table 2.

Table 2: Number of patients in KEEPsAKE-2 BIO-IR population

		BIO-IR (number of prior biologics ≥1)	
		Risankizumab 150 mg (N=105) n (%)	**Placebo (N=101) n (%)**
Moderate-to-severe psoriasis (BSA≥3% and PASI>10)		[redacted]	[redacted]
Prior treatment with two csDMARDs		[redacted]	[redacted]
Moderate-to-severe psoriasis (BSA≥3% and PASI>10) and prior treatment with two csDMARDs		[redacted]	[redacted]
With concomitant medication at baseline	MTX	[redacted]	[redacted]
	csDMARD other than MTX	[redacted]	[redacted]
	MTX and other csDMARD	[redacted]	[redacted]
	No concomitant treatment	[redacted]	[redacted]

Abbreviations: BIO-IR: biologic inadequate responder; BSA: Body Surface Area; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; MTX: Methotrexate; PASI: Psoriasis Area Severity Index.

A5. CS page 47. Please clarify if the FAS and SAS were identical as the numbers by arm suggest.

In KEEPsAKE-2, both the Full Analysis Set (FAS) and the Safety Analysis Set (SAS) included 443 patients (224 in the risankizumab arm; 219 in the placebo arm).[10]

A6. PRIORITY. CS Table 9 page 49. For the overall group and the BIO-IR and csDMARD-IR subgroups please provide the estimate of the relative effect together with associated 95% confidence intervals. Please also add the subgroup results for patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD.

Risk differences for the key clinical outcomes in KEEPsAKE-2 are reported in Table 3. Odds ratios or risk ratios between risankizumab and placebo are not available.

As per the response to Question A7, it is assumed that the relative efficacy of risankizumab versus guselkumab in the population of relevance to this appraisal (adult patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD) would be similar to the overall BIO-IR subgroup as a whole. This approach has been validated by clinical experts.

As highlighted in the response to Question A4, the number of patients in the overall group and the BIO-IR and csDMARD-IR subgroups with moderate-to-severe psoriasis, two prior csDMARD and one prior bDMARD are small ([redacted]% [n=[redacted]] and [redacted]% [n=[redacted]] in the risankizumab and placebo arms, respectively). Therefore estimates of relative effect in these groups have not been provided.

Table 3: Overview of KEEPsAKE-2 efficacy results (FAS, NRI-C)

Efficacy endpoint	Risk difference for risankizumab versus placebo		
	Overall population	BIO-IR	csDMARD-IR
Primary endpoint			
ACR20 at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]
Ranked secondary endpoints			
PASI 90 at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]
ACR20 at Week 16, % (95% CI)	[redacted]	[redacted]	[redacted]
MDA at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]
CFB in HAQ-DI score at Week 24, LS-Mean (95%CI)	[redacted]	[redacted]	[redacted]
CFB in SF-36 PCS score at Week 24, LS-Mean (95%CI)	[redacted]	[redacted]	[redacted]
CFB in FACIT-Fatigue score at Week 24, LS-Mean (95%CI)	[redacted]	[redacted]	[redacted]
Non-ranked secondary endpoints			
ACR50 at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]

ACR70 at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]
Resolution of enthesitis at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]
Resolution of dactylitis at Week 24, % (95% CI)	[redacted]	[redacted]	[redacted]

***, **, * p value ≤ 0.001, 0.01 and 0.05, respectively.
Abbreviations: ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CrI: credible interval; CfB: change from baseline; csDMARD-IR: conventional synthetic disease modifying anti-rheumatic drug – inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; FAS: full analysis set; HAQ-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; OR: odds ratio; PASI: psoriasis area severity index; SF-36 PCS: short form-36 physical component summary.

A7. PRIORITY. CS Figure 22 page 63 and Figure 27 page 68 show that a greater improvement compared with placebo was observed in the BIO-IR subgroup compared to the csDMARD-IR subgroup for ACT20 at Week 24. In CS appendix D.9.2., it was determined that BSA ≥3% and PASI are treatment effect modifiers and included in the MAIC. Please comment on the appropriateness of assuming the efficacy of risankizumab in the BIO-IR population is the same as in the specific subgroup relevant to this appraisal (adult patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD).

In the absence of data for the specific subgroup of relevance to this appraisal (adult patients with active PsA who have moderate-to-severe psoriasis and have had two csDMARDs and at least one bDMARD), it was assumed that the relative efficacy of risankizumab versus guselkumab in this restricted subgroup would be similar to the overall BIO-IR subgroup as a whole.

While BSA and PASI scores were identified as treatment effect modifiers, they are expected to have a similar impact on the efficacy of guselkumab and risankizumab, given these therapies share a therapeutic class. Furthermore, clinician expert opinion indicated there would not be a difference in treatment outcomes between risankizumab and guselkumab.

Finally, the assumption that efficacy in the BIO-IR population is generalisable to the specific subgroup relevant to this appraisal was accepted in TA711, where data for the biologic-experienced subgroup of DISCOVER-1 were used to inform the efficacy of guselkumab in the restricted subgroup for which it received a recommendation.[3]

A8. CS Appendix D page 120. The network meta-analysis (NMA) models were implemented in JAGS but "The scripts in the NICE Decision Support Unit Technical Support Document 2 and 3 were used and leveraged." Please clarify the ways in which the NMA coding differed from that in the DSU documents.

As JAGS and BUGS share syntax substantially, the BUGS codes from the Technical Support Document 2 and 3 were directly used in JAGS. The JAGS model scripts used for the NMAs are also provided in the input files in response to Question A9.

A9. PRIORITY. Please provide all relevant data used to perform the NMAs, sufficient to permit the ERG to check and/or reanalyse the NMAs, including:

A. All data files (in the format ready to be loaded in R) and the treatment coding (e.g., 1 for placebo, etc)
B. All BUGS "initial value" files
C. All CODA samples generated from the NMAs
D. Tables of all trial effectiveness data used in the NMAs

The ZIP file ("Week 24 NMA JAGS inputs and CODA_03.14.22.zip") contains items a-c for the Week 24 efficacy and safety NMAs. For each NMA, two RData files were prepared:

- An *input* file containing input data for JAGS, JAGS initial values, and JAGS code ("outcome"_24_input_"modeltype".RData)
- An *output* file for the run.jags output ("outcome"_24_output_"modeltype".RData)
    - Outcome = PsARC, PASI (PASI 50/75/90/100), HAQ (HAQ-DI change), HAQ_NRes (HAQ-DI change among PsARC non-responders), HAQ_Res (HAQ-DI change among PsARC responders), anyAE (any adverse events), anySAE (any serious adverse events)
    - Modeltype = FE (fixed-effects), RE (random-effects), FEPBO (fixed-effects with placebo response adjustment), REPBO (random-effects placebo response adjustment).

The trial effectiveness data used in the NMAs are provided in Table 4, Table 5, Table 6, Table 7 and Table 8.

Table 4: PsARC data of the included trials at Week 24 among the biologic-experienced patient population

Trial and Arm	Week 24		
	Total N	n	%
SPIRIT-P2, PBO	118	24	20.3
SPIRIT-P2, IXE 80 Q4W	122	68	55.7
KEEPsAKE 2, PBO	[redacted]	[redacted]	[redacted]
KEEPsAKE 2, RISA	[redacted]	[redacted]	[redacted]
NCT02719171, PBO	[redacted]	[redacted]	[redacted]
NCT02719171, RISA	[redacted]	[redacted]	[redacted]
PSUMMIT 2, PBO	62	16	25.8
PSUMMIT 2, UST 45	60	33	55.0
PSUMMIT 2, UST 90	58	27	46.6

Specification:
In the KEEPsAKE 2 trial, results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. The number of responders (n) is calculated based on the total number of patients and estimated response rate, rounding to the nearest integer. For the other trials, when the number of responder was not reported for a binary or ordinal endpoint, it was calculated using the sample size in conjunction with the response rate, rounded to the nearest integer.
Abbreviations: IXI: ixekizumab; PsARC: Psoriatic Arthritis Response Criteria; PSO: placebo; RISA: Risankizumab; Q4W: once every 4 weeks; UST: ustekinumab.

Table 5: PASI data of the included trials at Week 24 among the biologic-experienced patient population

Trial and Arm	Week 24								
	Total N	PASI 50		PASI 75		PASI 90		PASI 100	
		n	%	n	%	n	%	n	%
DISCOVER-1, PBO	26	NR	NR	2	7.7	2	7.7	0	0.0
DISCOVER-1, GUS Q8W	29	NR	NR	23	79.3	12	41.4	3	10.3
DISCOVER-1, GUS Q4W	28	NR	NR	22	78.6	15	53.6	10	35.7
COSMOS, PBO	53	NR	NR	5	9.4	4	7.5	2	3.8
COSMOS, GUS Q8W	133	NR	NR	79	59.4	68	51.1	41	30.8
SPIRIT-P2, PBO	67	NR	NR	10	14.9	8	11.9	3	4.5
SPIRIT-P2, IXE 80 Q4W	68	NR	NR	38	55.9	30	44.1	24	35.3
KEEPsAKE 2, PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.8	[redacted]	[redacted]
KEEPsAKE 2, RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53.4	[redacted]	[redacted]
NCT02719171, PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCT02719171, RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUTURE 2, PBO	12	NR	NR	1	8.3	1	8.3	NR	NR
FUTURE 2, SEC 150	22	NR	NR	8	36.4	5	22.7	NR	NR
FUTURE 2, SEC 300	11	NR	NR	7	63.6	4	36.4	NR	NR
PSUMMIT 2, PBO	50	NR	NR	1	2.0	NR	NR	NR	NR
PSUMMIT 2, UST 45	44	NR	NR	20	45.5	NR	NR	NR	NR
PSUMMIT 2, UST 90	41	NR	NR	20	48.8	NR	NR	NR	NR

Specifications:
In the KEEPsAKE 2 trial, results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. The number of responders (n) is calculated based on the total number of patients and estimated response rate, rounding to the nearest integer. For the other trials, when the number of responder was not reported for a binary or ordinal endpoint, it was calculated using the sample size in conjunction with the response rate, rounded to the nearest integer.
In the NCT02719171 trial, different data imputation rules were used for PASI 50/75 compared with PASI 90/100, which caused the sample sizes for PASI 50/75 to be potentially different from those for PASI 90/100. In the event that the sample sizes of PASI 50/75 differ from the sample sizes of PASI 90/100, only PASI 90/100 data were included in the NMA.
Abbreviations: GUS: guselkumab; IXI: ixekizumab; NMA: network meta-analysis; NR: not reported; PASI: Psoriasis Area Severity Index; PSO: placebo; RISA: Risankizumab; Q4W: once every 4 weeks; SEC: Secukinumab; UST: ustekinumab.
Source: Lidar et al. 2021[11]

Table 6: HAQ-DI change data of the included trials at Week 24 among the biologic-experienced patient population

Trial and Arm	Week 24	
	Mean	SE
COSMOS, PBO	-0.01	0.06
COSMOS, GUS Q8W	-0.18	0.05
SPIRIT-P2, PBO	-0.20	0.10
SPIRIT-P2, IXE 80 Q4W	-0.60	0.10
KEEPsAKE 2, PBO	0.04	[redacted]
KEEPsAKE 2, RISA	-0.19	[redacted]
NCT02719171, PBO	[redacted]	[redacted]
NCT02719171, RISA	[redacted]	[redacted]
FUTURE 2, PBO	-0.23	0.11
FUTURE 2, SEC 150	-0.35	0.08
FUTURE 2, SEC 300	-0.53	0.09
PSUMMIT 2, PBO	-0.03	0.04
PSUMMIT 2, UST 45	-0.17	0.08

Specifications:
The LOCF approach was used to impute missing HAQ-DI in the NCT02719171 trial. After imputation, 24-week data were available for [redacted] patients in the placebo arm and [redacted] patients in the risankizumab 150 mg arm.
In the absence of reported data for HAQ-DI change from baseline, the PsARC and HAQ-DI change conditional on PsARC data were used to calculate the HAQ-DI change from baseline.
Abbreviations: HAD-DI: health assessment questionnaire-disability index; IXI: ixekizumab; LOCF: last observed carried forward; PsARC: Psoriatic Arthritis Response Criteria; PSO: placebo; RISA: Risankizumab; Q4W: once every 4 weeks; SEC: Secukinumab; UST: ustekinumab.
Source: Lidar et al. 2021[11]

Table 7: HAQ-DI change conditional on PsARC response data of the included trials at Week 24 among the biologic-experienced patient population

Trial and Arm	Week 24			
	PsARC Responders		PsARC Non-Responders	
	Mean	SE	Mean	SE
KEEPsAKE 2, PBO	[redacted]	[redacted]	[redacted]	[redacted]
KEEPsAKE 2, RISA	[redacted]	[redacted]	[redacted]	[redacted]
NCT02719171, PBO	[redacted]	[redacted]	[redacted]	[redacted]
NCT02719171, RISA	[redacted]	[redacted]	[redacted]	[redacted]
PSUMMIT 2, PBO	-0.15	0.09	0.01	0.05
PSUMMIT 2, UST 45	-0.32	0.11	0.01	0.13

Specifications:
The LOCF approach was used to impute missing HAQ-DI in the NCT02719171 trial. After imputation, 24-week data were available for [redacted] patients in the placebo arm, [redacted] of whom was a PsARC responder, and [redacted] patients in the risankizumab 150 mg arm, [redacted] of whom were PsARC responders.
In the NCT02719171 trial, at week 24, there was only [redacted] patient in the placebo arm who achieved PsARC response, making it infeasible to estimate the standard error associated with the mean change in HAQ-DI among PsARC responders. Thus, the NCT02719171 trial was not included for the NMA for HAQ-DI change among PsARC responders at week 24 for the biologic-experienced population.
Abbreviations: HAD-DI: health assessment questionnaire-disability index; LOCF: last observed carried forward; NR: not reported; PSO: placebo; PsARC: Psoriatic Arthritis Response Criteria; RISA: Risankizumab; Q4W: once every 4 weeks; UST: ustekinumab.

Table 8: ACR data of the included trials at Week 24 among the biologic-experienced patient population

Trial and Arm	Week 24						
	Total N	ACR 20		ACR 50		ACR 70	
		n	%	n	%	n	%
Deodhar 2018, PBO	4	0	0.0	NR	NR	NR	NR
Deodhar 2018, GUS Q8W	9	6	66.7	NR	NR	NR	NR
DISCOVER-1, PBO	39	7	17.9	2	5.1	1	2.6
DISCOVER-1, GUS Q8W	41	23	56.1	11	26.8	1	2.4
DISCOVER-1, GUS Q4W	38	22	57.9	13	34.2	8	21.1
COSMOS, PBO	96	19	19.8	5	5.2	1	1.0
COSMOS, GUS Q8W	189	84	44.4	37	19.6	15	7.9
SPIRIT-P2, PBO	118	23	19.5	6	5.1	0	0.0
SPIRIT-P2, IXE 80 Q4W	122	65	53.3	43	35.2	27	22.1
KEEPsAKE 2, PBO	101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KEEPsAKE 2, RISA	105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCT02719171, PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCT02719171, RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FUTURE 2, PBO	35	5	14.3	3	8.6	0	0.0
FUTURE 2, SEC 150	37	11	29.7	7	18.9	4	10.8
FUTURE 2, SEC 300	33	15	45.5	9	27.3	5	15.2
FUTURE 3, PBO	44	4	9.1	1	2.3	NR	NR
FUTURE 3, SEC 150	44	15	34.1	3	6.8	NR	NR
FUTURE 3, SEC 300	44	18	40.9	9	20.5	NR	NR
FUTURE 5, PBO	98	18	18.4	9	9.2	5	5.1
FUTURE 5, SEC 150	65	28	43.1	17	26.2	10	15.4
FUTURE 5, SEC 300	68	36	52.9	24	35.3	16	23.5
FUTURE 5, SEC 150 without LD	64	20	31.3	15	23.4	10	15.6
PSUMMIT 2, PBO	62	9	14.5	4	6.5	1	1.6
PSUMMIT 2, UST 45	60	22	36.7	9	15.0	3	5.0
PSUMMIT 2, UST 90	58	20	34.5	9	15.5	3	5.2

Specification:
In the KEEPsAKE 2 trial, results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. The number of responders (n) is calculated based on the total number of patients and estimated response rate, rounding to the nearest integer. For the other trials, when the number of responder was not reported for a binary or ordinal endpoint, it was calculated using the sample size in conjunction with the response rate, rounded to the nearest integer.
Abbreviations: ACR: American college of Rheumatology; NR: not reported; PSO: placebo; PsARC: Psoriatic Arthritis Response Criteria; RISA: Risankizumab; Q4W: once every 4 weeks; Q8W: once every 8 weeks; SEC: Secukinumab; UST: ustekinumab.
Source: Lidar et al. 2021[11]

A10. Please comment on whether the definition of adverse events (AEs) and serious adverse events (SAEs) differed between the studies included in the NMA of AEs and

SAEs. If there were any differences on the definition please comment on how this may impact on the outputs of the corresponding NMA.

The trials included in the NMAs of adverse events (AEs) and serious adverse events (SAEs) used similar definitions for AEs and SAEs. Five trials used the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE),[12-16] and two trials used the Medical Dictionary for Regulatory Activities (MedDRA) to define AEs and AE grades.[17, 18] Of the trials which used the NCI-CTCAE, SPIRIT-P2 and Deodhar trials used Version 4.03, KEEPsAKE-2 trial used Version 5.0 and the version used was not reported in the DISCOVER-1 and COSMOS trials.[12-16] Of the trials which used the MedDRA, ASTRAEA used Version 14.1 and PSUMMIT-2 used Version 18.0.[17, 18]

Since NCI-CTCAE Version 4.0 (May 2009), all the terms used are themselves "lowest level terms" included in the MedDRA and no mapping would be required between NCI-CTCAE and MedDRA definitions. As such, the definitions for AEs and SAEs across trials included in the NMA are assumed to be interchangeable and would not impact the results of the corresponding NMA.[19]

A11. PRIORITY. CS Appendix Table 12 page 92 states that there were 42 patients from the risankizumab 150mg Q12W arm and 42 patients from the placebo arm from the NCT02719171 trial included in the NMAs. Please clarify if all of these patients were BIO-IR. If not, please provide the number of patients and the percentage who are BIO-IR.

Of the 42 patients in each treatment arm, [redacted] ([redacted]) patients from the risankizumab 150 mg arm (Weeks 0, 4 and 16) and [redacted] ([redacted]%) patients from the placebo arm of the NCT02719171 trial were biologic-experienced patients. The data for this biologic-experienced subgroup were used in the NMAs.

A12. PRIORITY. Please provide updated NMAs excluding the NCT02719171 trial if the population in this trial was not BIO-IR.

As per the response to Question A11, data for the biologic-experienced subgroup were used in the NMAs, and thus updated NMAs are not required.

A13. PRIORITY. No details of the NCT02719171 trial could be found in the CS. As this trial is included in the NMAs, please provide the details of this study. Please also explain why this trial was not included in the MAICs.

The KEEPsAKE-2 and DISCOVER-1 trials are the key trials in the NMA, influencing the effect estimates of risankizumab and guselkumab respectively in the biologic-experienced population. The MAIC therefore focused on these pivotal trials for both treatments.

A summary of the NCT02719171 trial is provided in Table 4 of the company submission, with further details provided in Appendix D.8.1. NCT02719171 was a 16-week dose selection study and was not designed as a pivotal trial. In addition, the sample size is small (number of patients for PASI endpoint: [redacted] [placebo] and [redacted] [risankizumab]; number of patients for ACR endpoint: [redacted] [placebo] and [redacted] [risankizumab]) with large imprecision of the estimates as consequence. Full

baseline characteristics for patients in NCT02719171 trial are presented in Table 9. Further details are available in the CSR included in the reference pack accompanying these responses.

Table 9: Baseline characteristics in NCT02719171

Baseline characteristics	Risankizumab 150 mg Weeks 0, 4, and 16 (Arm 2) (N=42)	Placebo (N=42)
Female, n (%)	[redacted]	[redacted]
Age (years), mean (SD)	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Black or African	[redacted]	[redacted]
Asian	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]
PsA duration (years), mean (SD)	[redacted]	[redacted]
Tender joint count, mean (SD)	[redacted]	[redacted]
Swollen joint count, mean (SD)	[redacted]	[redacted]
Presence of psoriasis affecting ≥3% BSA, n (%)	[redacted]	[redacted]
BSA (%), mean (SD)	[redacted]	[redacted]
PASI, mean (SD)	[redacted]	[redacted]
Prior csDMARDs, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥3	[redacted]	[redacted]
Any prior biologic, n (%)	[redacted]	[redacted]
Prior failed biologics, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
≥2	[redacted]	[redacted]
Prior TNF antagonist, n (%)	[redacted]	[redacted]
Concomitant medication at baseline, n (%)		
MTX	[redacted]	[redacted]

Abbreviations: BMI: body mass index; BSA: Body Surface Area; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; TNF: tumour necrosis factor.
Source: NCT02719171 Clinical Study Report.[20]

A14. CS, page 74. Text describing the modelling approach for the NMAs appears to be missing for bullet point "Adverse events (AE), serious AE and AE leading to treatment discontinuation". Please provide the description.

Adverse events (AE), serious AE and AE leading to treatment discontinuation follows a binomial distribution. Logistic regressions were used to model these outcomes. Fixed-effects models were

used due to the sparsity of the data, as the number of trials was insufficient for an accurate estimation of the cross-trial heterogeneities in a random-effects model. As the loops in the networks are contributed by multi-arm trials, no further assessment was conducted to compare direct vs. indirect treatment contrasts (i.e., assessing potential inconsistency).

A15. CS Table 11 page 75. The ACR results suggest a better response in risankizumab. Please clarify why the ORs of comparing risankizumab and guselkumab are less than one.

The ORs comparing risankizumab and guselkumab for ACR results have been reported incorrectly. The ORs provided in Table 11 are for the inverse comparison (i.e. guselkumab versus risankizumab). The results for ACR have been corrected in Table 10 below.

Table 10: Risankizumab 150 mg vs guselkumab 100 mg Q8W: ACR results from the biologic-experienced efficacy NMA (Week 24)

Endpoint[a]	Response rates % (95% CI)		OR (95% CrI) for risankizumab versus guselkumab[b]
	Risankizumab	Guselkumab	
ACR 20	[redacted]	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]	[redacted]
ACR 70	[redacted]	[redacted]	[redacted]

[a]Results presented vs guselkumab Q8W, given a dose of Q4W is only recommended for patients at high risk for joint damage according to clinical judgement. [b]A random-effects model was selected for ACR 20/50/70.
Abbreviations: ACR: American College of Rheumatology; CrI: credible interval; OR: odds ratio.

A16. CS Table 14 page 76. Risankizumab was associated with a lower SAE rate compared to guselkumab. Please clarify why the ORs of comparing risankizumab and guselkumab are greater than one.

The ORs comparing risankizumab and guselkumab for ACR results have been reported incorrectly. The ORs provided in Table 11 are for the inverse comparison (i.e. guselkumab versus risankizumab). The results for SAEs have been corrected in Table 11 below.

Table 11: Risankizumab 150 mg vs guselkumab 100 mg Q8W: SAE results from the safety NMA (Week 24)

Endpoint	Rate % (95 CI)		OR (95% CrI) for risankizumab versus guselkumab
	Risankizumab	Guselkumab	
SAE	[redacted]	[redacted]	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio; SAE: serious adverse event.

A17. PRIORITY. The new guidance for NICE's methods and processes[21] suggests that in cases where there are few included studies in networks, it may be preferable to use informative prior distributions for the between-study heterogeneity parameter.

Please provide an updated analysis for the random effects model using such informative priors.

The following informative prior distributions as discussed in Ren *et al.* (2018)[22] were applied to the random-effects NMAs of PsARC, PASI, HAQ-DI change, and HAQ-DI change conditional on PsARC response at Week 24. Specifically,

- For PsARC, the between-trial variance parameter was assumed a priori to follow lognormal (-2.56, 1.74^2) truncated at an upper bound of 0.345.
- For PASI, the between --trial variance parameter was assumed a priori to follow lognormal (-2.56, 1.74^2) truncated at an upper bound of 0.345, which was further divided by 1.81^2.
- For the two HAQ-DI outcomes, the between trial variance parameter was assumed a priori to follow lognormal (-2.56, 1.74^2) truncated at an upper bound of 0.345, which was further multiplied with the square of the average individual level standard deviation and divided by 1.81^2.

The truncation represents a weak prior belief that ratio of odds ratios would not exceed a maximum of R_{max} = 10 as in Ren *et al.* (2018).[22]

The results of these models are provided below,.

A summary of the results from the biologic-experienced NMA using informative priors for risankizumab and guselkumab at Week 24 are presented in Table 12 and Table 13, which had similar posterior medians but wider 95% credible intervals compared with the fixed-effects model. Results for all comparators are presented in Appendix A.

Table 12: Risankizumab 150 mg vs guselkumab 100 mg Q8W: Summary results from the biologic-experienced efficacy NMA at Week 24 (Informative Prior Random-effects)

Endpoint[a]	Response rates % (95% CI)		OR (95% CrI) for risankizumab versus guselkumab[b]
	Risankizumab	Guselkumab	
PsARC response	[redacted]	[redacted][c]	[redacted][c]
PASI 50	[redacted]	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]	[redacted]

[a]Results presented vs guselkumab Q8W, given a dose of Q4W is only recommended for patients at high risk for joint damage according to clinical judgement. [b]Fixed-effects model were selected for PsARC and PASI 50/75/90/100. A random-effects model was selected for ACR 20/50/70. [c]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; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area Severity Index.

Table 13: Risankizumab 150 mg vs guselkumab 100 mg Q8W: HAQ-DI Change from Baseline from the biologic-experienced efficacy NMA at Week 24 (Informative Prior Random-effects

Endpoint	Posterior Median (95% CrI)		Estimated Differences [Posterior Median (95% CrI)]
	Risankizumab	Guselkumab	

HAQ-DI CFB	[redacted]	[redacted]	[redacted]
HAQ-DI CFB among PsARC responders	[redacted]	[redacted]	[redacted]
HAQ-DI CFB among PsARC non-responders	[redacted]	[redacted]	[redacted]

Abbreviations: CFB: change from baseline; CrI: credible interval; HAQ-DI: health assessment questionnaire-disability index; NMA: Network Meta Analysis; PsARC: psoriatic arthritis response criteria.

A18. PRIORITY. Please provide the results of the probability of the point estimate within the interval where clinical equivalence could be claimed for each of the endpoints analysed using the CODA samples from the NMAs.

Additional analyses were conducted to estimate the probabilities of clinical equivalence for risankizumab relative to guselkumab Q8W in the NMAs for PASI and ACR. In these NMAs, input data were available for both risankizumab and guselkumab Q8W. A margin (M2) for clinical equivalence was defined in accordance with an approach for the non-inferiority trial design. Specifically, the contrast of guselkumab Q8W vs. placebo for PASI 75/90/100 and ACR 20/50/70 were obtained using a fixed-effects meta-analysis with (response rate) difference as the metric. The upper or lower bound of the 95% confidence interval (whichever was closer to the null) was taken as M1, which was a conservative estimate of the (response rate) difference. The reason for conducting a separate meta-analysis instead of directly using the NMA results to define M1 was to rule out the potential impact of data from other treatments on the estimation of the guselkumab Q8W vs. placebo contrast (particularly for the PASI and ACR outcomes). The margin for clinical equivalence (M2) was defined as a proportion of M1, representing the proportion of the guselkumab Q8W treatment effect observed in its clinical trials that is preserved.

Given the tight timelines for this analysis, AbbVie were unable to clinically validate an appropriate margin for clinical equivalence, which is a matter of clinical judgment. Therefore, to address the ERG's request, a number of exploratory analyses were conducted utilising margins of differing stringency. Two analyses are provided below, where M2 was defined as 50% or 20% of M1, representing a 50% or 20% preservation of the guselkumab Q8W treatment effect. Then based on the CODA samples, the probability of clinical equivalence for risankizumab and guselkumab Q8W (i.e., differing by at most M2) was estimated. The results are presented in Table 14.

The probability of clinical equivalence is lower for some outcomes (namely PASI 100, ACR 50 and ACR 70) because the results for guselkumab versus placebo for these outcomes had a very low level of statistical significance likely due to the low number of patients achieving these outcomes. This causes the M2 margin to be very stringent and therefore these results should be interpreted with caution. Furthermore, the results of the MAIC presented in the original company submission demonstrated there is heterogeneity in the baseline characteristics of the risankizumab and guselkumab trials which, if anything, may be biasing the results in favour of guselkumab in the NMA. Therefore, the estimates from the NMA for the comparison between risankizumab and guselkumab can be considered conservative.

Table 14: Probability of clinical equivalence for risankizumab vs. guselkumab Q8W at Week 24

Outcome	NMA model	50% preservation of the guselkumab Q8W treatment effect		20% preservation of the guselkumab Q8W treatment effect	
		M2	P(clinical equivalence)	M2	P(clinical equivalence)
PASI 75	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	Random effects with informative prior	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	Random effects with informative prior	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	Random effects with informative prior	[redacted]	[redacted]	[redacted]	[redacted]
ACR 20	Random-effects with placebo-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]
ACR 50	Random-effects with placebo-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]
ACR 70	Random-effects with placebo-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: PASI 50, PsARC and HAQ-DI change conditional on PsARC data, data were not reported in the guselkumab trials. Thus, the probabilities were not estimated for these outcomes.
Abbreviations: ACR, American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire - Disability Index; PASI: Psoriasis Area and Severity Index

A19. CS Appendix D Table 15 page 117. Please clarify what pD and 1/τ stand for.

pD stands for the effective number of parameters in the Bayesian NMA model, which was used in the calculation of DIC. 1/τ is the between-trial variance for the treatment effects in a random-effects model.

A20. PRIORITY. CS Appendix D Table 18 page 121. The text highlights that "there were significant differences in baseline age, disease duration, swollen joint counts, body surface area (BSA) affected, HAQ-DI, C-reactive protein (CRP, a marker of inflammation), DMARD use at baseline and PASI". The p-value for disease duration suggests that this is not a statistically significant difference. Please clarify if that is the case. For all these factors, please comment on which ones are considered to have differences that are clinically significant and considered treatment effect modifiers.

The inclusion of disease duration in the list of baseline characteristics with a significant difference between DISCOVER-1 and KEEPsAKE-2 was a typographical error. There were not significant differences in disease duration; the p-value of [redacted] reported in the table is correct.

According to UK clinical experts, differences in individual characteristics were deemed to be clinically significant between KEEPsAKE-2 and DISCOVER-1 (Table 15). UK clinical experts also noted that the variation across multiple characteristics can contribute combined effects, meaning that while individual differences may not be statistically significant, in combination there were clinically significant differences resulting in the risankizumab group being a harder to treat population. Based on a targeted literature review and in line with the approach used in Philippo *et al.* in 2020 in their worked example in plaque psoriasis,[23] a subset of these baseline characteristics were considered treatment effect modifiers and included in the MAIC. The remaining characteristics were considered to be prognostic in nature, rather than acting as treatment-effect modifiers.

In line with the NICE DSU guidance for population-adjusted indirect comparisons (TSD18), all identified treatment-effect modifiers (BMI, disease duration, BSA ≥3% and PASI) were adjusted for, whether imbalanced between KEEPsAKE-2 and DISCOVER-1 or not.[24] In addition, prognostic factors that are not considered treatment effect modifiers were not adjusted for in order to prevent over-matching.

A21. CS Appendix D.9.2. Table 18 page 121. Please add to the table the baseline covariates summaries after weighting using MAIC.

Baseline covariate summaries from KEEPsAKE-2 after weighting are provided in Table 16.

Table 15: Baseline covariate summaries for DISCOVER-1 and KEEPsAKE-2

Baseline covariate		DISCOVER-1[a] N=118	KEEPsAKE-2[a] N=206	p value	Clinically significant	Prognostic factor or treatment effect modifier[b]
Age (years), mean (standard deviation)		50.2 (10.5)	[redacted]	[redacted]	Yes	Prognostic
Sex	Male, n (%)	62 (52.5%)	[redacted]	[redacted]	No	NA
	Female, n (%)	56 (47.5%)	[redacted]			
BMI (kg/m^2),[b] mean (standard deviation)		29.9 (5.5)	[redacted]	[redacted]	Yes	Treatment effect modifier
PsA disease duration[b] (years) mean (standard deviation)		9.4 (6.9)	[redacted]	[redacted]	Yes	Treatment effect modifier
Joint counts, mean (SD)	Tender (0–68)	22.4 (15.3)	[redacted]	[redacted]	No	NA
	Swollen (0–66)	10.6 (8.7)	[redacted]	[redacted]	No	NA
BSA ≥3%[b], n (%)		90 (76.3%)	[redacted]	[redacted]	Yes	Treatment effect modifier
HAQ-DI score, mean (standard deviation)		1.40 (0.70)	[redacted]	[redacted]	No	NA
CRP mg/l, mean (standard deviation)		19.0 (23.0)	[redacted]	[redacted]	Yes	Prognostic
DMARD use at baseline, n (%)		87 (73.7%)	[redacted]	[redacted]	Yes	Prognostic
Methotrexate		78 (66.1%)	[redacted]	[redacted]		
Other		9 (7.6%)	[redacted]	[redacted]		
PASI[b] mean (standard deviation)		9.8 (11.2)	[redacted]	[redacted]	Yes	Treatment effect modifier

[a]the data for DISCOVER-1 and KEEPsAKE-2 has been pooled across both treatment arms. [b]Covariate considered a potential effect modifier and included in population adjustment
Abbreviations: BMI: Body mass index, BSA: Body surface area; CRP: C-reactive protein, DMARD: Disease-modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index, PsA: Psoriatic arthritis.
Sources: Ritchlin et al. (2021)[25] and NICE TA711[3]

Table 16: Bio-experienced – Baseline covariate summaries from the DISCOVER 1 and KEEPsAKE-2 trials

Baseline covariate	Before weighting			After weighting	
	DISCOVER-1 N=118	KEEPsAKE-2 N=206	p value	DISCOVER-1 N=118	KEEPsAKE-2 ESS=[redacted]
Age (years), mean (SD)	50.2 (10.5)	[redacted]	[redacted]	50.2 (10.5)	[redacted]
Sex					
Male, n (%)	62 (52.5%)	[redacted]	[redacted]	62 (52.5%)	[redacted]
Female, n (%)	56 (47.5%)	[redacted]		56 (47.5%)	[redacted]
BMI (kg/m^2),[a] mean (standard deviation)	29.9 (5.5)	[redacted]	[redacted]	29.9 (5.5)	[redacted]
PsA disease duration (years),[a] mean (standard deviation)	9.4 (6.9)	[redacted]	[redacted]	9.4 (6.9)	[redacted]
Joint counts, mean (SD)					
Tender (0–68)	22.4 (15.3)	[redacted]	[redacted]	22.4 (15.3)	[redacted]
Swollen (0–66)	10.6 (8.7)	[redacted]	[redacted]	10.6 (8.7)	[redacted]
BSA ≥3%,[a] n (%)	90 (76.3%)	[redacted]	[redacted]	90 (76.3%)	[redacted]
HAQ-DI score, mean (SD)	1.40 (0.70)	[redacted]	[redacted]	1.40 (0.70)	[redacted]
CRP mg/l, mean (SD)	19.0 (23.0)	[redacted]	[redacted]	19.0 (23.0)	[redacted]
DMARD use at baseline, n (%)	87 (73.7%)	[redacted]	[redacted]	87 (73.7%)	[redacted]
Methotrexate	78 (66.1%)	[redacted]	[redacted]	78 (66.1%)	[redacted]
Other	9 (7.6%)	[redacted]	[redacted]	9 (7.6%)	[redacted]
PASI,[a] mean (SD)	9.8 (11.2)	[redacted]	[redacted]	9.8 (11.2)	[redacted]

For DISCOVER 1, baseline covariate summaries of patients included in placebo arm (n=39), guselkumab Q8W arm (n=41) and Q4W arm (n=38) are showed
[a]Covariate considered a potential effect modifier, to be included in population adjustment.
Abbreviations: ACR: American college of Rheumatology; AE: adverse event; BMI: body mass index; BSA: body surface area; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; HAQ-DI: health assessment questionnaire-disability index; PASI: psoriasis area severity index; PsARC: Psoriatic arthritis Response Criteria; SD: standard deviation.

A22. CS Appendix D.9.2 page 122. The CS states that *"Individual patient data derived from the biologic-experienced subgroup in KEEPsAKE-2 for risankizumab and summary data from the biologic-experienced subgroup of DISCOVER-1 for guselkumab were used to carry out"* the unadjusted Bucher ITCs and anchored MAICs. However, Figure 27 of the CS appendix D with the network diagram for unadjusted Bucher ITC shows that KEEPsAKE-1, KEEPsAKE-2, DISCOVER-1 and DISCOVER-2 (COSMOS: safety outcomes only) were included in the Bucher ITC. Please clarify which studies were included in the Bucher ITCs and anchored MAICs.

The description of these analyses was misreported:

- The MAIC was conducted to compare risankizumab to guselkumab using only KEEPsAKE-2 and DISCOVER-1.
- The following trials were included in the Bucher ITC: DISCOVER-1; KEEPsAKE-2; and COSMOS (safety outcomes only).
- KEEPsAKE-1 and DISCOVER-2 were not included in the MAIC or Bucher ITC.

A23. CS Appendix D.9.2. page 126 states that Bucher ITCs were conducted for AE, SAE and AE leading to discontinuation, however, only the results for AE and SAE were presented in Table 96. Please provide the results for AE leading to discontinuation from the Bucher ITC.

The results from the Bucher ITC for AEs leading to discontinuation are provided in Table 17 below.

Table 17: Risankizumab 150 mg vs guselkumab 100 mg every 8 weeks: unadjusted ITC safety results

Endpoint	Bucher ITC		
	OR (95% CI)	RR (95% CI)	RD (95% CI)
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; OR: odds ratio; RR: risk ratio; RD: risk difference.

A24. Please provide the references for studies in NMA: COSMOS, NCT02719171, FUTURE 3:

a) Coates LC, Gossec L, Theander E, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS). Annals of the Rheumatic Diseases 2021.

b) CSR for NCT02719171. BI 655066/ABBV-066/Risankizumab Compared to Placebo in Patients With Active Psoriatic Arthritis, 2016.

c) Nash P, Mease PJ, McInnes IB, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: Results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Research and Therapy 2018;20 (1) (no pagination)

The Coates (2021) reference and the CSR for NCT02719171 are included in the reference pack accompanying these responses.

The Nash (2018) reference is not sharable due to copyright restrictions. However it is freely available at this link: Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3) (nih.gov)

Section B: Clarification on cost-effectiveness data

B1. CM Model, worksheet 'Base-case results'. Please provide further detail and justification regarding the different approaches to estimate the drug acquisition and drug administration costs in the cost-minimisation (CM) analysis (where the drug acquisition cost is applied only at cycles where the drug is administered according to the drug schedule vs a mean drug administration cost per cycle is applied at every cycle of the 'Treatment Trial Period').

The drug administration cost is calculated as a mean cost per cycle to allow for a variable cycle length to be implemented in the model. Once the user sets the number of administrations required per treatment trial period, that cost is spread evenly across the treatment trial period as noted by the reviewer, adjusting for the set cycle length. We acknowledge that this adjustment should, in principle, be also performed for the drug acquisition cost, but due to the complexity of the treatment scheduling this has not been implemented in the similar fashion, and instead the precise timing of dosing is conserved in the evaluation of the acquisition cost. Nevertheless, the difference caused by this simplification is negligible to the model results, being caused only by applying different mortality rate in the treatment period, which is insignificant, and hence has no material effect on the final incremental cost of the intervention.

B2. CM Model. Please justify the following assumptions regarding drug administration costs used in the CM analysis (provide evidence if possible):

a) Drug administration costs were assumed to be the same for drugs with different regimen schedules;

Risankizumab and guselkumab are administered via subcutaneous injection. Patients may self-inject after training if deemed appropriate by a physician from the first injection. AbbVie funds a homecare service to facilitate self-administration, so no administration costs were included in the base case analysis. It is understood that administration of guselkumab follows a similar scenario,

with homecare service provided by the manufacturer; therefore no administration cost was applied in the comparator arm. This approach has been validated by UK clinical experts.

The dosing schedule for risankizumab (Weeks 0, 4 and every 12 weeks thereafter), is less frequent than guselkumab (Weeks 0, 4 and every 8 weeks thereafter). Therefore, the assumption of equivalent administration costs between risankizumab and guselkumab is conservative.

b) The exclusion of administration costs for both treatments in the analysis, based on the provision of a homecare service by the company to facilitate these administrations (CS, page 89). Please also comment if this service would be provided to all patients eligible for treatment with risankizumab in case it is recommended by NICE, and for how long

Currently, the homecare service to facilitate these administrations is offered to all patients and we foresee that this will continue to be the case, similar to other established biologics. As per the response to Question B2 a), patients may self-inject after training if deemed appropriate by a healthcare professional from the first injection, and this applies to the vast majority of patients. It is understood that administration of guselkumab follows a similar scenario, with homecare service provided by the manufacturer, and the majority of patients subsequently able to self-inject. In the event that homecare services were no longer provided by the company, the associated costs would be limited and likely equivalent between risankizumab and guselkumab.

c) The assumption that treatment is administered by a professional only during the treatment trial period (scenario analysis).

This scenario analysis was performed to assess the impact on results when risankizumab and guselkumab is administered by a healthcare professional for an initial trial period (assumed to be the doses administered in the first 24 weeks of treatment, in line with the KEEPsAKE-2 trial) before continuing the course of treatment. In this scenario, the doses of risankizumab and guselkumab administered within the trial period are associated with a cost of £42, sourced from Curtis *et al.* Unit Costs of Health and Social Care (2020).[26] All subsequent treatments are assumed to be self-administered, with no costs incurred to the NHS. As per the responses to the other parts of Question B2, it is anticipated that the vast majority of patients will be able to self-administer following the first injection.

d) CS, page 85. The CS states that “patients can self-inject at home if this is deemed appropriate by a physician” after training. Would any prescription or dispensing costs be incurred by the proportion of patients for whom this approach would be feasible? In addition, please clarify the proportion of patients who would not be expected to self-administer treatment.

Risankizumab is administered in a pre-filled pen. This is an easy-to-use auto injector which patients can self-administer at home after initial training. The product is delivered directly to the patents’ home for self-injection or for administration by a healthcare professional, therefore no additional prescription or dispensing charges are incurred. The same home delivery system is already in place for the psoriasis indication.

The ease of self-administration has been demonstrated through a Phase 3, single-arm, open-label study in patients with moderate to severe psoriasis in which all patients achieved successful self-administration using the pen and reported high acceptability of the pen using the Self Injection Assessment Questionnaire (SIAQ) at Weeks 0, 4, 16 and 28.[27] UK Clinical experts have estimated that >98% of patients are able to self-inject. Therefore no additional prescription or dispensing charges are incurred for patients in whom self-injection is not possible.

B3. CS, Section B.4.2.1. The summary of product characteristics (SmPC) for guselkumab states that *"consideration should be given to stopping treatment when disease has not responded after 24 weeks of treatment"*, whilst for risankizumab the response assessment should be considered after 16 weeks of treatment initiation. Please comment on the choice of the period before assessment of response (trial treatment period) of 24 weeks for both drugs and how the choice of an alternative trial period of 16 weeks may affect the total costs of risankizumab and guselkumab.

The wording used in the risankizumab SmPC states that "Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some plaque psoriasis patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks." This wording is largely focused on the plaque psoriasis indication. In clinical practice for PsA, the choice of timepoint (Week 16 or Week 24) for response assessment is patient-dependent rather than treatment-dependant, and thus would apply to both risankizumab and guselkumab; patients who show no response after 16 weeks of treatment with either risankizumab or guselkumab would be considered for treatment discontinuation. This is in line with comments from the committee in TA711, who noted that, in addition to the primary response timepoint of 24 weeks, clinicians would value the option of assessing response to guselkumab at Week 16.[3]

A scenario analysis was provided in the original company submission using the Week 16 timepoint for response assessment, which demonstrated that costs are insensitive to the choice of timepoint for response assessment.

B4. CS, Section B.4.2.1, page 86. The CS states that PsARC has been chosen by the company as the measurement of treatment response in the cost-comparison analysis as has been used *"in economic analyses submitted in all prior appraisals and accepted by the committee"*. In TA711, two alternative response definitions were used in sensitivity analyses presented in the company's economic analysis: i) joint PsARC and PASI 75 response, and ii) ARC response. Please comment on the choice of alternative measurements of treatment response and how these could affect results for risankizumab.

As part of the cost-minimisation approach, the model assumes clinical equivalence between risankizumab and guselkumab based on the NMA results provided in the Company submission. The same response rate is therefore always applied to both risankizumab and guselkumab. In the original submission, the company provided a scenario analysis using a different response

rate from TA711. This scenario analysis demonstrated that costs are insensitive to the choice of response rate.

The NMA provides alternative treatment response measures, including PASI 75 and ARC response. It is not possible to provide joint PsARC and PASI 75 response, as this analysis was not conducted. Please see Table 18 for the results of the cost-comparison analysis, with alternative treatment response measures (PASI 75 response rate at week 24, ARC 70 response rate at week 24). As the results demonstrate, the model outcomes, specifically the incremental cost of treatment with risankizumab versus guselkumab, are not sensitive to different response definitions, this result does not change substantially from the base case results.

Table 18: Alternative treatment response measures, scenario analyses at list price

Technologies	Acquisition costs	Administration costs	Monitoring costs	Total costs
PsARC Response: [redacted] *(Week 24)*				
Risankizumab	£46,646	N/A	N/A	£46,646
Guselkumab	£45,733	N/A	N/A	£45,733
Difference	£914	N/A	N/A	£914
PASI 75 Response: [redacted] *(Week 24)*				
Risankizumab	£49,921	N/A	N/A	£49,921
Guselkumab	£49,013	N/A	N/A	£49,013
Difference	£908	N/A	N/A	£908
ARC 70 Response: [redacted] *(Week 24)*				
Risankizumab	£17,177	N/A	N/A	£17,177
Guselkumab	£16,211	N/A	N/A	£16,211
Difference	£966	N/A	N/A	£966

Abbreviations: ACR: American college of Rheumatology; PASI: psoriasis area severity index; PsARC: Psoriatic arthritis Response Criteria.

B5. Model, worksheet 'Base-case results' cells N32:O554. Please provide evidence for the assumption made in the CM analysis that the PsARC response rate is maintained constant throughout the maintenance treatment period.

PsARC response rate is not assumed to be constant throughout the maintenance treatment period. This is because an additional discontinuation rate of 16.5% is applied to the response rate in the maintenance treatment period in order to reflect the loss of response and treatment discontinuation due to AEs.

B6. Model and CS, Section B4.2.3. Please clarify why health care costs associated with the management of arthritis and psoriasis were excluded from the CM analysis.

The cost-minimisation analysis assumes clinical equivalence between risankizumab and guselkumab. As a result, the severity and incidence, and therefore the health care costs associated with management, of arthritis and psoriasis are assumed to be equal. These were therefore not included in the cost-minimisation analysis.

B7. CS, Section B.4.2.4. Please provide an explanation for the exclusion of treatment specific adverse events associated costs, and why the distribution of adverse events in KEEPSAKE-2 and DISCOVERY clinical trials data have not been used in the CM analysis.

The cost-minimisation analysis assumes clinical equivalence between risankizumab and guselkumab. This assumption is based on the NMA presented in the company submission, which [redacted] between risankizumab and guselkumab. As a result, the severity and incidence of AEs, and therefore the health care costs associated with their management, are assumed to be equal. Adverse events were therefore not included in the cost-minimisation analysis.

B8. The summary of product characteristics (SmPC) for risankizumab and guselkumab state that these treatments may increase the risk of infections. Please clarify if and how this has been accounted for in the CM analysis. If it has not been accounted for, comment on its potential impact on the costs of monitoring for each treatment group.

The relative impact of risankizumab and guselkumab on the risk of infections, and therefore costs associated with infections, was assumed to be equal. This assumption is based on the NMA presented in the company submission, which [redacted] between risankizumab and guselkumab as well as the fact that risankizumab and guselkumab are administered subcutaneously. The costs associated with infections were therefore not included in the cost-minimisation analysis. Whilst no NMA has been conducted on infection rates specifically, the proportion of patients experiencing upper respiratory tract infections (the most common infection associated with risankizumab and guselkumab) were similar between the KEEPsAKE-2 and DISCOVER-1 trial, as shown in Table 19.

Table 19: Proportion of patients with upper respiratory tract infection in KEEPsAKE-2 and DISCOVER-1 through Week 24

Patients with 1 or more AE, n (%)	KEEPsAKE-2		DISCOVER-1			
	Placebo (n=219)	Risankizumab 150 mg (n=224)	Placebo (n=126)	Guselkumab 100 mg		
				Q4W (n=128)	Q8W (n=127)	Combined (n=255)
Upper respiratory tract infection	12 (5.5)	17 (7.6)	8 (6.3)	11 (8.6)	7 (5.5)	18 (7.1)

Abbreviations: Q4W: every four weeks; Q8W: every 8 weeks.
Source: Deodhar *et al.* (2020),[13] Östör *et al.* (2021).[15]

B9. Model. Please justify why relative dose intensity (RDI) has not been included for any treatment in the CM analysis?

Relative dose intensity is the ratio of the dose intensity delivered to the reference standard dose intensity for a chemotherapy regimen, where dose intensity is the total amount of drug delivered over a total time course of treatment.[28] This is relevant for indications such as oncology, in which

most patients are not expected to receive full dose of the planned treatment due to high toxicity of a treatment.

The recommended dose for PsA patients receiving Risankizumab is 150 mg administered as a subcutaneous injection at Week 0, Week 4 and every 12 weeks thereafter.[29] The recommended dose for PsA patients receiving guselkumab is 100 mg administered by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks.[2] The Q4W dosing schedule for guselkumab is only recommended for patients at high risk for joint damage according to clinical judgement and was therefore not included in the model. Risankizumab has a fixed recommended dose. Dose escalation or alteration of dose interval are not within the marketing authorisation or permitted in the KEEPsAKE-2 trial.

Therefore, as no toxicity concerns are highlighted for the intervention and comparator, it is anticipated that patients treated with risankizumab or guselkumab will receive the specified dose, as per the prescribing information, therefore no relative dose intensity is applied to either of the drugs in the model.

Section C: Textual clarification and additional points

C1. CS Table 10 page 74. The model specification presented in Table 10 does not match the description stated on the same page. Please clarify if this was a typo and provide the correct model used.

The corrected description of the models implemented for each outcome in each network are provided in Table 20.

Table 20. NMA models used in the analysis

Analysis	Primary analysis
PsARC	Fixed-effects binary model (primary) Random-effects binary model
PASI 50/75/90/100	Fixed-effects ordinal model (primary) Random-effects ordinal model
HAQ-DI change	Fixed-effects continuous model (primary) Random-effects continuous model
HAQ-DI change conditional on PsARC response	Fixed-effects continuous model (primary) Random-effects continuous model
ACR 20/50/70	Selected from the following four candidate models: • Fixed-effects ordinal model • Fixed-effects ordinal model with placebo-response adjustment • Random-effects ordinal model • Random-effects ordinal model with placebo-response adjustment
AEs and serious AEs	Fixed-effects binary model

Abbreviations: ACR: American college of Rheumatology; AE: adverse event; HAQ-DI: health assessment questionnaire-disability index; PASI: psoriasis area severity index; PsARC: Psoriatic arthritis Response Criteria.

References

1. European Medicines Agency (EMA). Human Medicine European Public Assessment Report: Skyrizi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi. [Last accessed: 01/11/2021]. 2019.
2. Electronic Medicines Compendium (EMC). Guselkumab (Tremfya) summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/9587/smpc#AUTHDATE. [Last accessed: 03/02/2022], 2021.
3. National Institute for Health and Care Excellence (NICE). TA711: Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta711 [Last accessed: 31/01/2022], 2021.
4. National Institute for Health and Care Excellence (NICE). TA445: Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta445 [Last accessed: 31/01/2022]. 2017.
5. National Institute for Health and Care Excellence (NICE). TA543: Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta543 [Last accessed: 31/01/2022]. 2018.
6. National Institute for Health and Care Excellence (NICE). TA537: Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta537 [Last accessed: 31/01/2022]. 2018.
7. National Institute for Health and Care Excellence (NICE). TA340: Ustekinumab for treating active psoriatic arthritis. Available from https://www.nice.org.uk/guidance/ta340 [Last accessed: 31/01/2022] 2017.
8. Warren RB, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy-assessor-blinded clinical trial. Br J Dermatol 2021;184:50-59.
9. National Institute for Health and Care Excellence (NICE). TA596: Risankizumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta596. [Last accessed: 10/11/2021], 2019.
10. AbbVie. Data on File: Clinical Study Report (CSR) for KEEPsAKE-2.
11. Lidar M AJ, Tarr G, Papp K, Barcomb L, Soliman A, Lu W, Eldred A, Ostor A. Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 24-Week Results from the Phase 3, Randomized, Double-blind Clinical Trial for CsDMARD-IR and Bio-IR Patients [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). Available from: https://acrabstracts.org/abstract/efficacy-and-safety-of-risankizumab-for-active-psoriatic-arthritis-24-week-results-from-the-phase-3-randomized-double-blind-clinical-trial-for-csdmard-ir-and-bio-ir-patients/. [Accessed: 10/01/2022]. 2021.
12. Deodhar A, Gottlieb AB, Boehncke WH, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. The Lancet 2018;391:2213–2224.
13. Deodhar A, Helliwell PS, Boehncke W-H, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. The Lancet 2020;395:1115–1125.
14. Coates LC, Gossec L, Theander E, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIB, randomised, controlled study (COSMOS). Ann Rheum Dis 2021.
15. Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis 2021;Epub ahead of print.
16. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results

from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317-2327.
17. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Annals of the Rheumatic Diseases 2017;76:1550-1558.
18. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Annals of the Rheumatic Diseases 2014;73:990-9.
19. Medical Dictionary of Regulatory Activities. Mapping. Available at: https://www.meddra.org/mapping [Last accessed: 14/02/2022].
20. AbbVie. Data on File: Clinical Study Report (CSR) for NCT02719171
21. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual (NICE). London: NICE, 2022:181.
22. Ren S, Oakley JE, Stevens JW. Incorporating Genuine Prior Information about Between-Study Heterogeneity in Random Effects Pairwise and Network Meta-analyses. Medical Decision Making 2018;38:531-542.
23. Phillippo DM, Dias S, Ades AE, et al. Multilevel network meta-regression for population-adjusted treatment comparisons. J R Stat Soc Ser A Stat Soc 2020;183:1189-1210.
24. Phillippo D, Ades T, Dias S, et al. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). NICE Decision Support Unit. Available at: http://www.nicedsu.org.uk/Populationadjusted-ICs-TSD(3026862).htm [Last accessed: 14/03/2022]. 2016.
25. Ritchlin CT, Helliwell PS, Boehncke WH, et al. Guselkumab, an inhibitor of the IL-23p19 subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1 year results of a phase III randomised study of patients who were biologic-naïve or TNFα inhibitor-experienced. RMD Open 2021;7.
26. Curtis LA, Burns A. Unit Costs of Health & Social Care 2020. Available at: https://www.pssru.ac.uk/pub/uc/uc2015/full.pdf: PSSRU, University of Kent, 2020.
27. Blauvelt A, Gordon KB, Lee P, et al. Efficacy, safety, usability, and acceptability of risankizumab 150 mg formulation administered by prefilled syringe or by an autoinjector for moderate to severe plaque psoriasis. Journal of Dermatological Treatment 2021:1-9.
28. Vavra KL, Saadeh CE, Rosen AL, et al. Improving the relative dose intensity of systemic chemotherapy in a community-based outpatient cancer center. J Oncol Pract 2013;9:e203-11.
29. Electronic Medicines Compendium (EMC). Risankizumab (Skyrizi) summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/12625/smpc. [Last accessed: 03/02/2022], 2022.

Appendix A

Results for all comparators for the biologic-experienced population at Week 24 using informative priors are presented in Table 21 to Table 32.

The level of cross-trial heterogeneity was measured by 1/τ ,with a larger 1/τ, corresponding to a more heterogeneous treatment effect. DIC is a measure of model fitting that penalizes model complexity. A smaller DIC value suggests a better balance of model fit versus model complexity. The statistics for the models for informative priors NMAs among the biologic-experienced population at Week 24 are presented in Table 33.

Table 21: Estimated Probabilities of Achieving PsARC Response [Posterior Median (95% CrI)] among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

Treatment	Probability of Achieving PsARC Response Posterior Median (95% CrI)
PBO	[redacted]
UST 90	[redacted]
UST 45	[redacted]
RISA	[redacted]
IXE 80 Q4W	[redacted]

Abbreviations: CrI: credible interval; IXE, ixekizumab; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; Q4W, every four weeks; RISA, risankizumab; UST, ustekinumab.

Table 22: Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PsARC Response among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

PBO	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	UST 90	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	UST 45	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	RISA	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q4W

An odds ratio >1 indicates that the treatment in that column has a higher probability of achieving PsARC response compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.
Abbreviations: CrI: credible interval; IXE, ixekizumab; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; Q4W, every four weeks; RISA, risankizumab; UST, ustekinumab.

Table 23: Estimated Probabilities of Achieving PASI Response [Posterior Median (95% CrI)] among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

Treatment	Probability of Achieving PASI 50 Response Posterior Median (95% CrI)	Probability of Achieving PASI 75 Response Posterior Median (95% CrI)	Probability of Achieving PASI 90 Response Posterior Median (95% CrI)	Probability of Achieving PASI 100 Response Posterior Median (95% CrI
PBO	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]	[redacted]	[redacted]

IXE 80 Q4W	[redacted]	[redacted]	[redacted]	[redacted]
RISA	[redacted]	[redacted]	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]	[redacted]	[redacted]
GUS Q8W	[redacted]	[redacted]	[redacted]	[redacted]
GUS Q4W	[redacted]	[redacted]	[redacted]	[redacted]
UST 45	[redacted]	[redacted]	[redacted]	[redacted]
UST 90	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations CrI: credible interval; GUS, guselkumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

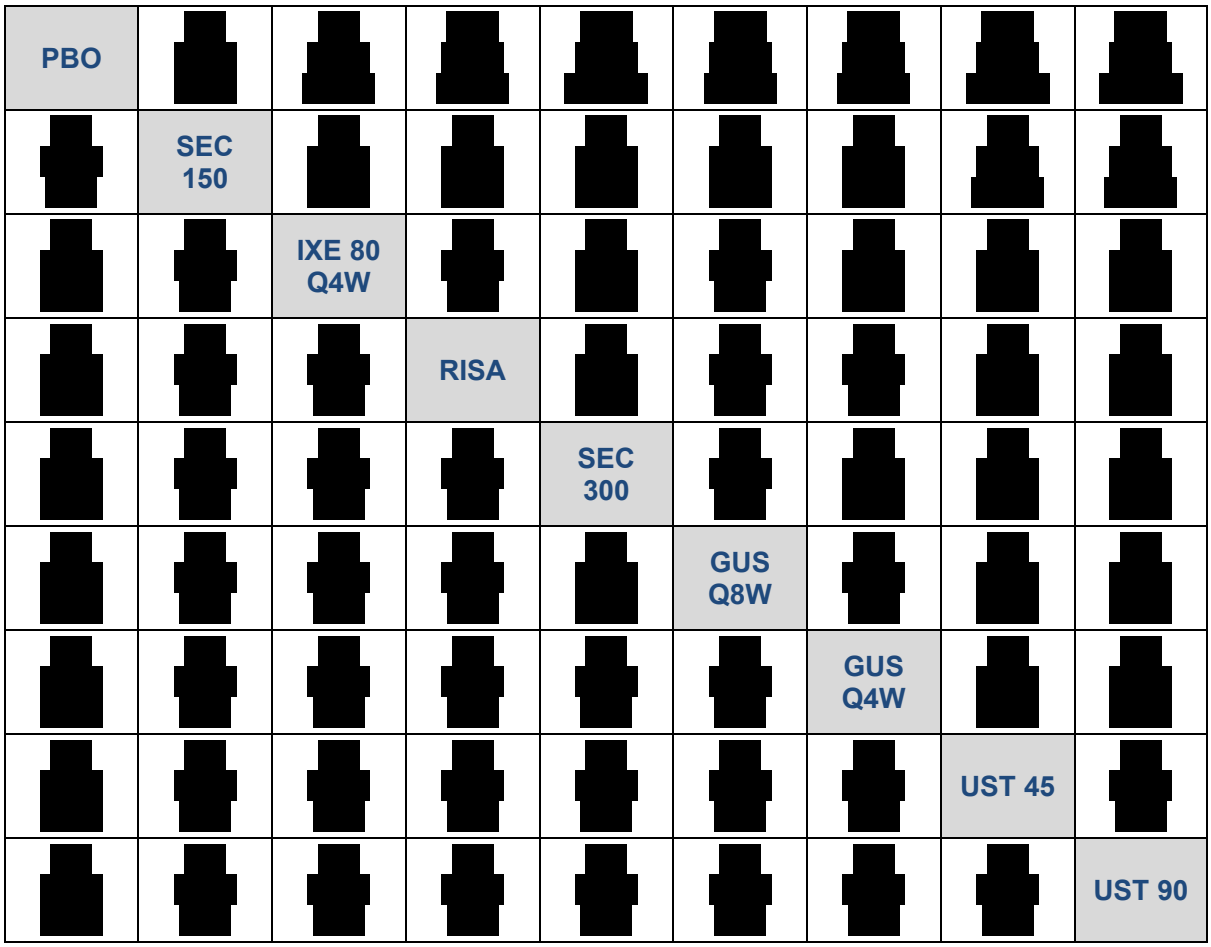
Table 24: Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 50 Response among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	SEC 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	IXE 80 Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	SEC 300	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	GUS Q8W	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	GUS Q4W	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UST 45	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UST 90

An odds ratio >1 indicates that the treatment in that column has a higher probability of achieving PASI 50 response compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.

Abbreviations: CrI: credible interval; GUS, guselkumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

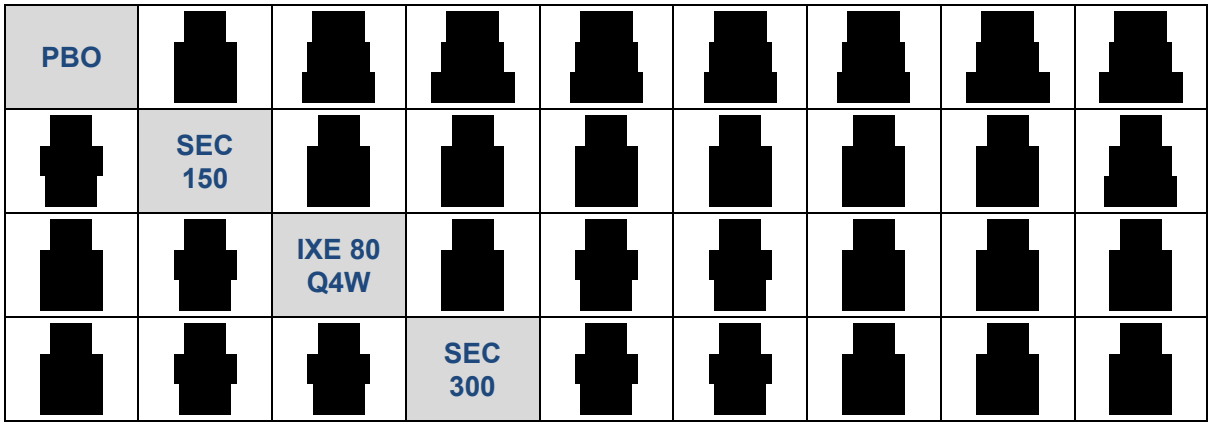
Table 25. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 75 Response among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

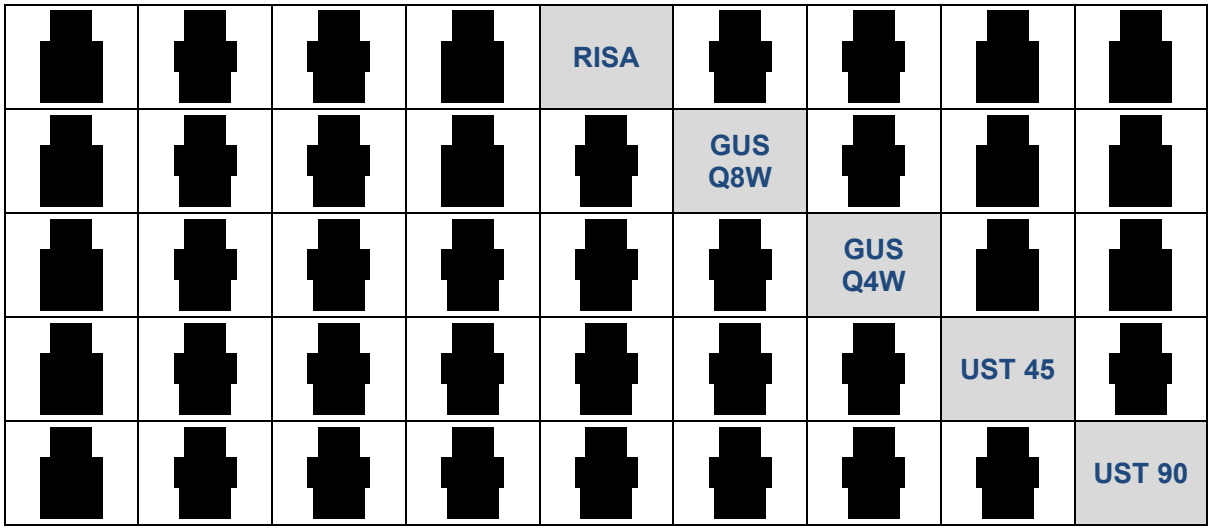


An odds ratio >1 indicates that the treatment in that column has a higher probability of achieving PASI 75 response compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.

Abbreviations: CrI: credible interval; GUS, guselkumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

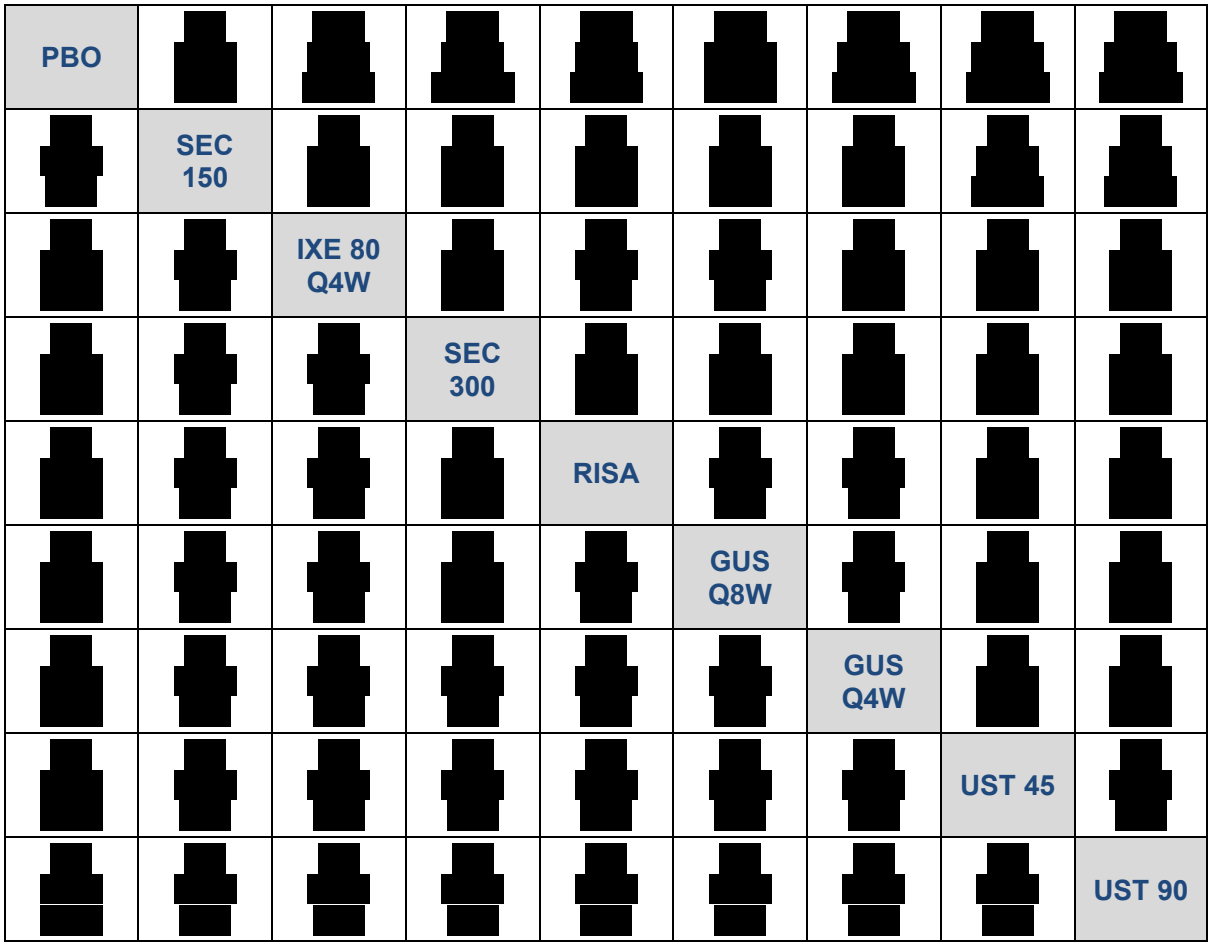
Table 26: Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 90 Response among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)





An odds ratio >1 indicates that the treatment in that column has a higher probability of achieving PASI 90 response compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.
Abbreviations: CrI: credible interval; GUS, guselkumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

Table 27: Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 100 Response among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)



An odds ratio >1 indicates that the treatment in that column has a higher probability of achieving PASI 100 response compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.

Abbreviations: CrI: credible interval; GUS, guselkumab; IXE, ixekizumab; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

Table 28: Estimated HAQ-DI Change from Baseline [Posterior Median (95% CrI)] among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

Treatment	HAQ-DI Change Posterior Median (95% CrI)
PBO	[redacted]
SEC 150	[redacted]
UST 45	[redacted]
GUS Q8W	[redacted]
RISA	[redacted]
SEC 300	[redacted]
IXE 80 Q4W	[redacted]

Abbreviations: CrI: credible interval; GUS, guselkumab; HAQ-DI: Health Assessment Questionnaire - Disability Index; IXE, ixekizumab; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab.

Table 29: Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	SEC 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	UST 45	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	GUS Q8W	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	RISA	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SEC 300	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q4W

A difference <0 indicates that the treatment in that column has a larger reduction in HAQ-DI from baseline compared with the treatment in that row. An asterisk (*) indicates a significant difference between two treatments.
Abbreviations: CrI: credible interval; GUS, guselkumab; HAQ-DI: Health Assessment Questionnaire - Disability Index; IXE, ixekizumab; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks; RISA, risankizumab; SEC, secukinumab; UST, ustekinumab

Table 30: Estimated HAQ-DI Change from Baseline among PsARC Responders and PsARC Non-Responders [Posterior Median (95% CrI)] among the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

Treatment	HAQ-DI Change among PsARC Responders Posterior Median (95% CrI)	HAQ-DI Change among PsARC Non-Responders Posterior Median (95% CrI)
PBO	[redacted]	[redacted]
RISA	[redacted]	[redacted]
UST 45	[redacted]	[redacted]

Abbreviations: CrI: credible interval; HAQ-DI: Health Assessment Questionnaire - Disability Index; PBO, placebo; RISA, risankizumab; UST, ustekinumab

Table 31: Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among the PsARC Responders of the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

PBO	[redacted]	[redacted]
[redacted]	RISA	[redacted]
[redacted]	[redacted]	UST 45

A difference <0 indicates that the treatment in that column has a larger reduction in HAQ-DI from baseline among PsARC responders compared with the treatment in that row.
Abbreviations: CrI: credible interval; HAQ-DI: Health Assessment Questionnaire - Disability Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; RISA, risankizumab; UST, ustekinumab

Table 32: Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among PsARC Non-responders of the Biologic-experienced Population at Week 24 (Informative Prior Random-effects NMA)

PBO	[redacted]	[redacted]
[redacted]	UST 45	[redacted]
[redacted]	[redacted]	RISA

A difference <0 indicates that the treatment in that column has a larger reduction in HAQ-DI from baseline among PsARC non-responders compared with the treatment in that row.
Abbreviations: CrI: credible interval; HAQ-DI: Health Assessment Questionnaire - Disability Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; RISA, risankizumab; UST, ustekinumab

Table 33: Statistics for Models for Informative Priors NMAs Among the Biologic-experienced Population at Week 24

Outcome	Data Points	$1/\tau$ Median (95% CrI)	Mean Residual Deviance	pD	DIC
PsARC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI among PsARC responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI among PsARC non-responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

pD stands for the effective number of parameters in the Bayesian NMA model, which was used in the calculation of DIC. $1/\tau$ is the between-trial variance for the treatment effects in a random-effects model.
Abbreviations: CrI: credible interval; DIC: Deviance Information Criteria; HAQ-DI: Health Assessment Questionnaire - Disability Index; PASI: Psoriasis Area and Severity Index; PsARC: Psoriatic Arthritis Response Criteria.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The reach of the Psoriasis Association now extends much further than that of the original member. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). The Psoriasis Association has three main aims; to provide information advice and support, to raise awareness and to fund and promote research. In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (~17,500 registered users), and Social Media (~7,200 registered users on closed Facebook group). The main Psoriasis Association website averages 48,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to "raising awareness" include Twitter (~14,000 followers) and Instagram (~12,450 followers), along with a YouTube channel offering further information. The Psoriasis Association has been passionate about research throughout its 50+ year history. Regularly funding PhD studentships, alongside supporting the PPI of bigger research collaborations, always seeking to improve the lives of those affected by psoriatic disease and in 2021 awarded £1 million to the Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP) research project based at Kings College, London.
4b. Has the organisation received any funding from the	Yes – Abbvie - £1,500 corporate membership, £8,500 core support Amgen - £1,500 corporate membership, £690 honorarium

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Eli Lilly - £1,500 corporate membership Janssen - £1,500 corporate membership, £8,500 core support UCB - £1,500 corporate membership, £5,100 honorarium, £300 sponsored project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (570,297 visitors in 2021) helpline (973 enquiries in 2021) online forums (17, 520 registered users in 2021) social media channels (including Facebook Group, Twitter and Instagram, 33,499 people in 2021) The Psoriasis Association analyses the data gathered from all communication channels (mentioned above) and monitors for trends in addition to interesting new requests. We have completed a Priority

	Setting Partnership on Psoriasis which gave valuable insight into issues affecting people living with psoriasis and supported a Priority Setting Partnership on Psoriatic Arthritis (including membership of the Steering Committee).
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriatic Arthritis is a complex inflammatory musculoskeletal and skin disease with additional challenges owing to the heterogeneity of it. Psoriatic Arthritis is a destructive form of arthritis with a peak onset in people between 30 and 40 years of age. Owing to the age of onset of the condition (and the joints affected often being the fingers and toes right through to larger joints) impact on work, social life and relationships can be marked. Being unable to do top buttons up on a shirt can be frustrating, but being unable to change your baby's nappy, run with your toddler or take the dog for a walk due to the pain and destruction of your joints can be utterly devastating. Many jobs now have an element of computer work associated with them, but if you have PsA in the finger joints it can be extremely difficult to do any dexterous work. For those for whom PsA affects the joints in the toes, walking can be extremely painful and therefore impacts again on the types of job an individual can do, if they can work at all. PsA, unlike other more common forms of arthritis is often worse after a period of rest, and so early morning tasks may not be possible, or would take a longer amount of time compared to someone without PsA. Symptoms of PsA vary from mild to very severe, and can include swollen fingers and toes through to larger joints such as elbows and knees, tendonitis (particularly in the Achilles) and joints in the back. It is a destructive form of arthritis and so without timely, suitable treatment, joints can be destroyed quickly owing to the quick onset of inflammation. Patients therefore experience pain associated with the inflammation and current destruction of their joints, but also once the flare-up has subsided are left with pain due to the damage caused by the flare. It is key then that patients should have access to the relevant therapies to prevent the destruction (hence avoiding the need for joint replacement operations) and to continue to lead a full and active life. Nail psoriasis is common in people with psoriatic arthritis, and this too can be extremely disabling, painful and limits the tasks that a person can perform. Nail psoriasis affecting the toenails can make it difficult to wear shoes, which in turn can affect employment eligibility not to mention negatively impacting someone's quality of life. Fingernail psoriasis is painful and unsightly, limiting a person's day-to-day activities.

	Of course many people with psoriatic arthritis have a level of skin involvement also. Combined Dermatology / Rheumatology clinics are rare yet provide much needed expertise in managing two inflammatory diseases. Owing to the rarity of the combined clinics, patients frequently have the added pressure of attending double the amount of appointments as necessary, putting added pressure on work situations. With psoriatic arthritis affecting the fine motor joints as well as the larger mechanical joints, application of topical treatments to manage psoriasis can be difficult and patients become reliant on carers to help, or watch their skin condition deteriorate owing to inability to apply treatments. Sadly, and in part due to the variability in clinical presentation, it can take several years before a correct diagnosis is made and access to a suitable clinician. During this time, patients make lifestyle and behaviour changes which can in the long-term impact on the efficacy and availability of treatments e.g. avoid walking so as not to be in pain (and inevitably gain weight), become increasingly socially isolated and suffer with low mood or depression. Fatigue is a common co-morbidity of PsA, yet it is poorly understood, addressed and treated. This also causes issues for those in employment, and also places extra strain on relationships. Many people living with a family member with PsA would not classify themselves as a "carer", but adapt their lives or carry out tasks because their loved one requires it. Often this begins as small things such as opening bottles or jars, which then increase in number and impact as the condition deteriorates, when allowances have to be made on leisure activities previously enjoyed together, or further assistance is required to maintain the home. This can sometimes cause resentment that the family members' life has also been negatively impacted by PsA.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients report many unwanted side effects, particularly in relation to the conventional oral DMARDs with much trial and error to achieve a useful dose. For many, a long time is spent adjusting oral doses of DMARDs when treatment escalation to biologics or small molecules may be more appropriate. Feedback from patients consistently reports the need for long-term relief from PsA symptoms, and for those who are affected with both PsA and skin psoriasis one treatment that works for both conditions is always more favourable than multiple treatments. Combined dermatology / rheumatology clinics would

	improve the treatment pathway for people with concomitant psoriasis and psoriatic arthritis greatly. Access to early treatment for this disease population is vital owing to the disabling nature of the condition that affects young adults, consequently impacting on work, life and family prospects. Recent events regarding COVID-19 have inevitably made patients more aware and perhaps more cautious when taking immunomodulatory agents or biologics and so further information, advice and support should be made available. The pandemic has also seen a further delay in patients accessing healthcare in order to get a diagnosis and treatment for PsA for a variety of reasons and so they could inevitably require more aggressive treatment than would have been used earlier in the diagnosis / treatment pathway. Waiting times from referral to appointment are consistently in excess of 12 months for either Rheumatology or Dermatology specialties. The in access of services not only causes worsening of disease when patients are finally assessed, but has a devastating impact on the patients and family members quality of life, mental health, ability to work / study and lead a fulfilling life.
8. Is there an unmet need for patients with this condition?	Yes. Whilst treatments have become increasingly efficacious, access to them is an issue for many patients. As mentioned above, the heterogeneity of the disease means that there is not a “one size fits all” in terms of which treatment will work, for how long and with manageable side effects.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As treatments for psoriasis and PsA become ever more refined patients can become optimistic as to what the future holds for them. Whilst treatment response may not be adequate via one targeted therapy, it is now possible to target different chemical pathways in order to get a response to treatment. This gives patients stability in knowing that there are now treatment options should one fail. Thought around ease of use of the pen device for administration ensuring that people with arthritis affecting hands / fingers or perhaps with nail psoriasis is welcomed – being able to actually administer the treatment is of great benefit as no treatment will have the opportunity to work to full potential if it remains unused, or can’t be administered correctly!

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The COVID-19 pandemic has made patients more wary / concerned with regards to taking any immunomodulatory / biologic treatment and the affect it may have on the immune system, and their susceptibility of acquiring infections. The Psoriasis Association advocates the participation of patients on biologics registries such as those overseen by the British Association of Dermatologists and the British Society for Rheumatology.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients whose skin psoriasis is moderate-severe, or in a high impact site would benefit from this treatment being used to treat their PsA. Those who find it difficult to inject other treatments may find the administration device much more manageable and less fiddly than traditional “pens” or “injections”.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The treatment options for those whose skin responds but joints don’t (or vice versa)

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Untreated and under-treated psoriatic arthritis can not only destroy the joints of those affected, but the lives of those affected • Having a treatment that can work on the joints, skin and where appropriate bowel is of importance to patient choice • There are currently few treatments available to treat psoriatic arthritis over the life time, and so an extension to the treatment armoury is most welcome • Having a self-administration device that can be used easily by patients affected by the condition is of great value. • Comorbidities such as fatigue, sleep disturbance, pain, diminished work capacity and social participation should be included when assessing adequate treatment response

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient organisation submission

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	A patient-centred charity that exists to support people affected by psoriasis and psoriatic arthritis. Activities include information both in print and via a comprehensive website. Telephone support offering help, advice and a sign-posting service to other resources is also available. The organisation also supports research via a small grants scheme. Health care professionals continued professional development is promoted and supported with an accredited online *Psoriasis in Practice* training resource (free to NHS staff). There is no formal membership of the organisation, but subscriptions are available to receive a bi-annual *Skin 'n' Bones Connection* journal, all other patient resource and support are free and can be accessed anonymously. Access to the website is also free, with limited sign-up details needed to enter the PAPAA *Knowledge Bank* and online subscriber's area. Use of social media is also part of the organisations activities, but with a strict policy of only publishing evidenced-based and reliably sourced content. Funding is via donations, journal subscriptions, online shop sales, fundraising activities and an ethical investment portfolio. No funds are currently accepted from commercial organisations (including the pharmaceutical industry) or third-party agents representing or supporting those sectors.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information used in this submission has been gathered and based on direct feedback from people affected by psoriatic arthritis, and my personal experience of living with psoriatic arthritis. PAPAA also has a continuing data gathering process, and since 2014 via the PAPAA survey.
Living with the condition	
6. What is it like to live with the condition? What do carers	There is often a wildly held view, where arthritis is dismissed and accepted as part of getting old and an inevitable consequence of being human and part a wear and tear process. For those who develop psoriatic arthritis, this dismissal of symptoms is not only frustrating but also insulting. Early development of joint and connective tissue pain and swelling can be very alarming, particularly when tests fail to identify the cause.

experience when caring for someone with the condition?	The prior development of psoriasis often as a teenager, has an enormous detrimental effect, to then develop joint and connective tissue disease a few years later perhaps, before the age of 30, life can be very difficult. This early onset not only comes as a surprise, but also not always identified, diagnosis is often missed due the intermittent symptoms, lack of radiographic changes and limited available inclusive tests. Therefore, people are often dismissed or not believed when reporting symptoms. Those symptoms include pain, swollen joints, fatigue and a general tiredness, which added to an itchy, dry scaly skin, where, painful disfigured nails, also cause dexterity and mobility issues. It is unsurprising that people with psoriatic arthritis find it too difficult to cope with. Many find that they can no longer continue in their chosen profession or work activity, the psychological effect is also an issue, with uncertainty of whether the condition will progress causing permanent disability and how that will affect lifestyle, relationships and long term-future all weigh heavily. The surprise and sometimes sudden initial flare of the condition also affects family and carers, particularly given that onset at such a relatively young age, is when people are in relationships, thinking about starting families and looking towards a long and perhaps fruitful career, is often stopped or totally destroyed. For those who do get a diagnosis and some form of treatment, and given there is no cure but just progression, have to come to terms with being blighted by a condition that may progress slowly or flare and cause irreversible joint damage. This brings with it a lifetime of medication, tests, appointments, daily treatments and constant awareness that psoriatic arthritis is an unpredictable disease that will get in the way of daily life. A destroyer of hopes, dreams and ambition. The following are free text quotes submitted via our surveys: *“It makes me feel old (I'm very active for my age, do everything at top speed etc. and most friends are younger than me) if I can't do things because of the psoriatic arthritis”* *“Fed up telling people as they ask what is the matter all the time”* *“Can’t cope with disability”* *“Had to give up work. Felt I couldn’t do much, was unreliable, felt useless I'm self-conscious of my deformed fingers “*

	"I feel self-conscious that I cannot do things, I feel my family don't realise how bad it is at times, and I am sure they think that I am making it up" *"Exhausted. Get fed up with cancelling plans."* *"I'm not the person I was and that can be hard to accept, it depresses me"* *"Don't enjoy having to use a mobility scooter or crutches"* *"No self-esteem left with my lack of ability to do much of anything "* *"The physical side of arthritis effects my self-esteem. Walking upstairs in train stations for example. I look drunk or unfit... no one can see the illness so they make assumptions"* *"I at times worry and feel embarrassed by my mobility being affected so young "* *"Some people don't believe there is anything wrong because they can't see it"* *"I feel useless, and like I have no independence now feel useless most of the time due to pain"* *"Feel old before my time, unable to do the things I'd like to do"* *"I don't know how to manage or control my psoriatic arthritis and I struggle to look at the positives."* *"I feel like I have lost everything I held dear, working, traveling, drawing and going to see my favourite rugby team."* *"Psoriatic arthritis has really turned my day-to-day life, relationship and mental health upside down."*

	"It's hard to plan ahead as you just don't know how you are going to be feeling, so have had to cancel so many things as I was in a flare or just down to the pain and fatigue." *"I often think how to prepare financial, health and home. The future in unknown and a little concerning. It worries and saddens me."* *"It's getting worse so I don't know how long I'll be able to work & consequently I can't plan for anything."* *"I will have to choose things to do that are within my physical capabilities and comfort levels. I don't go on holiday abroad and even in the UK as I find beds make my condition worse."*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are currently a number of effective therapies for psoriatic arthritis, but given the long-term nature and potential adverse events or the often issue of treatments beginning to fail, alternate therapies are needed in order to provide patients with options and choice.
8. Is there an unmet need for patients with this condition?	It would be extremely useful for patients if a treatment could be found that provides skin clearance and stops progression of psoriatic arthritis at the same time. Reversal of joint damage would be valued too.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Although we have no patient or carer views from those who are actively on risankizumab. We can offer general thoughts, the mode of action is similar to other injectable same class treatments, and safety profiles look similar. Patients will expect that as an interleukin-23 inhibitor, this could provide a beneficial option, when other different targeted therapies have failed to provide the improvement needed to reverse psoriatic arthritis, therefore an option that may prevent permanent joint damage and disability. Reduction in psoriasis skin scores would be seen as an advantage in those patients who have extensive skin

	involvement. Therefore, and potential useful option for those where current therapies have failed to control both psoriasis and psoriatic arthritis.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There doesn't appear to be any obvious disadvantages to this technology versus those already in use, the safety profile appears to be similar to same class therapies.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that are obvious.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None**
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Often starts at a young age
- Life-long disabling condition, which flares and remits
- Not just a joint disease
- Treatments fail, therefore alternate options needed

- Causes depressive psychological impact

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient expert statement

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with active psoriatic arthritis or caring for a patient with active psoriatic arthritis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Wednesday 23 March**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with active psoriatic arthritis

Table 1 About you, active psoriatic arthritis, current treatments and equality

1. Your name	Helen McAteer
2. Are you (please tick all that apply)	☐ A patient with active psoriatic arthritis ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with active psoriatic arthritis ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Psoriasis Association
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with active psoriatic arthritis? **If you are a carer (for someone with active psoriatic arthritis) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for active psoriatic arthritis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for active psoriatic arthritis (for example, how risankizumab is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of risankizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does risankizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	

10. If there are disadvantages of risankizumab over current treatments on the NHS please describe these. For example, are there any risks with risankizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from risankizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering active psoriatic arthritis and risankizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement

Risankizumab for previously treated active psoriatic arthritis [ID1399]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with active psoriatic arthritis or caring for a patient with active psoriatic arthritis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Deadline for comments by **5pm** on **Wednesday 23 March**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with active psoriatic arthritis

Table 1 About you, active psoriatic arthritis, current treatments and equality

1. Your name	David Chandler
2. Are you (please tick all that apply)	☒ A patient with active psoriatic arthritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with active psoriatic arthritis ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Psoriasis and Psoriatic Arthritis Alliance
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the

	expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with active psoriatic arthritis? **If you are a carer (for someone with active psoriatic arthritis) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for active psoriatic arthritis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for active psoriatic arthritis (for example, how risankizumab is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of risankizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does risankizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	

10. If there are disadvantages of risankizumab over current treatments on the NHS please describe these. For example, are there any risks with risankizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from risankizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering active psoriatic arthritis and risankizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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
Authors	Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Kate Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Emma Simpson, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	21th April 2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/55/28.

Declared competing interests of the authors

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

Acknowledgements

We would like to thank Dr Lesley Kay, Newcastle upon Tyne Hospitals NHS Foundation Trust, for clinical advice relating to this project. We would also like to thank Geoff Holmes, ScHARR, for his input in writing the clarification letter, Professor Paul Tappenden, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

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.

This report should be referenced as follows:

Navega Biz A, Ren K. Simpson EL, Wong R. Risankizumab for previously treated active psoriatic arthritis: A Fast-Track Appraisal. School of Health and Related Research (ScHARR), 2022.

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.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

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

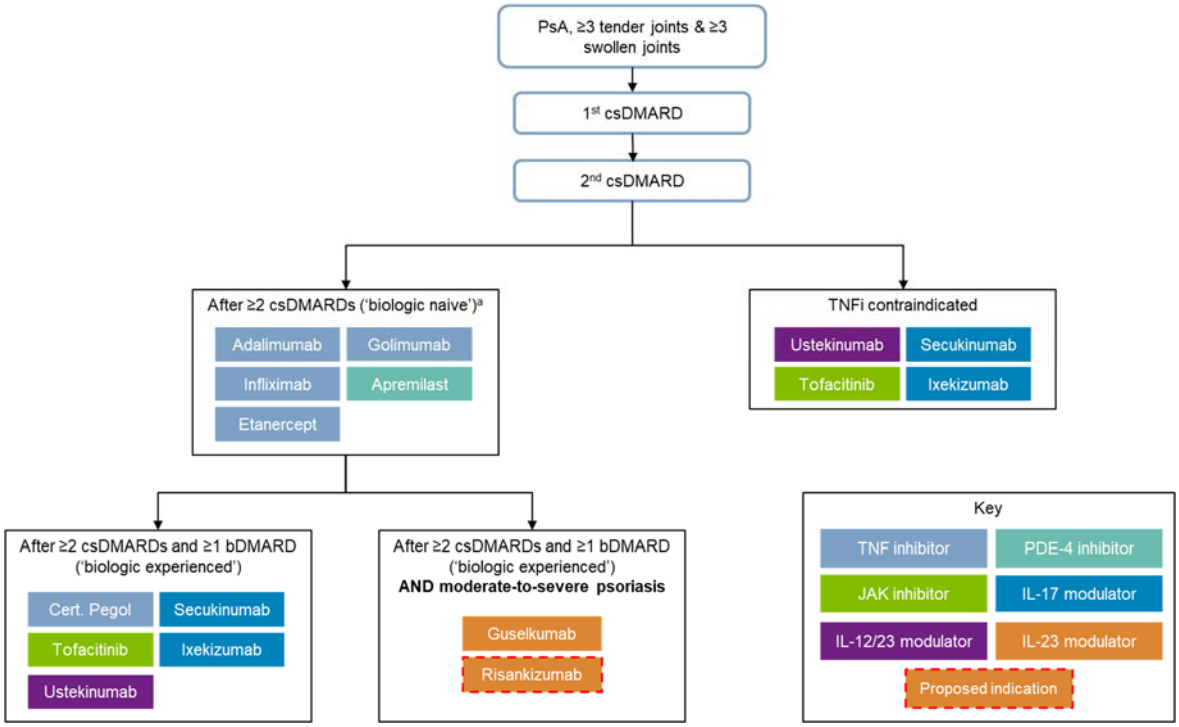
The description of the underlying health problem as presented in the company's submission (CS)[1] is considered appropriate and relevant to the decision problem. The decision problem addressed by the company is presented in Table 1 and Section B.1.1 of the CS. A summary of the points addressed, including 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 2 and Figure 3 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)

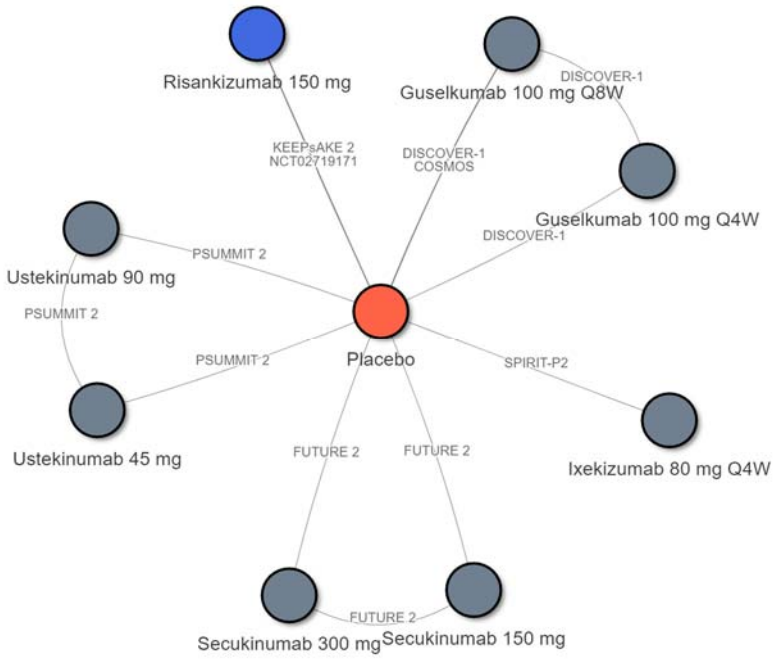
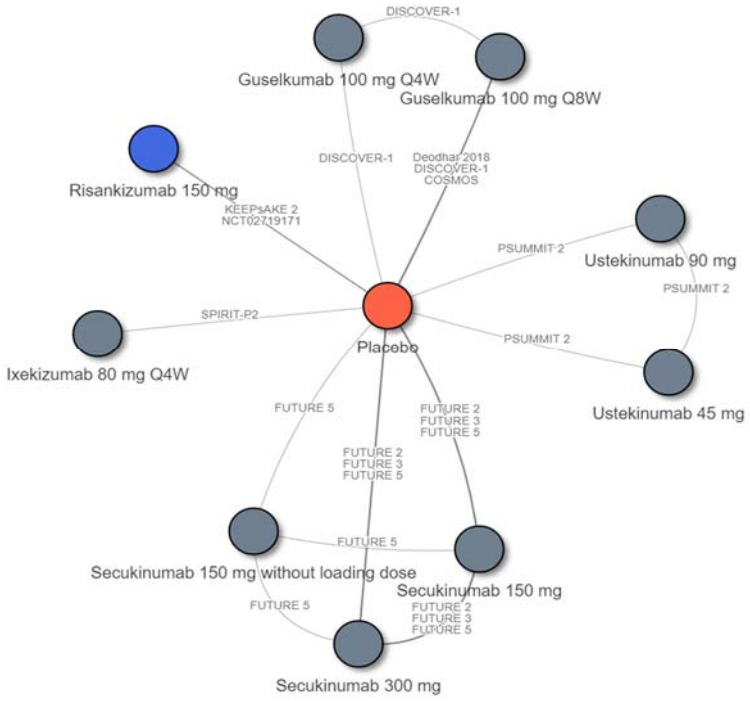


Figure 3: Network diagram for ACR among the BIO-IR population at Week 24 (reproduced from CS Appendix D)



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, Table 15), 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	-	-

5. REFERENCES

1. Abbvie. Risankizumab for previously treated active psoriatic arthritis [ID1399]. Company's evidence submission. North Chicago, U.S.A.; 2022.
2. European Medicines A. Human Medicine European Public Assessment Report: Skyrizi. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/skyrizi. [Last accessed: 01/11/2021]. 2019.
3. National Institute for H, Care E. TA711: Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta711 [Last accessed: 31/01/2022]. 2021
4. National Institute for H, Care E. Final scope for the appraisal of risankizumab for previously treated active psoriatic arthritis. Available from: https://www.nice.org.uk/guidance/gid-ta10819/documents/final-scope [Last accessed: 11/01/2021]. 2021.
5. National Institute for Health Care Excellence. NICE Fast track appraisals - guiding notes for ERGs v2. In. London; 2017.
6. Psoriasis and Psoriatic Arthritis Alliance. Risankizumab for previously treated active psoriatic arthritis [ID1399]. Patient organisation submission. In. St Albans, UK; 2022.
7. Psoriasis Association. Risankizumab for previously treated active psoriatic arthritis [ID1399]. Patient organisation submission. In. Northampton, UK.; 2022.
8. Tintle SJ, Gottlieb AB. Psoriatic arthritis for the dermatologist. *Dermatologic clinics* 2015;33:127–48.
9. Ogdie A, Langan S, Love T, Haynes K, Shin D, Seminara N, *et al.* Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology (Oxford)* 2013;52:568–75.
10. National Institute for H, Care E. TA199: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Available from: https://www.nice.org.uk/Guidance/TA199 [Last accessed: 31/01/2022]. 2010.
11. National Institute for H, Care E. TA220: Golimumab for the treatment of psoriatic arthritis. Available from: https://www.nice.org.uk/Guidance/TA220 [Last accessed: 31/01/2022]. 2011.
12. National Institute for H, Care E. TA445: Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta445 [Last accessed: 31/01/2022]. 2017.
13. National Institute for H, Care E. TA433: Apremilast for treating active psoriatic arthritis. Available from: https://www.nice.org.uk/guidance/ta433 [Last accessed: 31/01/2022]. 2017.
14. National Institute for H, Care E. TA537: Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta537 [Last accessed: 31/01/2022]. 2018.
15. National Institute for H, Care E. TA543: Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Available from: https://www.nice.org.uk/guidance/ta543 [Last accessed: 31/01/2022]. 2018.
16. National Institute for H, Care E. TA768: Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Availavle from: https://www.nice.org.uk/guidance/ta768 [Last accessed: 03/02/2022]. 2022.
17. National Institute for H, Care E. TA340: Ustekinumab for treating active psoriatic arthritis. Available from https://www.nice.org.uk/guidance/ta340 [Last accessed: 31/01/2022]. 2017.
18. AbbVie. AbbVie's SKYRIZI® Receives MHRA Approval For Use In Adults with Active Psoriatic Arthritis. Available from: https://news.cision.com/abbvie/r/abbvie-s-skyrizi-----risankizumab--receives-mhra-approval-for-use-in-adults-with-active-psoriatic-ar,c3459136. [Last accessed: 01/12/2021]. 2021
19. . Summary of product characteristics. Skyrizi 150 mg solution for injection in pre-filled pen. PLGB 41042/0045. London; 2021.
20. . Summary of product characteristics. Skyrizi 150 mg solution for injection in pre-filled syringe. PLGB 41042/0046. London; 2021.
21. Abbvie. Risankizumab for previously treated active psoriatic arthritis [ID1399]. Company's response to clarification questions from the ERG. In. North Chicago, U.S.A.; 2022.

22. European Medicines Agency. Guselkumab (Tremfya) summary of product characteristics. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tremfya. [Last accessed: 29/03/2022]. 2021
23. AbbVie. Data on File: PsA and Psoriasis Market Development - Germany. 2021.
24. AbbVie. Data on File: Clinical Study Report (CSR) for KEEPsAKE-2.
25. AbbVie. Data on File: Clinical Study Report (CSR) for NCT02719171.
26. Coates LC, Gossec L, Theander E, Bergmans P, Neuhold M, Karyekar CS, *et al.* Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS). *Annals of the Rheumatic Diseases* 2021.
27. Deodhar A, Helliwell PS, Boehncke W-H, Kollmeier AP, Hsia EC, Subramanian RA, *et al.* Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. *The Lancet* 2020;395:1115-25.
28. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, *et al.* Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *The Lancet* 2018;391:2213-24.
29. ClinicalTrials.gov website. U.S. National Library of Medicine. https://clinicaltrials.gov/ (Accessed 24/03/22).
30. Östör A, Van den Bosch F, Papp K, Asnal C, Blanco R, Aelion J, *et al.* Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. *Annals of the Rheumatic Diseases* 2021.
31. ClinicalTrials.gov. NCT02719171. BI 655066/ABBV-066/Risankizumab Compared to Placebo in Patients With Active Psoriatic Arthritis 2016. Available at: https://clinicaltrials.gov/show/NCT02719171. 30 November).
32. Abbvie. Risankizumab for previously treated active psoriatic arthritis [ID1399]. ERG report – factual accuracy check and confidential information check response. In. North Chicago, U.S.A.; 2022: 8.
33. . Non-Inferiority Clinical Trials to Establish Effectiveness. Guidance for Industry. Silver Spring, USA.: U.S. Department of Health and Human Services.; 2016.
34. National Institute for H, Care E. User guide for company evidence submission template: Fast track appraisal cost-comparison case. Available from: https://www.nice.org.uk/process/pmg32/resources/user-guide-for-the-cost-comparison-company-evidence-submission-template-pdf-72286772526277. [Last accessed: 12/11/2021]. 2017
35. British National F. Risankizumab Medicinal Forms. Available from: https://bnf.nice.org.uk/medicinal-forms/risankizumab.html. [Last accessed: 03/11/2021]. 2020
36. British National F. Guselkumab Medicinal Forms. Available from: https://bnf.nice.org.uk/medicinal-forms/guselkumab.html. [Last accessed: 03/11/2021]. 2020
37. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, *et al.* Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 2011;15:i–xxi, 1–329.
38. National Institute for H, Care E. TA511: Brodalumab for treating moderate to severe plaque psoriasis. Available from: https://www.nice.org.uk/guidance/ta511 [Last accessed: 03/02/2022]. 2018
39. Curtis LA, Burns A. Unit Costs of Health & Social Care 2020. Available at: https://www.pssru.ac.uk/pub/uc/uc2015/full.pdf: PSSRU, University of Kent; 2020.
40. Nhs. National Schedule of Reference Costs: The Main Schedule, in NHS Reference Costs 2019–2020. Available at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ [last accessed 31/01/2022].
41. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, *et al.* Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017;389:2317-27.

42. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, *et al.* Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386:1137-46.
43. Nash P, Mease PJ, McInnes IB, Rahman P, Ritchlin CT, Blanco R, *et al.* Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: Results from a randomized, placebo-controlled trial (FUTURE 3). *Arthritis Research and Therapy* 2018;20 (1) (no pagination).
44. Mease P, van der Heijde D, Landewe R, Mpofu S, Rahman P, Tahir H, *et al.* Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Annals of the Rheumatic Diseases* 2018;77:890-7.
45. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, *et al.* Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Annals of the Rheumatic Diseases* 2014;73:990-9.
46. Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, *et al.* Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Annals of the Rheumatic Diseases* 2017;76:1550-8.
47. Kivitz AJ, Nash P, Tahir H, Everding A, Mann H, Kaszuba A, *et al.* Efficacy and Safety of Subcutaneous Secukinumab 150 mg with or Without Loading Regimen in Psoriatic Arthritis: Results from the FUTURE 4 Study. *Rheumatology & Therapy* 2019;21:21.
48. Coates LC, Gossec L, Theander E, Bergmans P, Neuhold M, Karyekar CS, *et al.* Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIB, randomised, controlled study (COSMOS). *Ann Rheum Dis* 2021.
49. Register ECT. European Medicines Agency. https://www.clinicaltrialsregister.eu/ (Accessed 25/03/2022).

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.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Risankizumab for previously treated active psoriatic arthritis [ID1399]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 3 May 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Factual inaccuracies

Issue 1 Details of the technology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The description of the marketing authorisation for the intervention in Section 2.2 on page 10 of the ERG Report	Please could the sentence be amended to: "The marketing authorisation issued by the European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) for risankizumab states..."	To comprehensively describe the licence status of risankizumab	The amendment has been made as requested by the company. The ERG has also included references for the MHRA documents in page 11 and the abbreviation definition in page 5 of the report.
The 75mg/0.83ml solution for injection in a pre-filled syringe or pen is described on pages 11 and 32 of the ERG Report	Please remove reference to the pre-filled pens or syringes with 75mg/0.83ml solution for injection	This dose is no longer available; risankizumab is only available as 150mg/1ml solution for injection in a pre-filled syringe or pen.	The text on pages 11 and 32 of the ERG Report has been amended as requested.

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In a number of places in the ERG Report, guselkumab is misspelt as 'guselkizumab'	Please correct the spelling here	To avoid any misinterpretation of the relevant comparator	Apologies for the typos, the spelling for guselkumab has been amended accordingly.
On page 31 of the ERG Report, there is reference to a 'DISCOVERY' trial	This should be corrected to 'DISCOVER-1'	To remove confusion with regard to the relevant trials	Apologies for the typo, the name of the trial has been amended as requested.

On page 35 of the ERG Report, the word 'experiment' is used in place of 'experience'	The sentence should read: "The ERG's clinical advisor stated that patients receiving risankizumab and guselkumab usually experience similar AEs"	Typographical error	The text has been amended as suggested by the company.

Issue 3 ITC results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 1 of the ERG report, the results for ACR and HAQ-DI CFB for guselkumab are incorrect.	A corrected Table 1 has been provided in Appendix A. On page 20 of the ERG report the text should therefore be updated to read: "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 Company apologises for these errors. 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. Table 1 results have been updated using the random-effects model with placebo response adjustment. HAQ-DI CFB for guselkumab was reported incorrectly in the company submission.	Table 1 has been updated as suggested. Text on page 20 has been amended accordingly.
In Table 2 of the ERG report, the results for PASI, HAQ-DI CFB and PsARC response are incorrect.	A corrected Table 2 has been provided in Appendix A. On page 20 of the ERG report the text should therefore be updated to read: "The results at Week 16 were slightly further away from 1.0 for the OR measure (favouring risankizumab for PASI outcomes and favouring	The Company apologises for these errors in the company submission. PASI response rates were reported incorrectly and were flipped for risankizumab and guselkumab. HAQ-DI CFB MD was reported for the opposite comparison (i.e.,	Table 2 is updated as suggested. Text on page 20 (now page 21) has been amended accordingly.

	guselkumab for ACR outcomes and HAQ-DI change from baseline)." Note, the error in the PsARC response rate impacts the results of the scenario where response rate in the cost-minimisation model was based on Week 16 PsARC response rate from the NMA and assessment at 16 weeks. A corrected Table 9 has been provided in Appendix A. On page 35 of the ERG report, the text should be updated to reflect the smaller difference in cost savings compared with the base case: "The estimated cost savings are reduced if the analysis adopts the PsARC response rate for the shorter trial treatment period (from the NMA for the PsARC 16-weeks parameter)."	guselkumab versus risankizumab) and the PsARC response rate for risankizumab was reported incorrectly as the placebo response rate.	The ERG notes that the corrected estimate for PsARC response at 16 weeks, is much closer to the estimate at 24 weeks ([redacted] and [redacted], respectively), and that the cost-comparison analysis provided by the company uses these estimates with rounded to 2 decimal places, which virtually ends up using the same response rate ([redacted]) applied at different timepoints. Nonetheless, since the impact of including the third decimal place on the cost difference estimates between Risankizumab and guselkumab is small and does not change the overall conclusions of the report, the ERG decided not to change the results of all analyses from the original ERG report, with exception of scenario SA6. The ERG updated the results in Tables 10 and accompanying text accordingly to reflect the updated scenario analysis SA6, and the value reported in Table 8 and text on

			section 4.2.2 of the ERG report accordingly.
In Table 2 of the ERG Report, the column headings for HAQ-DI CFB appear to be incorrect	A corrected Table 2 has been provided in Appendix A.	To avoid misinterpretation of the ITC results	Table 2 has been updated as suggested.
In Table 3 of the ERG Report, the results appear to be incorrect	A corrected Table 3 has been provided in Appendix A.	Results in the company submission were provided using an older version of the safety NMA which was updated in January 2022 to incorporate additional published data. The company apologises for this error and have updated the results.	This is new evidence. It is not clear what changes were involved in this update and the company has not provided enough information to allow for the ERG to check the accuracy of the updated results. Therefore, Table 3 has not been amended.
In Table 11 of the ERG Report, the trials included in the Week 24 safety NMAs are not fully reported	The company would suggest splitting the right-most column in Table 11 into two columns for AEs and SAES. Studies reporting any AE among the BIO-IR population at Week 24 were PSUMMIT-2, SPIRIT-P2, KEEPsAKE-2, ASTREAEA and COSMOS, as per Figure 19 of the company submission appendices. Studies reporting any SAE among the BIO-IR population at Week 24 were PSUMMIT-2, SPIRIT-P2, KEEPsAKE-2, ASTREAEA, COSMOS, DISCOVER-1 and Deodhar 2018, as per Figure 20 of the company submission appendices	To avoid misinterpretation of which trials were included in the Week 24 safety NMAs	Table 11 has been updated as suggested.

Issue 4 Evidence sources used to inform the cost-comparison model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 8 of the ERG Report, the source for the discontinuation rate value used in scenario analysis (18.7%) is reported as TA711	This is incorrect; the value was taken from TA511	Typographical error	This was a typo; the text has been amended as requested.

Appendix A

Table 1: Summary of company's ITC analyses for efficacy outcomes of risankizumab 150mg versus guselkumab 100mg Q8W at Week 24 (corrected results)

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 (corrected results)

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)		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 (corrected results)

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.*

Table 4: 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