NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from AbbVie

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Psoriasis Association
   b. Psoriasis and Psoriatic Arthritis Alliance
   c. British Society for Rheumatology

4. **Evidence Review Group report** prepared by Liverpool Reviews & Implementation Group (LRiG)

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from from AbbVie

7. **Technical engagement response & expert statement from experts:**
   a. David Chandler, patient expert nominated by Psoriasis and Psoriatic Arthritis Alliance
   b. Dr James Galloway, clinical expert nominated by AbbVie

8. **Technical engagement response from consultees and commentators:**
   a. British Society for Rheumatology (Royal College of Physicians endorses the response from BSR)
   b. Janssen

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews & Implementation Group (LRiG)

10. **Request from NICE** to Centre for Reviews and Dissemination and Centre for Health Economics, University of York

11. **Response to NICE** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York

12. **Request to the company for further information** from NICE

13. **Response from the company to request for further information** from AbbVie

14. **Evidence Review Group critique of company response** prepared by Liverpool Reviews & Implementation Group (LRiG)

15. **Request to the company for further information** from NICE

16. **Response from the company to request for further information** from AbbVie

17. **ERG addendum following submission of corrected model** prepared by Liverpool Reviews & Implementation Group (LRiG)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Document B

Company evidence submission

9th December 2020

File name	Version	Contains confidential information	Date
2. ID2690_Upadacitinib_PsA_Document B_[REDACTED]_9Dec20	**Final**	**No**	**9/12/20**

Contents

Tables and figures

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

B.1.1. Decision problem

The anticipated marketing authorisation for upadacitinib 15 mg (RINVOQ™) is '[redacted].' Based on the final scope issued by the National Institute for Health and Care Excellence (NICE), these active PsA patients can be separated into four subpopulations:

1. People whose disease has not responded adequately to one conventional synthetic disease-modifying anti-rheumatic drug (csDMARD)
2. People whose disease has not responded adequately to at least two csDMARDs
3. People whose disease has not responded adequately to csDMARDs and one or more tumour necrosis factor alpha (TNFα) inhibitors
4. People in whom TNFα inhibitors are contraindicated or not tolerated

This submission focuses on part of the technology's anticipated marketing authorisation: patients who have previously been treated with ≥ 2 DMARDs (i.e. Subpopulations 2, 3 and 4 above). This aligns with the recommended use and positioning of advanced therapies, including biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) from recent NICE technology appraisals in patients with PsA (e.g. tofacitinib [TA480][1], ustekinumab [TA340][2], and ixekizumab [TA537][3]). Additionally, this aligns with expert clinical opinion sought by AbbVie at an advisory board.[4]

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 a previous DMARD therapy, or for whom DMARDs are not tolerated or contraindicated	Adults with active PsA whose disease has not responded adequately to a previous DMARD therapy, or for whom DMARDs are not tolerated or contraindicated	N/A
Intervention	Upadacitinib, alone or in combination with non-biological DMARDs	Upadacitinib, alone or in combination with non-biological DMARDs	N/A
Comparator(s)	For people whose disease has not responded adequately to one csDMARD: • csDMARDs For people whose disease has not responded adequately to ≥ 2 csDMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab) • Apremilast • Tofacitinib For those whose disease has not responded adequately to csDMARDs and one or more TNF-alpha inhibitors: • Ustekinumab • Secukinumab • Certolizumab pegol • Tofacitinib • Ixekizumab • Best supportive care For people in whom TNF-alpha inhibitors are contraindicated or not tolerated: • Ustekinumab	For people whose disease has not responded adequately to ≥ 2 csDMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab) • Apremilast • Tofacitinib For those whose disease has not responded adequately to csDMARDs and one or more TNF-alpha inhibitors: • Ustekinumab • Secukinumab • Tofacitinib • Ixekizumab • Best supportive care For people in whom TNF-alpha inhibitors are contraindicated or not tolerated: • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Best supportive care	This submission focuses on patients who have previously been treated with ≥ 2 DMARDs to align with the subpopulations that have received positive recommendations from NICE in previous technology appraisals, and as the most appropriate place in therapy for upadacitinib to be used, as validated by clinical experts.[4] Note that certolizumab pegol has been excluded from sub-population 3, as the RAPID-PsA trial was the only trial that excluded patients with primary failure of a previous anti-TNF (no response within the first 12 weeks), consistent

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Secukinumab • Ixekizumab • Tofacitinib • Best supportive care		with the recent NICE technology appraisals for secukinumab and certolizumab pegol and tofacitinib.[1, 5]
Outcomes	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression • Periarticular disease (for example enthesitis, tendonitis, dactylitis) • Axial outcomes (for example, spinal pain and fatigue) • Mortality • Adverse effects of treatment • Health-related quality of life	• Disease activity: ACR20/50/70, PASI 50/75/90, PsARC, MDA, sIGA, Modified PsA, SHS • Functional capacity: HAQ-DI, HAQ-DI conditional on PsARC response status • Disease progression: change from baseline in disease activity measures • Periarticular disease: enthesitis resolution (LEI), dactylitis resolution (LDI) • Axial outcomes: ASDAS and BASDAI • Mortality • Adverse effects of treatment • Health-related quality of life: EQ-5D-5L, SF-36 PCS, FACIT-F, SAPS	N/A
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	The reference case has been adhered to (Section B.3.2)	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 or comparator technologies and subsequent treatments will be taken into account. For the comparators the availability and cost of biosimilars should be taken into consideration.		
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	• Mechanism of action or number of previous treatments • Presence or severity of concomitant psoriasis (i.e. PASI75 in patients with ≥ 3% BSA-Ps [Section B.2.6])	The subgroups included reflect those in which there is sufficient evidence from the clinical trial programme to provide meaningful conclusions.
Special considerations including issues related to equity or equality	No equality issues are anticipated if upadacitinib is recommended for use by NICE	No equality issues are anticipated if upadacitinib is recommended for use by NICE	N/A

Key: ACR, American College of Rheumatology; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drug; BSA-Ps, body surface area psoriasis; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CSRs, clinical study reports; FACIT-F, Functional Assessment of Chronic Illness Therapy- Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; JAK, Janus kinase; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; PsARC, Modified Psoriatic Arthritis Response Criteria; SAPS, Self-Assessment of Psoriasis Symptoms; SF-36, Short Form 36 Physical Component Summary; SHS, Sharp van der Heijde Score; sIGA, Static Investigator Global Assessment; TNF, tumour necrosis factor.

B.1.2. Description of the technology being appraised

Upadacitinib targets the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway to reduce inflammation and modify the clinical course of PsA. A summary description of upadacitinib, including details of its mechanism of action and marketing authorisation, is provided in Table 2. A draft summary of product characteristics is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Upadacitinib (RINVOQ™)
Mechanism of action	Upadacitinib is an orally available selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.
Marketing authorisation status	An application for upadacitinib in PsA was filed to the EMA on 1 June 2020. CHMP opinion is expected in [redacted] with marketing authorisation expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Upadacitinib is currently indicated for: • 'The treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate.' The anticipated indication of interest within this submission is for: • '[redacted]
Method of administration and dosage	Upadacitinib is administered as a once-daily, oral, 15 mg dose, and can be given as monotherapy or in combination with methotrexate.
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: [redacted]
Patient access scheme (if applicable)	For the existing NICE-approved indication for upadacitinib in rheumatoid arthritis the company has agreed a simple discount patient access scheme with the Department of Health. This provides upadacitinib at a price of [redacted]. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.
Key: CHMP, Committee for Medicinal Products for Human Use; DMARD, disease-modifying anti-rheumatic drug; EMA, European Medicines Agency; JAK, Janus kinase; PsA, psoriatic arthritis; SmPC, summary of product characteristics; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase. **Source:** SmPC.[6]	

B.1.2.1 Changes in service provision and management

As an orally administered treatment, upadacitinib 15 mg provides a convenient once daily option for patients who may otherwise receive an alternative 'advanced therapy', which includes tsDMARDs and bDMARDs. The majority of bDMARDs are subcutaneously administered and are associated with additional health service needs. These service needs typically include patient training in self-injection techniques and approval from the relevant healthcare professional that their technique is appropriate.[7] Therefore, upadacitinib 15 mg is likely to have a positive impact on service provision compared with the majority of advanced treatments currently recommended by NICE for PsA. In addition, in light of the ongoing COVID-19 pandemic, the availability of an additional oral treatment option may provide more service provision and management benefits, as further described in Section B.1.3.5.

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

- PsA is a heterogeneous disease with a highly variable clinical presentation and hallmark features including coexisting progression of joint disease and psoriasis. Other distinguishing factors include asymmetrical axial involvement, peri-articular joint involvement, and extra-articular manifestations
- It is the second most common inflammatory joint disease (after rheumatoid arthritis),[8] and predominately impacts adults of working age[9]
- Clinically active PsA leads to progressively more functional disability over time, with reports of more than half of patients having ≥ 5 deformed joints at 10 years follow up.[10] Compared with the general population, PsA patients experience decreased physical function, social isolation, reduced work productivity, and lower life satisfaction[11]
- There is no cure for PsA, therefore the goal of treatment is to minimise disease activity, prevent joint damage, stop swelling, reduce pain and improve health-related quality of life (HRQL)[12] Minimal disease activity (MDA) is an outcome measure used in clinical trials of advanced therapy for PsA to define patients whose disease state meets pre-defined, established criteria for 'minimal activity'.[13] As a composite measure, MDA takes into account multiple domains of this heterogeneous disease, such as physical assessments of joint and skin involvement, and patient reported pain and health disability[14, 15]
- Patients with severe disease symptoms are treated with csDMARDs, although csDMARDs are not always associated with disease-modifying effects. NICE recommends the use of bDMARDs when the disease has not responded to ≥ 2 csDMARDs, with the choice of bDMARD driven by the disease domain with the most activity
- Few treatment options are able to offer meaningful improvement across the many joint and skin manifestations for patients, without sacrificing key domains like axial disease, enthesitis, or extra-articular manifestations. Owing to the chronic and progressive nature of disease, most patients with PsA are expected to become nonresponsive or intolerant to treatment over time.[16] As such, there is a need for treatment options to add to the clinician's armamentarium to manage PsA over patients' lifetimes. In particular, fast-acting treatment options with innovative mechanisms of action are required to address the heterogeneous nature of the disease and the multifactorial disease burden associated with PsA.
- Upadacitinib offers a well-characterised, well-tolerated, and orally available treatment option, that may be given as a monotherapy or in combination with methotrexate, to inhibit structural damage and minimise disease activity in PsA. It provides a beneficial treatment option in the ≥ 2 csDMARD setting with demonstrable improvements in disease activity scores, physical functioning and pain compared with placebo, and broadly equivalent efficacy compared with the current standard of care

B.1.3.1 Disease overview

PsA is a chronic and progressive inflammatory disease associated with severe detriment to physical function and HRQL. As a subtype of spondyloarthritis, its

manifestation is linked to an interaction between genetic, environmental, and immune mechanisms. The genetic aspect is often associated with genes encoding the Class I major histocompatibility complex (MHC).[17] In individuals with genetic susceptibility to PsA, environmental factors such as infections, trauma, stress, obesity and smoking can trigger autoimmune responses.

Once the immune system is activated, dendritic cells, mast cells and macrophages produce proinflammatory cytokines, including interleukins (ILs) and TNFα, and cause the aberrant production of osteolytic factors in synovial joints.[18] This inflammatory cell signalling results in bone erosion and cartilage destruction. The JAK family (JAK1, JAK2, JAK3, and TYK2) are tyrosine kinases that control the activation of signalling cascades for many cytokines in the pathogenic pathway of PsA.[19]

PsA is a heterogeneous disease with a highly variable clinical presentation. The hallmark feature is the coexisting progression of joint disease and psoriasis, with the exact pathogenesis varying between the anatomical sites affected. PsA affects up to 30% of patients with psoriasis, and the development of joint involvement usually follows psoriasis by approximately 10 years – although in 15% of cases, arthritis and psoriasis occur at the same time, or arthritis precedes psoriasis.[17] Factors that distinguish PsA from other spondyloarthropathies include asymmetrical distribution of axial involvement, peri-articular joint involvement and extra-articular manifestations.[10] Axial involvement, where inflammation progresses to the spine and causes chronic back pain, is present in 25% to 70% of PsA patients and indicates more severe disease with potentially significant effects on mobility.[20, 21] The presentation of peri- and extra-articular manifestations in PsA is dependent on the activity and severity of disease, and may include:

- Dactylitis: inflammation of the entire finger or toe, which is present in almost half of PsA patients[22]
- Enthesitis: inflammation of the sites where tendons or ligaments insert into the bone, which is present in over a third of PsA patients[23]
- Psoriasis: inflammation of the skin presenting as small, red, flaky patches and often preceding joint inflammation[17]

- Nail disease: presenting as pitting and depression of the nail plate surface, present in two-thirds of PsA patients[24]

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.[16] The Classification of Psoriatic Arthritis (CASPAR) criteria bases classification on clinical presentation, history, and radiographic and laboratory evidence, and has been identified as a useful tool for diagnosing PsA given its high sensitivity and specificity.[25, 26] Several other tools have been developed to measure disease activity and patient reported outcomes in PsA, and are described in detail in Appendix L.

Assessment of the severity of disease is informed by the number of joints affected and patient's responsiveness to treatment. The criteria commonly used to define active disease in trials of PsA includes:

- Peripheral arthritis with ≥3 tender joints and ≥3 swollen joints, and
- PsA that has not responded to adequate trials of at least two csDMARDs (see Section B.1.3.4)

Following diagnosis of PsA, constant management is required to improve HRQL in this lifelong, relapsing and remitting disease.

B.1.3.2 Epidemiology

PsA is the second most common inflammatory joint disease after rheumatoid arthritis.[8] It affects women and men equally and has a peak onset between the ages of 30 and 50, meaning it predominately impacts adults of working age.[9]

In a 2013 study of 4.8 million UK patients aged between 19 and 90 years from The Health Improvement Network, 9,045 patients had a diagnostic code for PsA which indicated an overall prevalence of 0.19%.[27] When this estimate is applied to the entire adult UK population, it implies a total of 123,006 PsA cases in the UK.[28]

Studies focusing on mortality rates among PsA patients are conflicting, either showing an increased risk of mortality or showing no difference in mortality, compared with the general population. An increased risk of mortality has been linked

to more severe forms of PsA.[29-31] If left untreated, patients with PsA have a reduced life expectancy.[32, 33]

B.1.3.3 Burden of disease

PsA is a severe disease that leads to progressively more functional disability over time, with reports of more than half of patients having ≥ 5 deformed joints at 10 years follow up.[10] Patients with active PsA may experience swelling and pain in multiple peripheral joints, fatigue, substantial skin and nail involvement, as well as extra-articular manifestations such as enthesitis and dactylitis.[17, 34-36] The multiple manifestations of PsA cause a combination of physical and psychological symptoms that contribute to significant reductions in HRQL and an inability to carry out daily activities.

Compared with the general population, PsA patients experience decreased physical function, social isolation, reduced work productivity, and lower life satisfaction.[11] Additionally, they are more likely to experience comorbidities such as cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, inflammatory bowel disease, osteoporosis, fibromyalgia,[37] anxiety and depression.[38] Among the multiple manifestations of PsA, joint inflammation is the most common and has the most significant role in the burden of disease.

Inflammation of the joint causes deformation leading to pain and limited physical movement. These effects are detrimental to several aspects of a patient's life, as the resulting functional impairment limits the ability to carry out normal daily functions.[39] In a global online survey of 1,286 patients with PsA, 97% of patients were reported as experiencing musculoskeletal symptoms in the past year, with the most frequently reported symptoms being joint pain (79%) and joint tenderness/swelling (60%).[40] Physical function generally worsens with disease progression, which is characterised by an increase in the number of inflamed and/or deformed joints.[41] Back pain caused by axial involvement in PsA, as with back pain in the general population, affects work productivity and social and mental aspects of HRQL.[20] The role of extra-articular joint involvement, such as enthesitis and dactylitis, further compounds the physical dysfunction and discomfort experienced by PsA patients.[41]

Pain and tenderness in joints and skin psoriasis are associated with fatigue, a common symptom of PsA that is ranked second in patient-perceived importance, after pain.[42] There are several contributors to the fatigue experienced by PsA patients; namely, the negative impact of joint and skin symptoms on sleep, carrying out daily activities, and psychological wellbeing.

Patients with PsA are at an increased risk of developing psychological comorbidities such as depression and anxiety, with increasing risk associated with greater PsA disease activity.[43] A major driver of the psychological burden experienced by PsA patients is the appearance of skin manifestations, which are associated with negative impacts on social interactions.[44] The impact of joint manifestations on the ability to work further contributes to the psychological conditions patients experience. In a survey of 1,286 responses on the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire from 2 November 2017 to 12 March 2018, the majority of patients (81%) reported an impact of PsA on their ability to work, with 42% reporting decreased productivity.[40]

The economic burden of PsA is significant given that patients require careful and timely disease management, resulting in high healthcare resource use and direct costs. Increased functional impairment, disease severity and disease duration are associated with higher direct costs.[45] In a study of UK PsA patients (n = 101), the total annual healthcare resource costs per patient (excluding medication costs) ranged between £174 and £8,554 with a mean of £1,586.[46] Further cost increases were associated with patient Health Assessment Questionnaire Disability Index (HAQ-DI) scores 2–3 and with disease duration greater than 10 years.

Indirect costs associated with PsA account for 52% to 72% of the total costs, and largely reflect the extent that functional impairment and mental burden of PsA has on patients' ability to work and remain in employment.[41]

B.1.3.4 Aims of treatment and pathway of care

Owing to heterogeneity in the presentation of PsA, treatment varies substantially by patient. It is common for PsA patients to suffer from multiple manifestations, and the manifestation that has the highest disease activity tends to drive the treatment

choice.[47] Whereas the former treatment paradigm involved a simple trade-off between joint and skin domains to determine specialist involvement (rheumatologist or dermatologist), the increasing availability of new treatments and evolution towards greater co-management allows clinicians to consider a more nuanced treatment paradigm. As such, consideration of disease activity in six domains, including peripheral arthritis, axial disease, enthesitis, skin manifestations, nail psoriasis and dactylitis, drives treatment choices (with nail psoriasis and dactylitis having a lower impact on treatment selection).[48] Given that joint inflammation plays the most significant role in the burden of disease of PsA, it is a major driver of treatment choice.

There is no cure for PsA, therefore the goal of treatment is to minimise disease activity, prevent joint damage, stop swelling, reduce pain and improve HRQL.[12]

Minimal disease activity (MDA) is an outcome measure used in clinical trials of advanced therapies for PsA, and is recognised as an important measure of success for the treatment of PsA. MDA defines patients whose disease state meets pre-defined, established criteria for ‘minimal activity’ or remission.[13] As a composite measure, MDA takes into account multiple domains of this heterogeneous disease, such physical assessments of joint and skin involvement, and patient reported pain and health disability.

A patient is classified as in MDA when five of the following seven criteria are met:[49, 50]

- Tender joint count 68 (TJC68) ≤ 1
- Swollen joint count 66 (SJC66) ≤ 1
- Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area psoriasis (BSA-Ps) ≤ 3%
- Patient's assessment of pain ≤ 1.5 (0–10 numeric rating scale [NRS])
- Patient's Global Assessment of disease activity ≤ 2 (0–10 NRS)
- HAQ-DI score ≤ 0.5
- Leeds Enthesitis Index (LEI) ≤ 1

Sustained achievement of MDA in real-world patients is associated with improved prognosis in terms of joint damage progression.[14, 15]

PsA treatment is often initiated using non-steroidal anti-inflammatory drugs (NSAIDs). Patients with more severe disease symptoms, and/or persistent arthritis not responding to NSAIDs, are treated with csDMARDs such as methotrexate. Insights gathered from clinicians indicate that whilst the efficacy of csDMARDs is well-established in patients with rheumatoid arthritis, csDMARDs are not typically associated with disease-modifying effects in patients with PsA.[4] The introduction of tsDMARDs/bDMARDs (‘advanced therapies’) into the PsA treatment landscape offers the possibility of controlling multiple aspects of the disease using a single drug, and minimises the need for concomitant therapies.[51] Nonetheless, over time patients may become unresponsive or intolerant to treatment with their initial bDMARD.[16] As such, patients require additional therapeutic options with different mechanisms of action to manage PsA over their lifetime.[4]

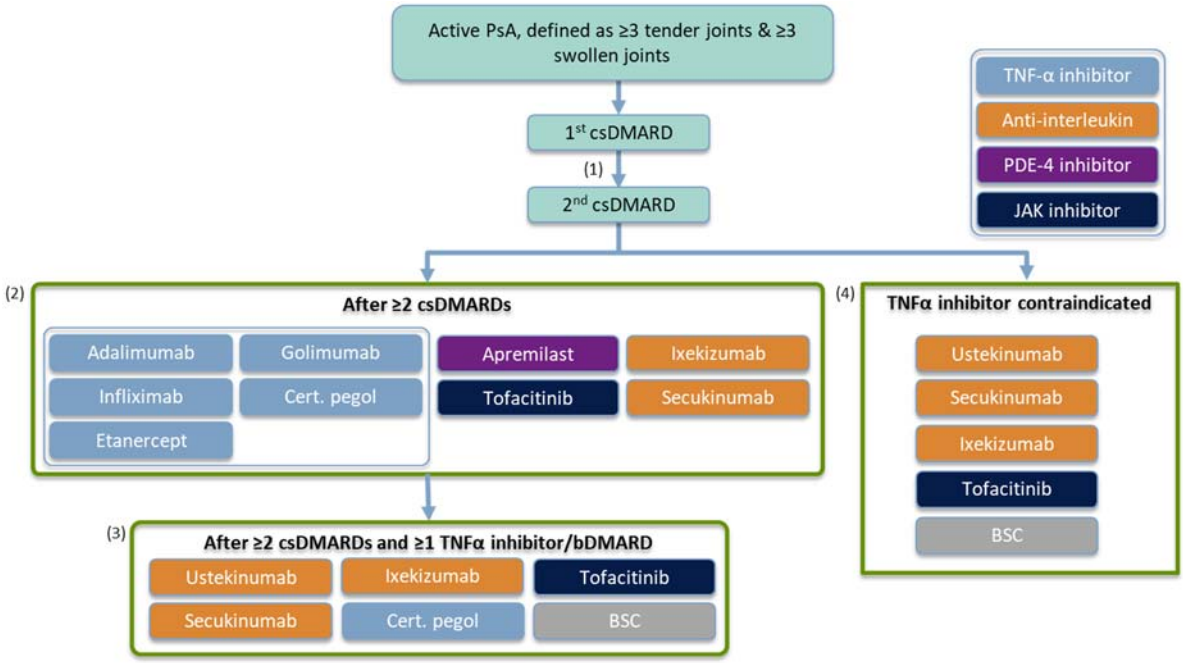
The most recently updated clinical guidelines for PsA were published in 2020 by the European League Against Rheumatism (EULAR).[52] The recommendations for the pharmacological management of PsA include NSAIDs for initial therapy, or csDMARDs (such as methotrexate) in patients with polyarthritis and poor prognostic factors. If treatment goals are not met using csDMARDs, bDMARDs should be initiated, with the choice of bDMARD determined based on the domain with the highest disease activity. The 2012 British Society for Rheumatology/British Health

Professionals in Rheumatology (BSR/BHPR) guidelines for PsA comment specifically on the use of bDMARDs and are broadly similar in terms of patient eligibility.[53]

Of patients who have previously been treated with ≥ 2 csDMARDs who go on to receive treatment with TNFα inhibitors, a considerable proportion experience limited efficacy and high treatment discontinuation rates due to tolerability issues.[54] This highlights a need for bDMARDs with a different mechanism of action than TNFα inhibitors, to optimise efficacy and tolerability in this patient population.

Given the chronic and progressive nature of PsA, disease activity is closely monitored, and patients exhibiting progression require immediate treatment escalation to avoid permanent structural joint damage. The Psoriatic Arthritis Response Criteria (PsARC) is the only measure developed specifically for patients with PsA and is the core response criterion used by UK clinicians. NICE recommends the use of bDMARDs in adults with active and progressive PsA when they have peripheral arthritis with ≥ 3 tender and ≥ 3 swollen joints, and when the disease has not responded to ≥ 2 csDMARDs, alone or in combination.[55, 56] The advanced therapies (i.e. tsDMARDs and bDMARDs) recommended in the NICE treatment pathway for PsA are summarised in Figure 1.

Figure 1: NICE treatment pathway for psoriatic arthritis



Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; cert. pegol, certolizumab pegol; JAK, Janus kinase; PDE-4, phosphodiesterase type 4; PsA, psoriatic arthritis; TNF, tumour necrosis factor.
Note: The bracketed numbers represent the NICE treatment pathway positions outlined in the scope and relate to the subpopulations discussed in Section B.1.1. Note that position (1) is not included in this diagram.

Of the estimated 123,006 adults diagnosed with PsA in the UK, market share estimates indicate that 50% of patients receive csDMARDs, 34% receive advanced therapy and 16% receive 'other' treatments (including NSAIDs, topical treatments and phototherapy).[28]

B.1.3.5 Unmet medical need

Due to the heterogeneous nature of the disease, treatment of PsA remains a challenge and treatment goals remain unmet, with many patients experiencing residual pain and functional impairment with current treatment options.[57, 58] Despite the beneficial results achieved with currently available advanced therapies, approximately 40% of patients do not experience at least a 20% improvement in American College of Rheumatology (ACR) scores (i.e. attainment of an ACR20 response),[59-66] and more than half of patients discontinue therapy due to safety concerns or lack/loss of efficacy.[22, 67]

Of the bDMARDs currently available to patients, most require an injectable mode of administration. This is considerably burdensome to patients as self-injection is associated with additional anxiety and pain compared with oral administration.[68] Feedback from a UK advisory board input indicates that there is a clinician preference for oral administration, given it allows for faster prescription, and therefore faster treatment response – which is essential for optimising the prevention of irreversible joint damage.[4]

Consideration of patient preferences is important for optimising treatment adherence in PsA, with patients expressing a strong preference for oral formulations to maximise treatment persistence.[4, 69, 70] Comparatively, treatment persistence on TNFα inhibitors is generally low, with approximately 30% to 50% of patients discontinuing their therapy during the first year of treatment.[71-74]

The availability of oral treatments for PsA represents an important opportunity to address additional unmet needs caused by the current COVID-19 pandemic.

Specifically, oral therapies can reduce the need for hospital or nurse visits (and thus infection risk) due to reduced monitoring and injection training requirements. Furthermore, the BSR COVID-19 guidance specifically recommends initiating vulnerable patients on JAK inhibitors, given they have a shorter half-life and a rapid wash out compared to other biologics.[75]

Even though the understanding of PsA pathophysiology has improved, with more targeted treatments available in clinical practice, there is still an unmet need for additional therapies that provide:[76]

- Improved efficacy, particularly for joint outcomes
- Greater achievement of MDA and remission
- A favourable safety profile that is sustained long-term
- Greater patient convenience

Owing to the chronic and progressive nature of disease, most patients with PsA are expected to become nonresponsive or intolerant to treatment over time.[16] As such, there is a need for treatment options to add to the clinician's armamentarium to manage PsA over patients' lifetimes. In particular, fast-acting treatment options with innovative mechanisms of action are required to address the heterogeneous nature of the disease and the multifactorial disease burden associated with PsA. Few treatment options are able to offer meaningful improvement across the many joint and skin manifestations for patients, without sacrificing on key domains like axial disease, enthesitis, or extra-articular manifestations.

Patients with inadequate responses to ≥ 2 csDMARDs currently have several TNFα or IL inhibitor options, one JAK inhibitor and one phosphodiesterase Type 4 (PDE-4) inhibitor. In a complex disease such as PsA, there may be multiple dysregulated cytokines, and blockading one cytokine alone may not inhibit all pathogenic pathways. Unlike individual cytokine inhibitors, JAK inhibitors can partially inhibit downstream signalling produced by more than one cytokine, therefore maximising the potential to alter the disease course.

The only other JAK inhibitor currently available, tofacitinib, is associated with safety concerns that limit the eligible patient population.[77] In a post-marketing study,

tofacitinib showed an increased risk of infection in patients aged over 65 years. Additionally, dose adjustment is required for patients with renal and hepatic impairment. Tofacitinib may only be used in combination with methotrexate,[55 77] which is associated with additional administrative burden to both healthcare professionals and patients, compared with monotherapy.

As such, there is an unmet need for a JAK inhibitor that:

- Is suitable for use across age groups, including patients aged over 65 years
- Does not require dose adjustment to mitigate safety concerns
- Offers the flexibility of monotherapy

B.1.3.6 Proposed position of upadacitinib

Upadacitinib offers a well-characterised, well-tolerated, and orally available treatment option. It is suitable for use across age groups, including patients aged over 65 years, and does not require dose adjustment to mitigate safety concerns.[6] It may be given as a monotherapy or in combination with methotrexate, to inhibit structural damage and minimise disease activity in PsA. It provides a beneficial treatment option in the ≥ 2 csDMARD setting, with demonstrable improvements in disease activity scores, physical functioning and pain compared with placebo, and broadly equivalent efficacy compared with the current standard of care.

Upadacitinib provides the potential to address the current unmet needs of patients with active PsA whose disease has not responded adequately to ≥ 2 csDMARDs, or ≥ 2 csDMARDs and ≥ 1 TNFα inhibitor, or in whom TNFα inhibitors are contraindicated or not tolerated.

B.1.4. Equality considerations

No equality issues are anticipated if upadacitinib is recommended for use by NICE. Upadacitinib is suitable for use across age groups, in contrast to tofacitinib which has a warning for use in patients aged over 65 years.[6, 77] As such, upadacitinib offers therapeutic benefit to a broader patient population compared to the only other JAK inhibitor currently available to PsA patients in the UK.

B.2. Clinical effectiveness

- The SELECT-PsA 1 and SELECT-PsA 2 clinical trial programme represents the largest clinical trial programme in PsA to date. Upadacitinib met its primary endpoints in these trials, with statistically significant improvements to ACR20 response compared with placebo, and a numerically greater advantage compared with adalimumab in biologic naïve patients.[78, 79] ACR20 response rates were consistent in patients with one versus two prior csDMARDs
- In both SELECT-PsA 1 and SELECT-PsA 2, the results for the ranked secondary endpoints were consistent with those of the primary analysis, with better efficacy for upadacitinib versus placebo observed for all measures.[78, 79] These measures demonstrate the benefit of upadacitinib for addressing clinically relevant manifestations of PsA, and therefore achieving key treatment goals such as preventing joint damage, stopping swelling, reducing pain and improving HRQL[12]
- MDA is a composite measure of multifactorial disease components that defines the key goal of treatment for PsA. In SELECT-PsA 1 and SELECT-PsA 2, a significantly greater proportion of patients achieved MDA with upadacitinib compared with placebo.[78, 79] While not powered for superiority, there was a numerically higher proportion of patients achieving MDA with upadacitinib compared with adalimumab in SELECT-PsA 1[78]
- An indirect treatment comparison (ITC) informs the comparative efficacy of upadacitinib in both biologic-naïve and biologic-experienced PsA patient populations. The results from this analysis demonstrate that upadacitinib has comparable efficacy versus other treatment options in terms of PsARC, PASI, HAQ-DI conditional on PsARC, and ACR responses
- Upadacitinib demonstrated a consistent safety profile, as observed in other indications, with no new safety signals.[78, 79] Upadacitinib has an established and acceptable tolerability profile while providing the simplicity of one dose, one pill, once a day

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

In summary, a systematic literature review (SLR) was conducted to identify clinical evidence on the efficacy and safety of upadacitinib for patients with active PsA. The SLR identified two key studies that evaluated upadacitinib as an active intervention in PsA patients:

- SELECT-PsA 1: Phase III, randomised, double-blind study comparing upadacitinib with placebo and with adalimumab in patients with active PsA who have a history of inadequate response (IR) to at least one csDMARD (csDMARD-IR)[78]

- SELECT-PsA 2: Phase III, randomised, double-blind study comparing upadacitinib with placebo in patients with active psoriatic arthritis who have a history of inadequate response to at least one bDMARD (bDMARD-IR)[79]

The SLR was designed to identify randomised controlled trials of upadacitinib and of potentially relevant comparators in patients with active PsA. These findings have informed the ITC of upadacitinib versus bDMARDs and tsDMARDs in biologic-experienced and biologic-naïve patients, described in further detail in Section B.2.9.

B.2.2. List of relevant clinical effectiveness evidence

The clinical development programme for upadacitinib in PsA includes two pivotal, Phase III studies: SELECT-PsA 1 (N = 1,705) and SELECT-PsA 2 (N = 642).[78, 79] These studies are the key trials informing the regulatory submission for upadacitinib in PsA, and form the key source of clinical and economic evidence in this submission. SELECT-PsA 1 and SELECT-PsA 2 both have long-term extension phases which are currently ongoing.

A summary of the clinical effectiveness evidence provided by SELECT-PsA 1 and SELECT-PsA 2 is provided in Table 3.

Note that while findings for the 30 mg dose were collected in the pivotal trials, given that the 30 mg dose is not included in the regulatory filing, results for this dose are not included in this submission.

Table 3: Clinical effectiveness evidence

Study	**SELECT-PsA 1 (NCT03104400)**					**SELECT-PsA 2 (NCT03104374)**				
Study design	A Phase III, randomised, double-blind study comparing upadacitinib with adalimumab and placebo					A Phase III, randomised, double-blind study comparing upadacitinib with placebo				
Population	Adult patients with active psoriatic arthritis who have a history of inadequate response to at least one csDMARD					Adult patients with active psoriatic arthritis who have a history of inadequate response to at least one bDMARD				
Intervention	Upadacitinib 15 mg or 30 mg once daily					Upadacitinib 15 mg or 30 mg once daily				
Comparators	Adalimumab 40 mg every other week and placebo					Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No		No			No	
Rationale for use/non-use in the model	Both trials were included in the model because support application for marketing authorisation and include a population directly relevant to the decision problem.									
Reported outcomes specified in the decision problem[a]	• Disease activity: ACR20/50/70, **PASI 50/75/90, PsARC**, MDA, sIGA, Modified PsA, SHS • Functional capacity: **HAQ-DI**, HAQ-DI conditional on PsARC response status • Disease progression: change from baseline in disease activity measures • Periarticular disease: enthesitis resolution (LEI), dactylitis resolution (LDI) • Axial outcomes: ASDAS, BASDAI • Mortality • Adverse effects of treatment • Health-related quality of life: **EQ-5D-5L**, SF-36 PCS, FACIT-F, SAPS					• Disease activity: ACR20/50/70, **PASI 50/75/90, PsARC**, • Functional capacity: **HAQ-DI**, HAQ-DI conditional on PsARC response status • Disease progression: change from baseline in disease activity measures • Periarticular disease: enthesitis resolution (LEI), dactylitis resolution (LDI) • Axial outcomes: ASDAS, BASDAI • Mortality • Adverse effects of treatment • Health-related quality of life: **EQ-5D-5L**, SF-36 PCS, FACIT-F, SAPS				

Key: ACR, American College of Rheumatology; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CSRs, clinical study reports; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; FACIT-F, Functional Assessment of Chronic Illness Therapy- Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; PsARC, Modified Psoriatic Arthritis Response Criteria; SAPS, Self-Assessment of Psoriasis Symptoms; SF-36, Short Form 36 Physical Component Summary; SHS, Sharp van der Heijde Score; sIGA, Static Investigator Global Assessment.
Source: SELECT-PsA 1 and SELECT-PsA 2 CSRs.[78, 79]
Notes: [a], bolded outcomes were used to inform the economic model.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 SELECT-PsA 1

B.2.3.1.1 Study design

SELECT-PsA 1 is a Phase III, randomised, double-blind study of upadacitinib 15 mg and 30 mg once daily versus adalimumab 40 mg and placebo in patients with PsA.[78] It provides information relevant to the decision problem, as it demonstrates the safety and efficacy of upadacitinib in a patient population with inadequate responses to csDMARDs (Population 2 in the decision problem, see Section B.1.1).

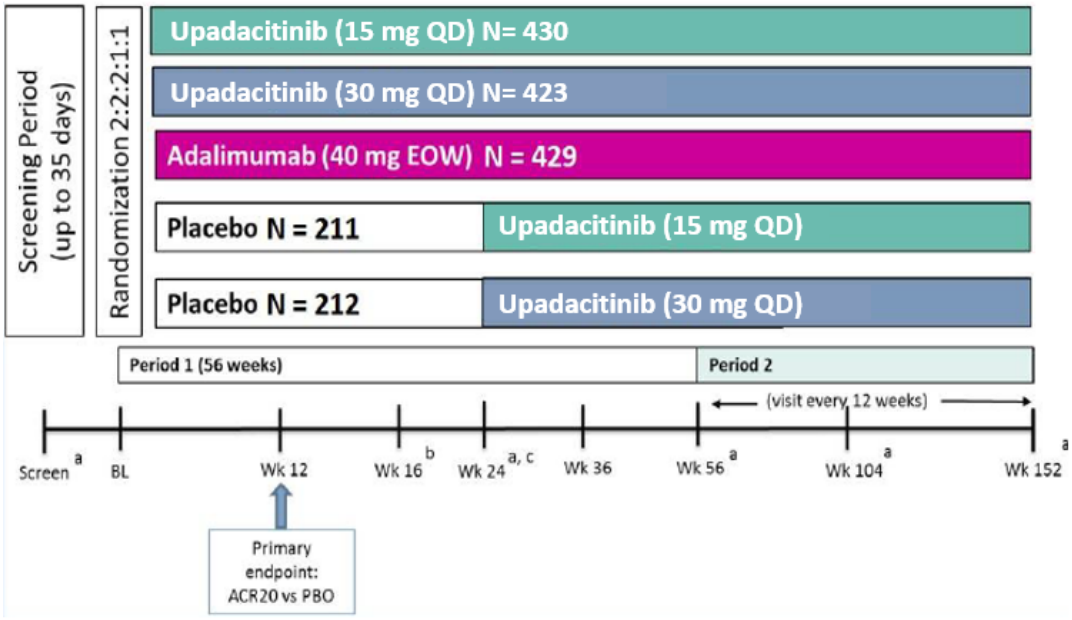
SELECT-PsA 1 consists of three phases: the first is an initial 35-day screening period, followed by Period 1 – a 56 week treatment phase comparing the safety, tolerability and efficacy of upadacitinib versus placebo and versus adalimumab every other week.[78] At Week 24, all placebo patients switch to upadacitinib, regardless of response. Period 2 is a long-term extension phase intended to evaluate the safety, tolerability and efficacy of upadacitinib in patients who complete Period 1. Patients originally randomised to placebo switch to upadacitinib for Period 2. Period 2 is designed to capture a total treatment duration of ~5 years.

Patients were randomised in a 2:2:2:1:1 ratio to one of the five following treatment groups:[78]

- Upadacitinib 15 mg once daily (n = 430)
- Upadacitinib 30 mg once daily (n = 423)
- Adalimumab 40 mg every other week (n = 429)
- Placebo (n = 211) (followed by upadacitinib 15 mg in Period 2)
- Placebo (n = 212) (followed by upadacitinib 30 mg in Period 2)

A study design schematic for SELECT-PsA 1 is presented in Figure 2.

Figure 2: SELECT-PsA 1 study design



Key: ACR, American College of Rheumatology; BL, baseline; EOW, every other week; QD, once daily; Wk, week.
Notes: a, all patients receive x-rays of hands and feet at screening, Wk 24, Wk 56, Wk 104, and Wk 152/PD; b, at Week 16, rescue therapy is offered to patients classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count and swollen joint count at both Week 12 and Week 16); c, at Week 24, all placebo patients switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.
Source: SELECT-PsA 1 clinical study report.[78]

Randomisation was stratified by extent of psoriasis (≥ 3% BSA or < 3% BSA), current use of at least one DMARD (Yes or No), presence of dactylitis, and presence of enthesitis.[78]

To be eligible for inclusion into the study, patients must have had active disease at baseline (defined as ≥ 3 tender joints and ≥ 3 swollen joints at screening and baseline visits) and an inadequate response after a minimum of 12 weeks of treatment with at least one csDMARD.[78] Patients were excluded if they had prior exposure to any JAK inhibitor or current treatment with > 2 csDMARDs.

The primary endpoint of the study was the proportion of patients achieving an ACR 20% (ACR20) response at Week 12.[78] The ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment (PtGA), physician global assessment (PGA), functional ability measure, visual analogue pain scale, and erythrocyte sedimentation rate or C-reactive protein. The ACR definition of improvement is often called the ACR20 because it requires at

least a 20% improvement in the core set of measures for improvement to be clinically meaningful.[80] Although developed to assess patients with rheumatoid arthritis, the appropriately modified ACR joint count has been demonstrated to be a reliable measure of activity in PsA.[81]

Secondary endpoints were designed to measure disease severity, HRQL and treatment response. The key multiplicity-adjusted secondary endpoints were ranked as follows:[78]

1. Change from baseline in HAQ-DI score at Week 12
2. Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16
3. PASI75 response at Week 16
4. Change from baseline in modified PsA Sharp van der Heijde Score (SHS) at Week 24
5. Percentage of patients with MDA at Week 24
6. Percentage of patients with resolution of enthesitis at Week 24
7. ACR20 non-inferiority versus adalimumab at Week 12
8. Change from baseline in the Short Form 36 Physical Component Summary (SF-36 PCS) at Week 12
9. Change from baseline in Functional Assessment of Chronic Illness Therapy fatigue (FACIT-F) at Week 12
10. ACR20 superiority versus adalimumab at Week 12
11. Percentage of patients with dactylitis resolution at Week 24
12. Pain superiority versus adalimumab at Week 12
13. HAQ-DI superiority versus adalimumab
14. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) at Week 16

A description of these measures is provided in Appendix L.

Table 4 presents a summary of the methodology of SELECT-PsA 1.

Table 4: Summary of methodology (SELECT-PsA 1)

Trial Name	**SELECT-PsA 1**
Location	SELECT-PsA 1 was conducted in 281 sites in 44 countries, including 5 sites and 26 patients in the UK.
Eligibility criteria for participants	**Key inclusion criteria:** • ≥ 18 years old at screening • Clinical diagnosis of PsA with symptom onset ≥ 6 months prior to screening and fulfilment of the CASPAR criteria • Active disease at baseline defined as ≥ 3 tender joints and ≥ 3 swollen joints • Presence at screening of either ≥ 1 erosion on x-ray as determined by central imaging review or hs-CRP > ULN • Diagnosis of active plaque psoriasis or documented history of plaque psoriasis • Inadequate response or intolerance to treatment with at least one csDMARD[a] • On ≤ 2 csDMARDs **Key exclusion criteria** • Prior exposure to any JAK inhibitor • Prior exposure to any bDMARD
Settings and locations where the data were collected	AbbVie qualified and selected the study sites and investigators and conducted the initiation visits, site monitoring visits, and post-study visits. The database for this study was created using a validated data management system at AbbVie, and designated statisticians at AbbVie were responsible for the statistical analysis of the data. Data were generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.
Trial drugs	**Period 1** Patients received oral upadacitinib 15 mg, upadacitinib 30 mg or matching placebo once daily. Adalimumab 40 mg and matching placebo were received subcutaneously every other week, beginning on Day 1. The study drug could be taken with or without food. **Period 2** Patients receiving placebo in Period 1 switched to upadacitinib 15 mg or 30 mg.

Trial Name	SELECT-PsA 1
Permitted and disallowed medication	Patients were permitted to continue background therapy with up to two csDMARDs only if DMARDs were started ≥ 12 weeks prior to the baseline visit and without dosing or administration changes ≥ 4 weeks prior to the baseline visit). The following csDMARDs were allowed as background therapy during the study: methotrexate (≤ 25 mg/week), sulfasalazine (≤ 3,000 mg/day), leflunomide (≤ 20 mg/day), apremilast (≤ 60 mg/day), hydroxychloroquine (≤ 400 mg/day), bucillamine (≤ 300 mg/day) and iguratimod (≤ 50 mg/day). For all patients taking methotrexate, a dietary supplement of oral folic acid was required throughout study participation.
Primary outcome	The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12.
Pre-planned subgroups	The primary efficacy endpoint was measured in pre-planned subgroups of demographic factors and baseline disease characteristics, including the number of prior csDMARDs (≤ 1 or > 1) and current csDMARD use (yes or no).

Key: ACR20, American College of Rheumatology 20%; bDMARD, biological disease-modifying anti-rheumatic drug; CASPAR, Classification Criteria for PsA; DMARD, disease-modifying anti-rheumatic drug; hs-CRP; high-sensitivity C-reactive protein; ICH GCP, International Conference on Harmonisation – Good Clinical Practice; JAK, Janus kinase; PsA, psoriatic arthritis; ULN, upper limit of normal.
Notes: [a], Lack of efficacy after ≥12 weeks of therapy; intolerance or contraindication as defined by investigator.
Source: SELECT-PsA 1 protocol and clinical study report.[49, 78]

B.2.3.1.2 Baseline characteristics

Baseline characteristics were generally balanced across the upadacitinib, adalimumab and placebo groups, with similar characteristics and disease activity in each study arm.[78] Patients had been diagnosed with PsA for a mean of [redacted] years, and experienced symptoms of PsA for a mean of [redacted] years. Patients had active disease as indicated by mean TJC68 of [redacted], mean SJC66 of [redacted], and [redacted]% of patients had BSA-Ps ≥ 3%.

Table 5 presents a summary of the baseline characteristics of SELECT-PsA 1.

Table 5: Baseline characteristics of full analysis set (SELECT-PsA 1)

Mean (SD) or n (%)	Upadacitinib 15 mg (n = 429)	Adalimumab 40 mg (n = 429)	Placebo (n = 423)
Female	[redacted]	[redacted]	[redacted]
Age, years	[redacted]	[redacted]	[redacted]
Duration of PsA symptoms, years	[redacted]	[redacted]	[redacted]
Duration of PsA diagnosis, years	[redacted]	[redacted]	[redacted]
TJC68	[redacted]	[redacted]	[redacted]
SJC66	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]
≥ 3% BSA-Ps	[redacted]	[redacted]	[redacted]
PASI (for baseline ≥ 3% BSA-Ps)	[redacted]	[redacted]	[redacted]
Presence of enthesitis (LEI > 0)	[redacted]	[redacted]	[redacted]
Presence of dactylitis (LDI > 0)	[redacted]	[redacted]	[redacted]

Key: BSA-Ps, body surface area psoriasis; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; SJC66, swollen joint count 66; TJC68, tender joint count 68.
Source: SELECT-PsA 1 clinical study report.[78]

Feedback from UK clinicians indicated that the baseline characteristics of patients in SELECT-PsA 1 were broadly generalisable to patients expected to receive upadacitinib in the UK.[4] Of note, the geographic distribution of SELECT-PsA 1

(namely, the high proportion of patients from Eastern Europe) potentially poses some issues, particularly with regards to expectation effects and high response rates in the placebo arm, but was not otherwise believed to affect the generalisability of the study results.

Prior and concomitant medications

[redacted] patients used one or more prior csDMARDs, including [redacted]% of patients who used one prior csDMARD, [redacted]% who used two prior csDMARDs, and [redacted]% who used three or more prior csDMARDs.[78]

Methotrexate was the most frequently reported prior csDMARD overall ([redacted]%).[78] At Week 24, most patients ([redacted]%) reported use of concomitant medications for any indication. The majority ([redacted]%) of patients reported concomitant use of csDMARDs, [redacted]% of patients reported concomitant use of NSAIDs, and a minority ([redacted]%) of patients reported concomitant use of systemic corticosteroids.

A summary of the prior and concomitant medications in each treatment arm in SELECT-PsA 1 is provided in Table 6.

Table 6: Prior and concomitant medications of full analysis set, SELECT-PsA 1

Mean (SD) or n (%)	**Upadacitinib 15 mg (n = 429)**	**Adalimumab 40 mg (n = 429)**	**Placebo (n = 423)**
Number of prior DMARDs used			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]

Concomitant medications used at baseline			
Monotherapy	[redacted]	[redacted]	[redacted]
Any csDMARD	[redacted]	[redacted]	[redacted]
MTX alone	[redacted]	[redacted]	[redacted]
MTX + another csDMARD	[redacted]	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]	[redacted]

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; SD, standard deviation.
Source: SELECT-PsA 1 clinical study report.[78]

In patients treated with upadacitinib 15 mg in SELECT-PsA 1, a higher proportion had received one prior DMARD ([redacted]%) than two prior DMARDs ([redacted]%).[78]

In the UK, patients must trial ≥ 2 csDMARDs before receiving a biological therapy.[55, 56] The inclusion of patients with ≥ 1 csDMARD in SELECT-PsA 1 aligns with criteria commonly used in PsA trials. The implications of this have been accepted in previous appraisals (e.g. tofacitinib [TA543] and ixekizumab [TA537]);[1, 82] with the understanding that the efficacy of biologics is not influenced by the prior number of csDMARDs (see Section B.2.7.1 and Section B.2.13).

B.2.3.2 SELECT-PsA 2

B.2.3.2.1 Study design

SELECT-PsA 2 is a Phase III, randomised, double-blind study of upadacitinib 15 mg and 30 mg once daily versus placebo in patients with PsA.[79] It provides information relevant to the decision problem, as it demonstrates the safety and efficacy of upadacitinib in a patient population with inadequate responses to bDMARDs (Populations 3 and 4 in the decision problem, see Section B.1.1).

SELECT-PsA 2 consists of three phases: first is an initial 35-day screening period, followed by Period 1 – a 56 week treatment phase comparing the safety, tolerability and efficacy of upadacitinib versus placebo.[79] At Week 24, all placebo patients switch to upadacitinib, regardless of response. Period 2 is a long-term extension phase intended to evaluate the safety, tolerability and efficacy of upadacitinib in patients who complete Period 1. Patients originally randomised to placebo switch to

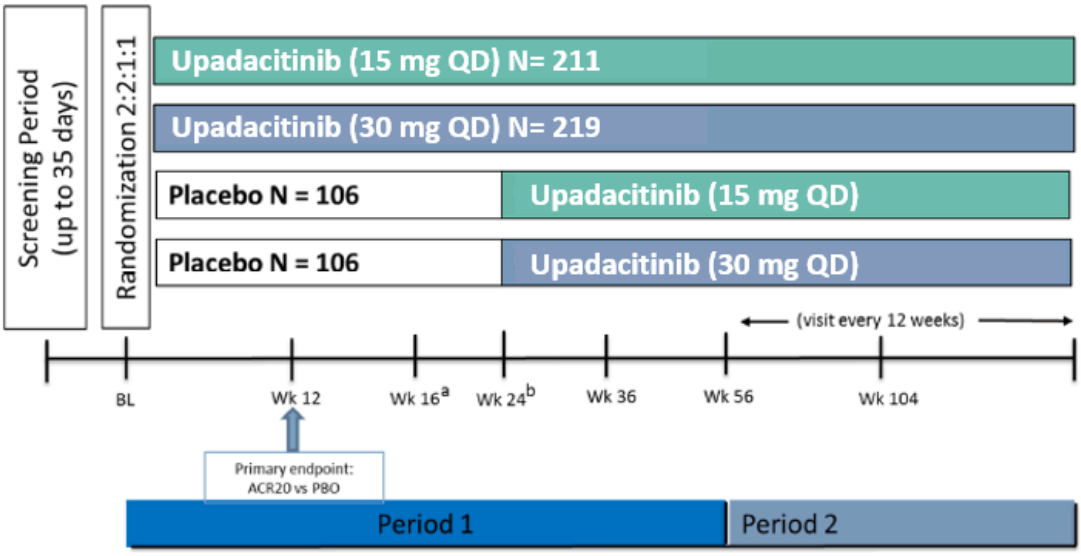
upadacitinib for Period 2. Period 2 is designed to capture a total treatment duration of ~3 years.

Patients were randomised in a 2:2:1:1 ratio into one of the four following treatment groups:[79]

- Upadacitinib 15 mg once daily (n = 211)
- Upadacitinib 30 mg once daily (n = 219)
- Placebo (n = 106) (followed by upadacitinib 15 mg in Period 2)
- Placebo (n = 106) (followed by upadacitinib 30 mg in Period 2)

A study design schematic for SELECT-PsA 2 is presented in Figure 3.

Figure 3: SELECT-PsA 2 study design



Key: ACR, American College of Rheumatology; BL, baseline; EOW, every other week; PBO, placebo; QD, once daily; Wk, week.
Notes: a, at Week 16, rescue therapy is offered to patients classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count and swollen joint count at both Week 12 and Week 16); b, at Week 24, all placebo patients switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.
Source: SELECT-PsA 2 clinical study report[79]

Randomisation was stratified by extent of psoriasis (≥ 3% BSA or < 3% BSA), current use of at least one DMARD (Yes or No), and number of prior failed biological DMARDs (1 vs > 1).[79]

To be eligible for inclusion into the study, patients must have had active disease at baseline (defined as ≥ 3 tender joints and ≥ 3 swollen joints at screening and

baseline visits) and an inadequate response after a minimum of 12 weeks of treatment with at least one bDMARD.[79] Patients were excluded if they had prior exposure to any JAK inhibitor or current treatment with > 2 csDMARDs.

The primary endpoint of the study was the proportion of patients achieving ACR20 response at Week 12.[79] Secondary endpoints were designed to measure disease severity, HRQL and treatment response. The key multiplicity-adjusted secondary endpoints were ranked as follows:[79]

1. Change from baseline in HAQ-DI at Week 12
2. sIGA of psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16
3. PASI75 response at Week 16
4. Change from baseline in the SF-36 PCS at Week 12
5. Change from baseline in FACIT-F at Week 12
6. Percentage of patients with MDA at Week 24
7. Change from baseline in SAPS at Week 16

A description of these measures is provided in Appendix L. Table 7 provides a summary of the methodology of SELECT-PsA 2.

Table 7: Summary of methodology (SELECT-PsA 2)

Trial Name	**SELECT-PsA 2**
Location	SELECT-PsA 2 was conducted in 123 sites in 16 countries, including six sites and 3 patients in the UK.
Eligibility criteria for participants	**Key inclusion criteria:** • ≥ 18 years old at screening • Clinical diagnosis of PsA with symptom onset ≥ 6 months prior to screening and fulfilment of the CASPAR criteria • Active disease at baseline defined as ≥ 3 tender joints and ≥ 3 swollen joints • Diagnosis of active plaque psoriasis or documented history of plaque psoriasis • Inadequate response or intolerance to treatment with at least one bDMARD[a] • On ≤ 2 csDMARDs **Key exclusion criteria** • Prior exposure to any JAK inhibitor
Settings and locations where the data were collected	AbbVie qualified and selected the study sites and investigators and conducted the initiation visits, site monitoring visits, and post-study visits. The database for this study was created using a validated data management system at AbbVie, and designated statisticians at AbbVie were responsible for the statistical analysis of the data. Data were generated, documented and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.
Trial drugs	**Period 1** Patients received oral upadacitinib 15 mg, upadacitinib 30 mg or matching placebo once daily. The study drug could be taken with or without food. **Period 2** Patients receiving placebo in Period 1 switched to upadacitinib 15 mg or 30 mg.
Permitted and disallowed medication	Patients were permitted to continue stable background DMARD therapy.
Primary outcome	The primary efficacy endpoint was the proportion of patients achieving ACR20 at Week 12.
Pre-planned subgroups	The primary efficacy endpoint was measured in pre-planned subgroups of demographic factors and baseline disease characteristics, including the number of prior failed bDMARDs (1 or > 1), and current csDMARD use (yes or no).
Key: ACR20, American College of Rheumatology 20%; bDMARD, biological disease-modifying anti-rheumatic drug; CASPAR, Classification Criteria for PsA; DMARD, disease-modifying anti-rheumatic drug; ICH GCP, International Conference on Harmonisation – Good Clinical Practice; JAK, Janus kinase; PsA, psoriatic arthritis.	

Trial Name	SELECT-PsA 2
Note: [a], Lack of efficacy after ≥ 12 weeks of therapy; intolerance or contraindication as defined by investigator. **Source:** SELECT-PsA 2 protocol and clinical study report.[50, 79]	

B.2.3.2.2 Baseline characteristics

Baseline characteristics were generally balanced across upadacitinib and placebo groups, with similar characteristics and disease activity in each study arm.[79] Patients had been diagnosed with PsA for a mean of [redacted] years, and experienced symptoms of PsA for a mean of [redacted] years. Patients had active disease as indicated by a mean TJC68 of [redacted] and a mean SJC66 of [redacted]. Table 8 provides a summary of the baseline characteristics of SELECT-PsA 2.

Table 8: Baseline characteristics of full analysis set (SELECT-PsA 2)

Mean (SD) or n (%)	Upadacitinib 15 mg (n = 211)	Placebo (n = 212)
Female	113 (53.6%)	120 (56.6%|)
Age, years	53.0 (12.0)	54.1 (11.5)
Duration of PsA symptoms, years	12.2 (8.8)	14.6 (11.7)
Time since PsA diagnosis, years	9.6 (8.4)	11.0 (10.3)
TJC68	24.9 (17.3)	25.3 (17.6)
SJC66	11.3 (8.2)	12.0 (8.9)
HAQ-DI	1.10 (0.6)	1.23 (0.7)
≥ 3% BSA-Ps	130 (61.6%)	131 (61.8%)
PASI (for baseline ≥ 3% BSA-Ps)	[redacted]	[redacted]
Presence of enthesitis (LEI > 0)	133 (63.0%)	144 (67.9%)
Presence of dactylitis (LDI > 0)	55 (26.1%)	64 (30.2%)

Key: BSA-Ps, body surface area psoriasis; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation; SJC66, swollen joint count 66; TJC68, tender joint count 68.
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

Feedback from UK clinicians indicated that the baseline characteristics of patients in SELECT-PsA 2 were broadly generalisable to patients expected to receive upadacitinib in the UK.[4]

Prior and concomitant medications

Overall, [redacted]% of patients had failed one prior bDMARD, [redacted]% had failed two prior bDMARDs, and [redacted]% had failed three or more prior bDMARDs, while [redacted]% of patients entered the study after intolerance but not failure of a prior bDMARD.[79] Adalimumab was the most frequently reported ([redacted]%) prior bDMARD overall. At Week 24, most patients ([redacted]%) reported use of concomitant medications for any indication. Approximately half ([redacted]%) of patients reported concomitant use of csDMARDs, the majority ([redacted]%) of patients reported concomitant use of NSAIDs, and a minority ([redacted]%) of patients reported concomitant use of systemic corticosteroids.

Table 9 presents a summary of the prior and concomitant medications in each treatment arm in SELECT-PsA 2.

Table 9: Prior and concomitant medications of full analysis set, SELECT-PsA 2

Mean (SD) or n (%)	Upadacitinib 15 mg (n = 211)	Placebo (n = 212)
Number of prior bDMARDs failed		
0[a]	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
≥ 3	[redacted]	[redacted]
Concomitant medications used at baseline		
Monotherapy	[redacted]	[redacted]
Any csDMARD	[redacted]	[redacted]
MTX alone	[redacted]	[redacted]
MTX + another csDMARD	[redacted]	[redacted]
csDMARD other than MTX	[redacted]	[redacted]

Key: bDMARD, biological disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; SD, standard deviation.
Note: [a], indicates patients enrolled due to intolerance to bDMARD therapy.
Source: SELECT-PsA 2 clinical study report.[79]

Methotrexate was the most frequently reported ([redacted]%) prior csDMARD overall.[79] The prior and concomitant use of methotrexate in SELECT-PsA 2 aligns with clinical practice, previous clinical trials, and appraisals in PsA.[1, 82]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The primary objective of SELECT-PsA 1 and SELECT-PsA 2 was to determine the efficacy of upadacitinib, as measured by the proportion of patients achieving an ACR20 response at Week 12.[84, 85] Both studies assumed 30% of patients treated with placebo would achieve an ACR20 response, which would provide at least 90% power (at a two-sided significance level of [redacted]) for a 20% difference in ACR20 response rate. Non-responder imputation (NRI) was used to account for missing data and patient withdrawals, such that patients with missing values at any visit were considered non-responders for that visit. Tipping point analysis was also used as a more systematic approach to the sensitivity analysis of the missing at random assumption. This involves replacing missing data with substitute data to test the extent to which this must change before results 'tip' from being significant to non-significant.

Table 10 provides a summary of the methodology of the statistical analyses. Efficacy analyses were carried out in the full analysis set (FAS) population, and safety analyses were carried out in the safety analysis set (SAS); both were defined as all randomised patients who received at least one dose of study drug.[84, 85]

The multiplicity-adjusted endpoint measures were designed to begin testing the primary endpoint before following a pre-specified α transfer path along the ranked endpoint sequences described in Section B.2.3.[84, 85] As such, a significant difference in treatment effect required all prior outcome measures in the ranked sequence to meet significance.

Assessments were scheduled for Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 56 and every 12 weeks thereafter until the study was completed, to capture long-term efficacy.[84, 85] After the last patient completed the Week 24 study visit, an unblinded analysis was planned for the purpose of initial regulatory submission. To maintain integrity of the trial during the blinded 56-week period (Period 1), study sites and patients will remain blinded until all patients have reached Week 56.

Patients who prematurely discontinue upadacitinib 15 mg are considered non-responders for all subsequent visits after discontinuation.[84, 85] As of the 24 week data cut-off analysis, this included [redacted] ([redacted]%) patients from the upadacitinib 15 mg arm of SELECT-PsA 1 and [redacted] ([redacted]%) patients from the upadacitinib 15 mg arm of SELECT-PsA 2.[78, 79]

Further information regarding participant flow in SELECT-PsA 1 and SELECT-PsA 2 is presented in Appendix D.

Table 10: Summary of statistical analyses (SELECT-PsA 1 and SELECT-PsA 2)

Trial Name	SELECT-PsA 1	SELECT-PsA 2
Hypothesis objective	Upadacitinib will improve ACR20 compared with placebo and adalimumab in csDMARD-IR PsA patients	Upadacitinib will improve ACR20 compared with placebo in bDMARD-IR PsA patients
Statistical analysis	Continuous variables were summarised using descriptive statistics (i.e. n, mean, median, SD, min, max) and binary endpoints described using frequencies and percentages with 95% CIs. All power and sample size calculations were performed at a two-sided significance level of [redacted] and accounted for a [redacted]% dropout rate.	
Sample size, power calculation	Assuming [redacted]% of patients treated with placebo achieved an ACR20 response, 1,640 evaluable patients were required to provide at least 90% power for a 20% difference in ACR20 response rate. This sample size provides at least 90% power for the majority of the key secondary endpoints and also provides at least 85% power for evaluating non-inferiority for upadacitinib vs adalimumab in ACR20 response rate at Week 12 (assuming 50% ACR20 response rates for adalimumab and upadacitinib and 30% ACR20 response rates for placebo).	Assuming 30% of patients treated with placebo achieved an ACR20 response, 630 evaluable patients were required to provide at least 90% power for a 20% difference in ACR20 response rate. This sample size provides at least 90% power for the majority of the key secondary endpoints.
Data management, patient withdrawals	Patients who prematurely discontinued upadacitinib were considered as non-responders for all subsequent visits after discontinuation (i.e. NRI). Any patient with any missing value for the binary endpoints at a specific visit were treated as a non-responder for that visit.	

Key: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; ITT, intent-to-treat; max, maximum; min, minimum; NRI, non-responder imputation; PsA, psoriatic arthritis; SD, standard deviation.
Source: SELECT-PsA 1 and SELECT-PsA 2 protocols.[84, 85]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

SELECT-PsA 1 and SELECT-PsA 2 are considered high-quality studies, being conducted in accordance with the ethical principles of Good Clinical Practice according to the International Council for Harmonisation guidelines.[78, 79]

Randomisation of patients was concealed using an interactive response technology; providers, participants and outcome assessors remained blinded to the treatment allocation.[78, 79] Baseline characteristics and disease activity were similar across treatment groups, with no major imbalances in prognostic factors.

The use of csDMARD background therapy may have influenced treatment effects in SELECT-PsA 1 and SELECT-PsA 2; however, background therapy was balanced between study arms (Table 6 and Table 9), indicating that the risk of bias on relative effect estimates is low.

Together, SELECT-PsA 1 and SELECT-PsA 2 demonstrate the safety and efficacy of upadacitinib 15 mg in patients with inadequate responses to both csDMARDs and bDMARDs, thus addressing the populations specified in the decision problem (see Section B.1.1). Similarly, the upadacitinib 15 mg dose in SELECT-PsA 1 and SELECT-PsA 2 trials aligns with the expected marketing authorisation and clinical use of upadacitinib. As such, this evidence is presented throughout Section B.2.6.

A summary of the quality assessment for SELECT-PsA 1 and SELECT-PsA 2 is provided in Table 11.

Table 11: Quality assessment (SELECT-PsA 1 and SELECT-PsA 2)

Study	SELECT-PsA 1	SELECT-PsA 2
Was randomisation adequate?	Yes, in a 2:2:2:1:1 ratio	Yes, 2:2:1:1 ratio
Was allocation adequately concealed?	Yes, using an IRT	Yes, using an IRT
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline patient characteristics and disease activity were similar across treatment groups and reflected the intended study population	Yes, baseline patient characteristics and disease activity were similar across treatment groups and reflected the intended study population
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, blinded until the last patient completes the last visit of Period 1 An independent external DMC reviewed unblinded safety data at regular intervals during the study The blind was broken by AbbVie pharmacovigilance for 62 patients, for regulatory reporting reasons	Yes, blinded until the last patient completes the last visit of Period 1 An independent external DMC reviewed unblinded safety data at regular intervals during the study The blind was broken by AbbVie pharmacovigilance for 36 patients, for regulatory reporting reasons
Were there unexpected imbalances in dropouts between groups?	No, the mean durations of study drug exposure were similar between treatment arms	No, the mean durations of study drug exposure were similar between treatment arms
Were any outcomes measured but not reported?	No, all measured outcomes were reported in the CSR	No, all measured outcomes were reported in the CSR
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No ITT analysis was conducted. Efficacy analyses were conducted in the FAS population defined as all randomised patients who received at least one dose of study drug. Data management and patient withdrawals were handled appropriately (see Section B.2.4)	No ITT analysis was conducted. Efficacy analyses were conducted in the FAS population defined as all randomised patients who received at least one dose of study drug. Data management and patient withdrawals were handled appropriately (see Section B.2.4)

Key: CSR, clinical study report; DMC, data monitoring committee; FAS, full analysis set; IRT, interactive response technology; ITT, intent-to-treat.
Source: SELECT-PsA 1 and SELECT-PsA 2 CSRs[78, 79] and protocols[84, 85]

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 Overview

At the 24-week analysis, [redacted]% of patients in SELECT-PsA 1 had completed up to Week 12 and [redacted]% up to Week 24.[78] For SELECT-PsA 2, [redacted]%[79] of patients had completed up to Week 12 and 84.6% up to Week 24. [83]

Both SELECT-PsA 1 and SELECT-PsA 2 met their primary endpoints and demonstrated a significantly higher proportion of ACR20 responders with upadacitinib versus placebo.[78, 79]

SELECT-PsA 1 demonstrated statistically significantly better efficacy for upadacitinib versus placebo for the primary endpoint and the first nine secondary ranked endpoints.[78] Upadacitinib met statistical significance for non-inferiority versus adalimumab; however, did not meet significance for superiority testing. Although not formally assessed in the hierarchical statistical testing structure, SELECT-PsA 1 demonstrated numerically better responses for upadacitinib compared with adalimumab in several outcome measures, some of which reached nominal significance.

SELECT-PsA 2 demonstrated statistically significantly better efficacy for upadacitinib versus placebo in all of the ranked endpoints measured.[79]

Table 12 summarises the results for the primary and secondary outcomes for upadacitinib 15 mg from SELECT-PsA 1 and SELECT-PsA 2. Note that results for the 30 mg dose are not presented given it was not included in the regulatory filing.

Key outcomes are presented in the following subsections, with full results presented in Appendix D.

Table 12: Results of primary and secondary outcome measures (SELECT-PsA 1 and SELECT-PsA 2)

% or least squares mean	Outcome measure	SELECT-PsA 1				SELECT-PsA 2		
		UPA 15 mg (n = 429)	PBO (n = 423)	ADA 40 mg (n = 429)	Multiplicity adjusted p value (UPA vs PBO)	UPA 15 mg (n = 211)	PBO (n = 212)	Multiplicity adjusted p value
Primary endpoint	ACR20 (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	56.9%	24.1%	< 0.001
Secondary endpoints	HAQ-DI (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	-0.30	-0.10	< 0.001
	sIGA (Week16)	[redacted]	[redacted]	[redacted]	[redacted]	36.8%	9.2%	< 0.001
	PASI75 (Week 16)	[redacted]	[redacted]	[redacted]	[redacted]	52.3%	16.0%	< 0.001
	SHS (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	MDA (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	25.1%	2.8%	< 0.001
	Enthesitis resolution (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	ACR20 NI vs ADA (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	SF-36 PCS (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	5.2	1.6	< 0.001
	FACIT-F (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	5.0	1.30	< 0.001

% or least squares mean	Outcome measure	SELECT-PsA 1				SELECT-PsA 2		
		UPA 15 mg (n = 429)	PBO (n = 423)	ADA 40 mg (n = 429)	Multiplicity adjusted p value (UPA vs PBO)	UPA 15 mg (n = 211)	PBO (n = 212)	Multiplicity adjusted p value
	ACR20 superiority vs ADA (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	Dactylitis resolution (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	Pain superiority vs ADA (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	HAQ-DI superiority vs ADA (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA
	SAPS (Week 16)	[redacted]	[redacted]	[redacted]	[redacted]	-24.4	-1.5	< 0.001
Key exploratory endpoints	PsARC (Week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PsARC (Week 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PsARC (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASDAS change from baseline (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI change from baseline (Week 24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

% or least squares mean	Outcome measure	SELECT-PsA 1				SELECT-PsA 2		
		UPA 15 mg (n = 429)	PBO (n = 423)	ADA 40 mg (n = 429)	Multiplicity adjusted p value (UPA vs PBO)	UPA 15 mg (n = 211)	PBO (n = 212)	Multiplicity adjusted p value
Key: ACR, American College of Rheumatology; ADA, adalimumab; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, minimal disease activity; MMRM, MMRM, Mixed-Effect Model Repeated Measurement; NA, not assessed; NI, non-inferiority; NR, not reported; NRI, non-responder imputation; PASI, Psoriasis Area Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; SAPS, Self-Assessment of Psoriasis Symptoms; SF-36 PCS, Short Form 36 Physical Component Summary; SHS, Sharp van der Heijde Score; sIGA, Static Investigator Global Assessment; UPA, upadacitinib; vs, versus. **Notes:** Endpoints are presented in ranked order for SELECT-PsA 1, but not SELECT-PsA 2. All results are from FAS populations with NRI, with the exception of BASDAI and ASDAS change from baseline which is FAS with MMRM. P values are adjusted for multiplicity adjusted endpoints. **Sources:** SELECT-PsA 1 and SELECT-PsA 1 clinical study reports,[78, 79] and Mease et al 2020[83]								

B.2.6.2 SELECT-PsA 1

B.2.6.2.1 Primary endpoint: ACR20 response rate at Week 12

Guidelines from the European Medicine Agency (EMA) indicate that the ACR20 response is a suitable determinant of a clinically meaningful response in PsA.[86] Of csDMARD-IR patients treated with upadacitinib 15 mg in SELECT-PsA 1, a significantly greater proportion of patients achieved the primary endpoint of ACR20 response at Week 12 compared with placebo ([redacted]) and a numerically greater proportion compared with adalimumab ([redacted])(Table 13 and Figure 4).[78] Tipping point analyses were conducted as a sensitivity check and supported the findings of the primary analysis.

Table 13: ACR20 response rate at Week 12 (SELECT-PsA 1, FAS NRI)

	UPA 15 mg (N = 429)	**PBO (N = 423)**	**ADA 40 mg (N = 429)**
n (%)	[redacted]	[redacted]	[redacted]
95% CI[a]	[redacted]	[redacted]	[redacted]
Response rate difference (UPA – PBO)			-
Point estimate	[redacted]		
95% CI[b]	[redacted]		
Nominal p value[c]	[redacted]		

Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation; [c], nominal p value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 1 clinical study report.[78]

Figure 4: ACR20 response rate at Week 12 (SELECT-PsA 1, FAS NRI)

Key: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: p ≤ 0.001 for all comparisons, no formal statistical comparisons were pre-specified for ADA vs PBO.
Source: SELECT-PsA 1 clinical study report.[78]

ACR20 responses for upadacitinib were observed as early as Week 2, at which point [redacted]% of patients in the upadacitinib arm achieved a response compared with [redacted]% in the placebo arm.[78] At Week 24, ACR20 response rates increased to [redacted]% for patients treated with upadacitinib 15 mg, compared with [redacted]% of patients receiving adalimumab and [redacted]% of patients receiving placebo (Figure 5).[87]

Figure 5: ACR20 response rate up to Week 24 (SELECT-PsA 1, FAS NRI)

Key: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Source: Data on file.[87]

ACR50 and ACR70 represent more stringent fulfilment criteria than ACR20 given that they require patients to achieve at least a 50% and 70% improvement (respectively) in the core set of ACR measures. At Week 12 in SELECT-PsA 1, treatment with upadacitinib was associated with an equal to or greater than proportion of patients achieving ACR50 or ACR70 compared with adalimumab or placebo (Figure 6 and Appendix D).[78]

Figure 6: ACR20/50/70 response rates at Week 12 (SELECT-PsA 1, FAS NRI)

Key: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: p ≤ 0.001 for all comparisons, no formal statistical comparisons were pre-specified for ADA vs PBO.
Source: Data on file.[87]

B.2.6.2.2 Secondary endpoints

The results for the ranked secondary endpoints were consistent with those of the primary analysis, with better efficacy for upadacitinib versus placebo observed for all measures (Table 12).[78] This benefit reached statistical significance for the first nine endpoints; however, owing to the hierarchical testing structure and upadacitinib not meeting superiority testing versus adalimumab – subsequent ranked endpoints could not be measured for significance (although numerically better results for upadacitinib versus placebo and adalimumab were observed).

For ACR20 at Week 12, SELECT-PsA 1 demonstrated statistically significant non-inferiority versus adalimumab and a numerically greater response versus adalimumab.[78]

The key secondary outcomes of interest to this submission are described in detail in the subsequent sections. Full details of all outcomes measured are described in Appendix D.

Change from baseline in HAQ-DI at Week 12

The HAQ-DI was originally developed for use in rheumatoid arthritis, but has since been validated as an appropriate measure for distinguishing changes in physical function in PsA.[88] The smallest difference in HAQ-DI score that patients perceive as beneficial (the minimal clinically important difference; MCID) varies among patient populations. In a study of etanercept in PsA, results indicated that the MCID was approximately -0.35, and a score of -0.45 was considered a clinically important improvement.[89]

In SELECT-PsA 1, patients treated with upadacitinib 15 mg had a significantly better change from baseline in HAQ-DI at Week 12 than those treated with placebo (and a numerically better change from baseline than those treated with adalimumab ( ) (Table 14).[78]

Table 14: Change from baseline in HAQ-DI at Week 12 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean (95% CI)	Between group LS mean difference (UPA – control)		
		Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 404)		–	–	–
PBO (N = 392)				
ADA 40 mg (N = 406)				

Key: ADA, adalimumab; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis uses observed longitudinal data up to Week 12 prior to study drug premature discontinuation.
Source: SELECT-PsA 1 clinical study report.[78]

sIGA of psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16

The sIGA is a measure of the severity of psoriatic symptoms based on the investigator's assessment of the average elevation, erythema and scaling of all

psoriatic lesions.[85] The sIGA is measured using a 5-point scoring system (0–4), with a lower score indicating less severe psoriasis and a higher score indicating more severe psoriasis.

In SELECT-PsA 1, there was a significantly higher proportion of patients in the upadacitinib 15 mg arm achieving a sIGA of psoriasis 0 or 1 and ≥ 2-point improvement from baseline at Week 16 than in the placebo arm ([redacted]).[78] While not powered for superiority, there was a numerically higher proportion of patients receiving upadacitinib achieving this outcome than of patients receiving adalimumab ([redacted]) (Table 15).

Table 15: sIGA of psoriasis score of 0 or 1 and ≥ 2-point improvement from baseline at Week 16 (SELECT-PsA 1, FAS NRI)

	n	Within group point estimate (95% CI)	Between group difference (UPA – control)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 322)	[redacted]	[redacted]	–	–	–
PBO (N = 313)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 330)	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, adalimumab; CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; sIGA, Static Investigator Global Assessment; UPA, upadacitinib.
Note: Includes patients with baseline sIGA > 2.
Source: SELECT-PsA 1 clinical study report.[78]

PASI75 response at Week 16

PASI75 is a binary outcome that indicates a 75% or greater improvement in psoriasis area and severity from baseline and is recommended for measuring the primary response of psoriasis in patients with PsA.[90]

In SELECT-PsA 1, PASI score was recorded in patients with ≥ 3% BSA-Ps involvement at baseline.[78] At Week 16, the proportion of patients with a PASI75 response was significantly higher for patients treated with upadacitinib 15 mg than for those treated with placebo ([redacted]). While not powered for superiority, the proportion of patients with a PASI75 response at Week 16 was

numerically higher for upadacitinib compared with patients treated with adalimumab ([redacted]) (Table 16).

Table 16: PASI75 response at Week 16 (SELECT-PsA 1, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – control)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 214)	[redacted]	[redacted]	–	–	–
PBO (N = 211)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 211)	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, adalimumab; BSA-Ps, body surface area psoriasis; CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area Severity Index; PBO, placebo; UPA, upadacitinib.
Note: Includes patients with ≥ 3% BSA-Ps at baseline.
Source: SELECT-PsA 1 clinical study report.[78]

Percentage of patients with minimal disease activity at Week 24

MDA is a comprehensive and clinically meaningful endpoint in PsA, that is used to assess between-group and within-patient changes in disease activity.[91] It comprises a composite of measures including tender and swollen joint counts, PASI, patient's assessment of pain and disease activity, HAQ-DI, and LEI.

At Week 24 in SELECT-PsA 1, treatment with upadacitinib 15 mg was associated with a significantly higher proportion of patients achieving MDA compared with placebo ([redacted]).[78] While not powered for superiority, there was a numerically higher proportion of patients achieving MDA when treated with upadacitinib compared with adalimumab ([redacted]) (Table 17).[78]

Table 17: MDA response at Week 24 (SELECT-PsA 1, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – control)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 429)	[redacted]	[redacted]	–	–	–
PBO (N = 423)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 429)	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; MDA, minimal disease activity; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: Nominal p value was constructed using the Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 1 clinical study report.[78]

Percentage of patients with resolution of enthesitis at Week 24

The proportion of patients with resolution of enthesitis was defined as the proportion of patients with an LEI of 0.[85] The LEI evaluates enthesitis at six entheseal sites. Tenderness on examination is recorded as either present (coded as 1) or absent (coded as 0) for each of the six sites. The LEI is calculated by taking the sum of the scores so that the final score ranges from 0 to 6.

At Week 24 in SELECT-PsA 1, treatment with upadacitinib was associated with a significantly higher proportion of patients achieving enthesitis resolution compared with placebo ([redacted]). While not powered for superiority, there was a numerically higher proportion achieving enthesitis resolution with upadacitinib compared with adalimumab ([redacted]) (Table 18).[78]

Table 18: Resolution of enthesitis at Week 24 (SELECT-PsA 1, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – control)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 270)	[redacted]	[redacted]	–	–	–
PBO (N = 241)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 265)	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LEI, Leeds Enthesitis Index; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: Resolution of enthesitis defined as LEI = 0. Nominal p value was constructed using the Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 1 clinical study report.[78]

ACR20 non-inferiority versus adalimumab at Week 12

The pre-specified threshold for defining the non-inferiority of upadacitinib versus adalimumab was defined as at least 50% of the placebo-subtracted adalimumab effect.[78] Adalimumab effect preservation was calculated as:

(upadacitinib 15 mg – placebo)/(adalimumab – placebo)

For ACR20 at Week 12 in SELECT-PsA 1, this came to [redacted]% (95% CI: [redacted]), demonstrating the non-inferiority of upadacitinib versus adalimumab.[78] The response rate difference in ACR20 at Week 12 between upadacitinib 15 mg and adalimumab was [redacted]% (95% CI: [redacted]).

Change from baseline in FACIT-F at Week 12

Pain and tenderness in joints and skin psoriasis are associated with fatigue, a common symptom of PsA that is ranked second in patient-perceived importance, after pain.[42] The FACIT-F is a 13-item tool used in SELECT-PsA 1 to measure the patient's level of fatigue during their usual daily activities over the past week.[85] The level of fatigue was measured on a four point scale with higher scores indicating less fatigue.

At Week 12 in SELECT-PsA 1, treatment with upadacitinib was associated with a significantly greater change from baseline in FACIT-F compared with placebo

(between group difference [redacted]).[78] While not powered for superiority, there were numerically better changes from baseline in FACIT-F scores observed for upadacitinib compared with adalimumab ([redacted]) (Table 19).[78]

Table 19: Change from baseline in FACIT-F at Week 12 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean	95% CI	Between group LS mean difference (UPA – PBO)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 404)	[redacted]	[redacted]	–	–	–
PBO (N = 394)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 410)[a]	[redacted]	[redacted]	–	–	–

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least square; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Note: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis uses observed longitudinal data up to Week 12 prior to study drug premature discontinuation.
Source: SELECT-PsA 1 clinical study report.[78]

Percentage of patients with resolution of dactylitis at Week 24

The proportion of patients with resolution of dactylitis was defined as the proportion of patients with a Leeds Dactylitis Index of 0.[85] The Leeds Dactylitis Index is a score based on finger circumference and tenderness, assessed and summed across all dactylitic digits. The presence of dactylitis is defined as ≥ 1 affected and tender digit with a circumference increase from a reference digit of ≥ 10%.

At Week 24 in SELECT-PsA 1, treatment with upadacitinib was associated with a higher proportion of patients achieving dactylitis resolution compared with placebo ([redacted]).[78] This endpoint did not meet statistical significance owing to the hierarchical order of testing. While not powered for superiority, there was a numerically higher proportion achieving dactylitis resolution with upadacitinib compared with adalimumab ([redacted]) (Table 20).[78]

Table 20: Resolution of dactylitis at Week 24 (SELECT-PsA 1, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – control)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 136)	[redacted]	[redacted]	–	–	–
PBO (N = 126)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 127)	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LDI, Leeds Dactylitis Index; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: Resolution of dactylitis defined as LDI = 0. Nominal p value was constructed using the Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (Yes/No).
Source: SELECT-PsA 1 clinical study report.[78]

Change from baseline in patient's assessment of pain at Week 12

Pain is a common symptom of PsA that is ranked highest in patient-perceived importance.[42] In SELECT-PsA 1, the superiority of upadacitinib versus adalimumab in terms of change from baseline in patient's assessment of pain at Week 12 was measured as a ranked secondary endpoint.[78] Patients rated their pain using the Patient's Assessment Pain NRS, which ranged from 0 to 10; with no activity being indicated by 0 and severe activity indicated by 10.[85]

Owing to the hierarchical testing structure and one of the prior endpoints not being met, a significant treatment benefit for this outcome could not be measured. However, at Week 12 in SELECT-PsA 1, treatment with upadacitinib was associated with an improvement from baseline in patient's assessment of pain that was equal to adalimumab ([redacted] for both treatment arms) (Table 21).[78]

Table 21: Change from baseline in patient's assessment of pain at Week 12, superiority of UPA vs ADA (SELECT-PsA 1, FAS MMRM)

	Within group LS mean	**95% CI**	**Between group LS mean difference (UPA – control)**		
			Point estimate (95% CI)	**Nominal p value**	**Multiplicity adjusted p value**
UPA 15 mg (N = 404)	[redacted]	[redacted]	–	–	–
PBO (N = 392)	[redacted]	[redacted]	–	–	–
ADA 40 mg (N = 406)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Note: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis uses observed longitudinal data up to Week 12 prior to study drug premature discontinuation.
Source: SELECT-PsA 1 clinical study report.[78]

B.2.6.2.3 Other key secondary and exploratory endpoints

Percentage of patients with a PsARC response

PsARC is the only measure developed specifically for patients with PsA. To achieve a PsARC response, a patient must achieve two of the following four items, one of which must be a TJC68 or SJC66, and patients must have no worsening of any measure:[85]

- ≥ 30% improvement in TJC68
- ≥ 30% improvement in SJC66
- Improvement in PtGA of disease activity NRS
- Improvement in PGA of disease activity NRS

PsARC was assessed as an exploratory endpoint in SELECT-PsA 1. At Week 12, treatment with upadacitinib was associated with a higher proportion of patients achieving a PsARC response compared with placebo ([redacted]) and a numerically higher proportion of patients compared with adalimumab ([redacted]).[78] At Weeks 20 and 24, treatment with upadacitinib lead to [redacted]% of patients achieving a PsARC response, which was higher than both adalimumab and placebo response rates at both time points (Table 22).

Table 22: Percentage of patients with a PsARC response (SELECT-PsA 1, FAS NRI)

	Responder, n (%)	95% CI	Between group difference (UPA – control)	
			Point estimate (95% CI)	Nominal p value
Week 12				
UPA 15 mg (N = 429)	[redacted]	[redacted]	–	–
PBO (N = 423)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 429)	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
UPA 15 mg (N = 429)	[redacted]	[redacted]	–	–
PBO (N = 423)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 429)	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
UPA 15 mg (N = 429)	[redacted]	[redacted]	–	–
PBO (N = 423)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 429)	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; UPA, upadacitinib.
Note: Nominal p value was constructed using the Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 1 clinical study report.[78]

Analysis of radiographic endpoints at Week 24

Radiographic outcomes were assessed and scored using the SHS, which equals the total sum of joint erosion and joint space narrowing (JSN) scores.[85] At Week 24 in SELECT-PsA 1, treatment with upadacitinib was associated with inhibition of radiographic progression as shown by smaller mean increases from baseline in SHS, joint erosion score, and JSN score compared with placebo group (Table 23).[78] Mean change in joint erosion score and JSN scores from baseline were comparable

between upadacitinib and adalimumab arms. These findings were consistent in supportive analyses using linear extrapolation (see Appendix D).

Table 23 Summary of Change from Baseline in SHS, Joint Erosion Score, and JSN Score at Week 24 (SELECT-PsA 1, FAS AO)

	Within group LS mean (95% CI)	Between group difference (UPA – PBO)	
		LS mean diff (95% CI)	P value
SHS			
UPA 15 mg (N = 387)	[redacted]	[redacted]	[redacted]
PBO (N = 365)	[redacted]		
ADA 40 mg (N = 391)	[redacted]	–	–
Joint Erosion Score			
UPA 15 mg (N = 387)	[redacted]	[redacted]	[redacted]
PBO (N = 365)	[redacted]		
ADA 40 mg (N = 391)	[redacted]	–	–
JSN			
UPA 15 mg (N = 387)	[redacted]	[redacted]	[redacted]
PBO (N = 365)	[redacted]		
ADA 40 mg (N = 391)	[redacted]	–	–

Key: ANCOVA, analysis of covariance; AO, as observed; ADA, adalimumab; CI, confidence interval; diff, difference; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; JSN, joint space narrowing; LS, least square; PBO, placebo; SHS, Sharp van der Heijde Score; UPA, upadacitinib.
Note: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value were based on ANCOVA model including treatment and the stratification factor current DMARD use (yes/no) as fixed factors and baseline value as covariate.
Source: SELECT-PsA 1 clinical study report.[78]

Analysis of axial outcomes at Week 24

Asymmetrical axial involvement is a distinguishing factor of PsA, with axial joint disease being one of the key considerations driving treatment choice (see Section B.1.3.4).[10, 48] In SELECT-PsA 1, axial outcomes were measured as an exploratory outcome using the Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[85] The BASDAI is composed of six items, each scored on a 0–10 NRS with a lower score indicating less disease activity. The ASDAS is a composite index that assesses disease activity by combining five disease activity variables, specifically:

1. The patient's assessment of total back pain (BASDAI Question 2)
2. PtGA of disease activity (0–10 NRS)
3. Peripheral pain/swelling (BASDAI Question 3)
4. Duration of morning stiffness (BASDAI Question 6)
5. High-sensitivity C-reactive protein (hs-CRP) in mg/L

At Week 24 in SELECT-PsA 1, patients with psoriatic spondylitis at baseline demonstrated greater axial outcomes in terms of BASDAI50 and ASDAS changes from baseline when treated with upadacitinib compared with placebo or adalimumab (Table 24).[78]

Table 24: Changes in BASDAI and ASDAS from baseline to Week 24 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean (95% CI)	**Between group difference (UPA – control)**	
		LS mean (95% CI)	**P value**
BASDAI, change from baseline to Week 24			
UPA 15 mg (N = 139)	[redacted]	-	-
PBO (N = 130)	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 127)	[redacted]	[redacted]	[redacted]
ASDAS, change from baseline to Week 24			
UPA 15 mg (N = 139)	[redacted]	-	-
PBO	[redacted]	[redacted]	[redacted]

	Within group LS mean (95% CI)	Between group difference (UPA – control)	
		LS mean (95% CI)	P value
(N = 130)			
ADA 40 mg (N = 127)	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; diff, difference; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LSM, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; NRI, non-responder imputation; UPA, upadacitinib.
Notes: Analysis includes patients with presence of psoriatic spondylitis at baseline. Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 1 clinical study report.[78]

Change from baseline in EQ-5D-5L at Week 24

The EuroQoL 5 Dimensions 5 Levels visual analogue scale (EQ-5D-5L VAS) is a quantitative measure of patient's self-rated health on a vertical visual analogue scale, where endpoints are labelled 'the best health you can imagine' and 'the worst health you can imagine'. At Week 24 in SELECT-PsA 1, treatment with upadacitinib was associated with greater improvements from baseline compared with adalimumab and compared with placebo (nominal p<[redacted]) (Table 25).[78]

Table 25: Change from baseline in EQ-5D-5L index and VAS score at Week 24 (SELECT-PsA 1, FAS MMRM)

	Baseline mean	Visit mean	Within group LS mean (95% CI)	Between group LS mean difference (UPA – control)	
				Point estimate (95% CI)	Nominal p value
EQ-5D-5L index					
UPA 15 mg (N = 387)	[redacted]	[redacted]	[redacted]	–	–
PBO (N = 369)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 387)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS					
UPA 15 mg (N = 387)	[redacted]	[redacted]	[redacted]	–	–
PBO (N = 369)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 387)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; CI, confidence interval; EQ-5D-5L VAS, EuroQoL 5 Dimensions 5 Levels Visual Analogue Scale; FAS, full analysis set; LS, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 1 clinical study report.[78]

B.2.6.3 SELECT-PsA 2

B.2.6.3.1 Primary endpoint: ACR20 response rate at Week 12

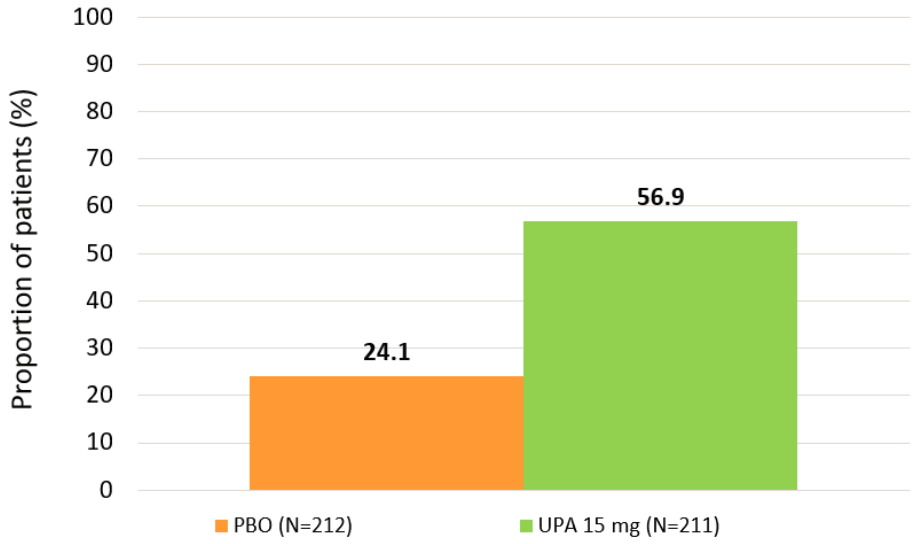
In SELECT-PsA 2, a significantly greater proportion of bDMARD-IR patients treated with upadacitinib achieved the primary endpoint of ACR20 response rate than patients treated with placebo at Week 12 (56.9% vs 24.1%, $p < 0.001$)(Table 26 and Figure 7).[83] Tipping point analyses were conducted as a sensitivity check and supported the findings of the primary analysis.

Table 26: ACR20 response rate at Week 12 (SELECT-PsA 2, FAS NRI)

	Upadacitinib 15 mg (N = 211)	**Placebo (N = 212)**
n (%)	120 (56.9)	51 (24.1)
95% CI[a]	[redacted]	[redacted]
Response rate difference (UPA – PBO)		
Point estimate	32.8	
95% CI[b]	24.0, 41.6	
p value[c]	<0.001	

Key: ACR, American College of Rheumatology; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation.
Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation; [c], nominal p value was constructed using the Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

Figure 7: ACR20 response rate at Week 12 (SELECT-PsA 2, FAS NRI)



Key: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: p ≤ 0.001 for UPA vs PBO.
Source: Adapted from SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

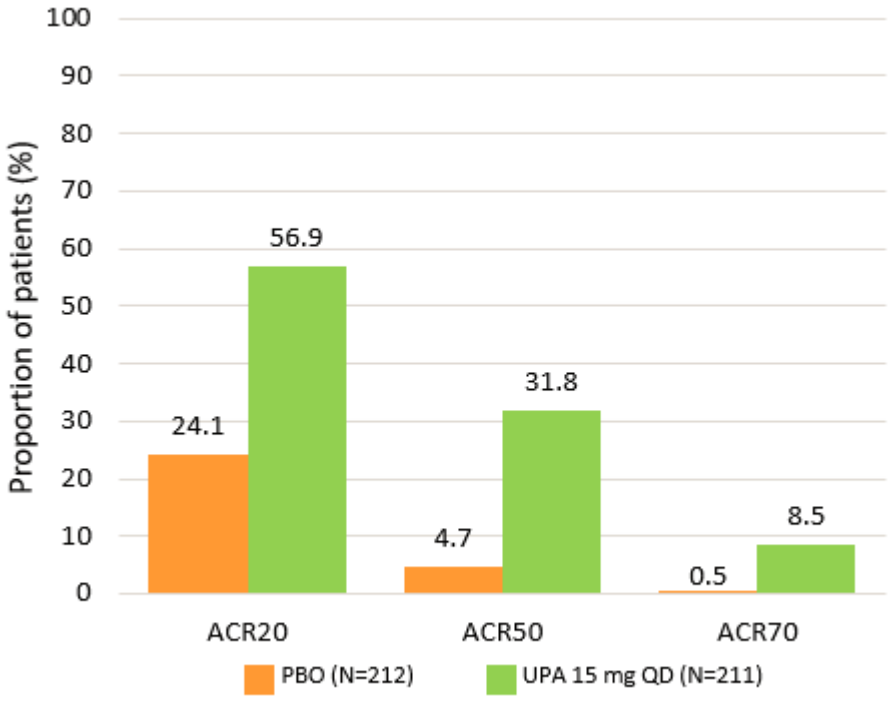
ACR20 responses for upadacitinib were observed as early as Week 2, at which point 32.7% of patients in the upadacitinib arm achieved a response compared with 10.8% in the placebo arm.[83] At Week 24, ACR20 response rates increased to [redacted]% for patients treated with upadacitinib, compared with [redacted]% of patients treated with placebo (Figure 8).[92]

Figure 8: ACR20 response rate up to Week 24 (SELECT-PsA 2, FAS NRI)

Key: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Source: Data on file.[92]

The benefit of upadacitinib was also observed using more stringent measures of ACR50 and ACR70 at Week 12, during which treatment with upadacitinib was associated with a greater proportion of patients achieving a response compared with placebo (Figure 9 and Appendix D).[79]

Figure 9: ACR20/50/70 response rates at Week 12 (SELECT-PsA 2, FAS NRI)



Key: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: p ≤ 0.001 for UPA vs PBO.
Source: Adapted from Mease et al 2020[83]

B.2.6.3.2 Secondary endpoints

The results for the ranked secondary endpoints were consistent with those of the primary analysis, with statistically significant improvements for upadacitinib compared with placebo for clinically relevant manifestations (Table 12).[79]

The key secondary outcomes of interest to this submission are described in detail in the subsequent sections. Full details of all outcomes measured are described in Appendix D.

Change from baseline in HAQ-DI at Week 12

In SELECT-PsA 2, patients treated with upadacitinib 15 mg had a significantly better change from baseline in HAQ-DI at Week 12 compared with placebo (-0.30 vs -0.10, p < 0.001) (Table 27).[83]

Table 27: Change from baseline in HAQ-DI at Week 12 (SELECT-PsA 2, FAS MMRM)

	Within group LS mean (95% CI)	**Between group LS mean difference (UPA – PBO)**		
		Point estimate (95% CI)	**Nominal p value**	**Multiplicity adjusted p value**
PBO (N = 180)	-0.10 (-0.16, -0.03)	-0.21 (-0.30, -0.12)	<0.001	[redacted]
UPA 15 mg (N = 199)	-0.30 (-0.37, -0.24)			

Key: CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; FAS, full analysis set; LS, least square; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean, 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

sIGA of psoriasis of 0 or 1 and ≥ 2-point improvement from baseline at Week 16

In SELECT-PsA 2, treatment with upadacitinib 15 mg was associated with a significantly higher proportion of patients achieving a sIGA of psoriasis of 0 or 1 and a ≥ 2-point improvement from baseline at Week 16 compared with placebo (36.8% vs 9.2%; p < 0.001)(Table 28).[83]

Table 28: sIGA of psoriasis score of 0 or 1 and ≥ 2-point improvement from baseline at Week 16 (SELECT-PsA 2, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – PBO)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
PBO (N = 163)	15 (9.2)	[redacted]	27.6 (19.2, 36.1)	<0.001	[redacted]
UPA 15 mg (N = 171)	63 (36.8)	[redacted]			

Key: CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; sIGA, Static Investigator Global Assessment; UPA, upadacitinib.
Notes: Includes patients with baseline sIGA > 2. Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no)
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

PASI75 response at Week 16

In SELECT-PsA 2, PASI score was recorded in patients with ≥ 3% BSA-Ps involvement at baseline.[83] At Week 16, the proportion of patients with a PASI75 was significantly higher for patients treated with upadacitinib 15 mg compared with those treated with placebo (52.3% vs 16.0%, p < 0.001) (Table 29).

Table 29: PASI75 response at Week 16 (SELECT-PsA 2, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – PBO)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
PBO (N = 131)	21 (16.0)	[redacted]	36.3 (25.6, 46.9)	<0.001	[redacted]
UPA 15 mg (N = 130)	68 (52.3)	[redacted]			

Key: CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area Severity Index; PBO, placebo; UPA, upadacitinib.
Note: Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no)
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

Change from baseline in FACIT-F at Week 12

At Week 12 in SELECT-PsA 2, treatment with upadacitinib was associated with a significantly greater change from baseline in FACIT-F compared with placebo (between group difference 3.7, 95% CI: 2.0, 5.4, p < 0.001) (Table 30).[83]

Table 30: Change from baseline in FACIT-F at Week 12 (SELECT-PsA 2, FAS MMRM)

	Within group LS mean	95% CI	Between group LS mean difference (UPA – PBO)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
UPA 15 mg (N = 201)	5.0	3.8, 6.1	3.7 (2.0, 5.4)	<0.001	[redacted]
PBO (N = 184)	1.3	0.1, 2.5			

Key: CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least square; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Note: Within group LS mean and 95% CI, and between group LS mean, 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

Percentage of patients with minimal disease activity at Week 24

At Week 24 in SELECT-PsA 2, treatment with upadacitinib 15 mg was associated with a significantly higher proportion of patients achieving MDA compared with treatment with placebo (25.1% vs 2.8%, p < 0.001)(Table 31).[83]

Table 31: Proportion of patients achieving MDA at Week 24 (SELECT-PsA 2, FAS NRI)

	Responders, n (%)	95% CI	Between group difference (UPA – PBO)		
			Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p value
PBO (N = 212)	6 (2.8)	[redacted]	[redacted]	<0.001	[redacted]
UPA 15 mg (N = 211)	53 (25.1)	[redacted]			

Key: CI, confidence interval; FAS, full analysis set; MDA, minimal disease activity; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.

Note: Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD
use (yes/no).
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

B.2.6.3.3 Other key secondary and exploratory endpoints

Percentage of patients with a PsARC response

PsARC was assessed as an exploratory endpoint in SELECT-PsA 2. At Week 12, treatment with upadacitinib was associated with a higher proportion of patients achieving a PsARC response compared with treatment with placebo ([redacted]).[79] This treatment effect was maintained at Weeks 20 and 24 (Table 32).

Table 32: Percentage of patients with a PsARC response (SELECT-PsA 2, FAS NRI)

	Responder, n (%)	95% CI	Between group difference (UPA – PBO)	
			Point estimate (95% CI)	Nominal p value
Week 12				
UPA 15 mg (N = 211)	[redacted]	[redacted]	[redacted]	[redacted]
PBO (N = 212)	[redacted]	[redacted]		
Week 20				
UPA 15 mg (N = 211)	[redacted]	[redacted]	[redacted]	[redacted]
PBO (N = 212)	[redacted]	[redacted]		
Week 24				
UPA 15 mg (N = 211)	[redacted]	[redacted]	[redacted]	[redacted]
PBO (N = 212)	[redacted]	[redacted]		

Key: CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; UPA, upadacitinib.
Note: Nominal p-value is constructed using Cochran-Mantel-Haenszel test adjusting for the main stratification factor of current DMARD use (yes/no).
Source: SELECT-PsA 2 clinical study report.[79]

Analysis of axial outcomes at Week 24

At Week 24 in SELECT-PsA 2, patients with psoriatic spondylitis at baseline demonstrated greater axial outcomes in terms of BASDAI50 and ASDAS changes from baseline when treated with upadacitinib compared with placebo (Table 33).[79]

Table 33: Changes in BASDAI and ASDAS from baseline to Week 24 (SELECT-PsA 2, FAS MMRM)

	Within group LS mean (95% CI)	Between group difference (UPA – placebo)	
		LS mean (95% CI)	P value
BASDAI, change from baseline to Week 24			
UPA 15 mg (N = 139)	[redacted]	-	-
PBO (N = 130)	[redacted]	[redacted]	[redacted]
ASDAS, change from baseline to Week 24			
UPA 15 mg (N = 139)	[redacted]	-	-
PBO (N = 130)	[redacted]	[redacted]	[redacted]

Key: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; diff, difference; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LSM, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; NRI, non-responder imputation; UPA, upadacitinib.
Notes: Analysis includes patients with presence of psoriatic spondylitis at baseline. Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 2 clinical study report.[79]

Change from baseline in patient's assessment of pain at Week 24

In SELECT-PsA 2, the change from baseline up to Week 24 in the patient's assessment of pain was measured as an exploratory endpoint.[79] Treatment with upadacitinib was associated with greater improvements in the patient's assessment of pain compared with placebo (between group difference [redacted]) (Table 34).[79]

Table 34: Change from baseline in patient's assessment of pain at Week 24, (SELECT-PsA 2, FAS MMRM)

	Within group LS mean	95% CI	Between group LS mean difference (UPA – PBO)

			Point estimate (95% CI)	Nominal p value
UPA 15 mg (N = 182)	[redacted]	[redacted]	[redacted]	[redacted]
PBO (N = 168)	[redacted]	[redacted]		

Key: CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least square; MMRM, Mixed-Effect Model Repeated Measurement; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Note: Within group LS mean and 95% CI, and between group LS mean, 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 2 clinical study report.[79]

Change from baseline in EQ-5D-5L at Week 24

At Week 24 in SELECT-PsA 2, treatment with upadacitinib was associated with greater EQ-5D-5L improvements from baseline compared with placebo (nominal p<[redacted] for EQ-5D-5L index and nominal p<[redacted] for EQ-5D-5L VAS) (Table 35).[79]

Table 35: Change from baseline in EQ-5D-5L index and VAS score at Week 24 (SELECT-PsA 2, FAS MMRM)

	Baseline mean	Visit mean	Within group LS mean (95% CI)	Between group LS mean difference (UPA – control)	
				Point estimate (95% CI)	Nominal p value
EQ-5D-5L index					
UPA 15 mg (N = 183)	[redacted]	[redacted]	[redacted]	–	–
PBO (N = 167)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS					
UPA 15 mg (N = 183)	[redacted]	[redacted]	[redacted]	–	–
PBO (N = 167)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; EQ-5D-5L VAS, EuroQoL 5 Dimensions 5 Levels Visual Analogue Scale; FAS, full analysis set; LS, least squares; MMRM, Mixed-Effect Model Repeated Measurement; PBO, placebo; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit,

treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.
Source: SELECT-PsA 2 clinical study report.[79]

B.2.7. Subgroup analysis

Prespecified subgroups for efficacy analyses included age, sex, body mass index (BMI), race, geographic region, time since PsA diagnosis, baseline high-sensitivity C-reactive protein, current use of csDMARDs, number of prior csDMARDs (SELECT-PsA 1 only), and number of prior failed bDMARDs (SELECT-PsA 2 only).[84, 85]

Results for subgroup analyses were consistent with those of the primary analysis in both SELECT-PsA 1 and SELECT-PsA 2.[78, 79] Subgroups of relevance to this submission are presented below. For full results of the prespecified subgroup analyses, see Appendix E.

B.2.7.1 Patients with prior csDMARD use

NICE recommends the use of bDMARDs in adults with PsA when the disease has not responded to ≥ 2 csDMARDs, alone or in combination (see Section B.1.3.4). SELECT-PsA 1 and SELECT-PsA 2 eligibility criteria stipulated that patients had an inadequate response or intolerance to treatment with at least one csDMARD. An assessment of the primary endpoint in patients with ≤ 1 versus > 1 prior csDMARD was a pre-specified subgroup analysis in SELECT-PsA 1.

In SELECT-PsA 1, the efficacy of upadacitinib was consistent regardless of the number of prior csDMARDs used. At Week 12 in patients receiving upadacitinib, [redacted]% of patients with ≤ 1 prior csDMARD achieved an ACR20 response compared with [redacted]% of patients with > 1 prior csDMARD.[78] ACR20 response rates in placebo and adalimumab arms were also consistent regardless of the number of prior csDMARDs used. The response rate difference between upadacitinib and placebo was [redacted] for patients with ≤ 1 prior csDMARD and [redacted] for patients with > 1 prior csDMARD (Table 36).

Table 36: Subgroup analysis of ACR20 response rate at Week 12 by number of prior csDMARDs (SELECT-PsA 1, FAS NRI)

	Responder, n (%)	95% CI[a]	Response rate difference (UPA – PBO)	
			Point estimate	95% CI[b]
≤ 1 prior csDMARD				
UPA 15 mg (N = 275)	[redacted]	[redacted]	–	–
PBO (N = 274)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 288)	[redacted]	[redacted]	–	–
> 1 prior csDMARDs				
UPA 15 mg (N = 154)	[redacted]	[redacted]	–	–
PBO (N = 149)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 141)	[redacted]	[redacted]	–	–

Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: [a], 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation.
Source: SELECT-PsA 1 clinical study report.[78]

B.2.7.2 Patients with prior biologic DMARD use

Over time, patients become unresponsive or intolerant to treatment with their initial bDMARD and require several lines of bDMARD therapy with different methods of action to manage PsA over their lifetime (see Section B.1.3.4).[4, 16] SELECT-PsA 2 was designed to assess the efficacy of upadacitinib in PsA patients who had previously received treatment with a bDMARD. An assessment of the primary endpoint in patients with 1 versus > 1 prior failed bDMARDs was a pre-specified subgroup analysis in SELECT-PsA 2.

Of patients receiving upadacitinib at Week 12 in SELECT-PsA 2, [redacted]% with 1 prior failed bDMARD and [redacted]% with > 1 prior failed bDMARD achieved an ACR20 response.[79] The response rate difference versus placebo was [redacted] for patients with

1 prior failed bDMARD and [redacted] for patients with > 1 prior failed bDMARD (Table 37).

Table 37: Subgroup analysis of ACR20 response rate at Week 12 by number of prior failed bDMARDs (SELECT-PsA 2, FAS NRI)

	Responder, n (%)	95% CI[a]	Response rate difference (UPA – PBO)	
			Point estimate	95% CI[b]
1 prior failed bDMARD				
UPA 15 mg (N = 126)	[redacted]	[redacted]	–	–
PBO (N = 135)	[redacted]	[redacted]	[redacted]	[redacted]
> 1 prior failed bDMARDs				
UPA 15 mg (N = 69)	[redacted]	[redacted]	–	–
PBO (N = 59)	[redacted]	[redacted]	[redacted]	[redacted]

Key: ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation.
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

A post-hoc analysis of SELECT-PsA 2 assessed more granular aspects of prior bDMARD exposure on upadacitinib efficacy.[93] Patients were assigned into subpopulations based on:

- The number of bDMARDs tried with inadequate response prior to enrollment (1, 2, or ≥ 3)
- Type of therapy for patients with inadequate response to one bDMARD prior to enrollment (TNF inhibitors and IL-17 inhibitors); other types of bDMARDs were excluded from this analysis due to small sample size
- Number of bDMARD mechanisms of action (MOA) tried prior to enrollment (1 MOA and ≥ 2 MOAs) for patients who had inadequate response to ≥ 2 bDMARDs; most patients were exposed to a TNF inhibitor or an IL-17 inhibitor

Compared to the overall population, upadacitinib 15 mg demonstrated generally consistent efficacy in patients with inadequate response to one or multiple prior bDMARDs, with similar efficacy observed whether inadequate response was to a TNF inhibitor or IL-17 inhibitor.[93] In addition, the proportion of patients on upadacitinib achieving comprehensive disease control, as measured by MDA, was generally comparable regardless of the number and type of prior bDMARDs, and number of MOAs tried. It is also important to note, however, that due to limited sample sizes for patients with inadequate response to > 1 bDMARD, these results should be interpreted with caution.

B.2.7.3 Patients with background csDMARD use

In SELECT-PsA 1 and SELECT-PsA 2, treatment with upadacitinib was associated with a consistent benefit regardless of background csDMARD use.[78, 79] In SELECT-PsA 1, the response rate difference (point estimate) between upadacitinib and placebo was [redacted] in patients currently using csDMARDs and [redacted] in patients not currently using csDMARDs. In SELECT-PsA 2, the response rate difference (point estimate) between upadacitinib and placebo was [redacted] in patients currently using csDMARDs and [redacted] in patients not currently using csDMARDs (Table 38). Together, these results suggest that background csDMARD use did not impact the treatment effect of upadacitinib in the SELECT-PsA trials.

Table 38: Subgroup analysis of ACR20 response rate at Week 12 by current use of csDMARDs (SELECT-PsA 1 and SELECT-PsA 2, FAS NRI)

	SELECT-PsA 1				SELECT-PsA 2			
	Responder, n/N (%)	95% CI[a]	Response rate difference (UPA – PBO)		Responder, n/N (%)	95% CI[a]	Response rate difference (UPA – PBO)	
			Point estimate	95% CI[b]			Point estimate	95% CI[b]
Current use of csDMARDs								
UPA 15 mg	[redacted]	[redacted]	–	–	[redacted]	[redacted]	–	–
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	–	–	–			
No current use of csDMARDs								
UPA 15 mg	[redacted]	[redacted]	–	–	[redacted]	[redacted]	–	–
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	–	–	–			

Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.
Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation.
Source: SELECT-PsA 1 and SELECT-PsA 2 clinical study reports.[78, 79]

B.2.8. Meta-analysis

Given the difference in patient populations of SELECT-PsA 1 and SELECT-PsA 2 trials, meta-analysis of these data is not appropriate.

An indirect treatment comparison (ITC) has been conducted to demonstrate the comparative efficacy of upadacitinib in biologic-naïve and biologic-experienced populations, and is described in detail in Section B.2.9. Note that the ITC includes findings for the upadacitinib 30 mg dose, although this dose is not included in the regulatory filing and is not being considered for use in PsA patients in the UK.

B.2.9. Indirect and mixed treatment comparisons

Other than the comparison with adalimumab in SELECT-PsA 1, there were no other studies identified through the SLR that investigated upadacitinib in comparison with bDMARDs/tsDMARDs in patients with PsA. Therefore, an ITC in the form of a network meta-analysis (NMA) was conducted.

B.2.9.1 Objective

The primary objective of the NMA was to compare the relative efficacy of upadacitinib, bDMARDs and tsDMARDs at Week 12 for the treatment of active PsA in biologic-naïve and biologic-experienced patients, measured by the following outcomes:

- Proportion of patients achieving a PsARC response (informing economic modelling)
- Proportion of patients achieving a PASI 50/75/90 response (informing economic modelling)
- HAQ-DI score change conditional on PsARC response status (responder vs non-responder; informing economic modelling)
- Proportion of patients achieving ACR 20/50/70 (an important determinant of a clinically meaningful response in PsA)

Comparisons of the relative efficacy of upadacitinib, bDMARDs and tsDMARDs at Week 24 were also measured, and are presented in Appendix D.1.3.

B.2.9.2 Methods

An SLR was conducted to identify clinical evidence on the efficacy and safety of products used for adult patients with active PsA (see Appendix D.1.3). The studies identified by the SLR were used to inform the NMA, which included randomised controlled trials (RCTs) with upadacitinib or treatments currently licensed by the EMA for adult patients with active PsA.

The NMA was performed separately for two subpopulations:

- Biologic-naïve population, defined as patients who had not previously been treated with a biological therapy
- Biologic-experienced population, defined as patients who had previously undergone treatment with a biological therapy

The statistical methods followed the recommended methods in the NICE Decision Support Unit Technical Support Document 2 and 3, conducted under a Bayesian generalised linear model framework. 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 models were used to model PsARC
- PASI 50/75/90 follows multinomial distributions; probit models were used to jointly model PASI 50/75/90
- HAQ-DI change conditional on PsARC response was assumed to follow a normal distribution; linear models were used to model HAQ-DI change among PsARC responders and PsARC non-responders, respectively
- ACR 20/50/70 follows multinomial distributions; probit models were used to jointly model ACR 20/50/70

In the main analysis, the following models were implemented for each outcome in each network:

- Biologic-naïve NMAs at Week 12: four sets of NMA models were implemented, due to observed trends in the initial random and fixed-effects models, indicating that placebo-response adjustment was required (see Appendix D.1.3):

  - Random-effects model
  - Random-effects model with placebo-response adjustment
  - Fixed-effects model
  - Fixed-effects model with placebo-response adjustment
- Biologic-experienced NMAs at Week 12: fixed-effects models were implemented (without placebo-response adjustment), because of the sparsity of the networks

When data stratified by biologic-naïve and biologic-experienced populations were not reported, the pooled data for an overall population that contains ≥ 50% patients with prior biologic use were considered for the biologic-experienced analysis; the results for an overall population that contains < 50% patients with prior biologic use were considered for the biologic-naïve analysis. This aligns with the approach used in the NICE appraisal of ixekizumab (TA537), whereby pooled data was used to inform the biologic-experienced network, given there would otherwise be very limited data available to estimate comparative efficacy in these patients.[82]

Data for pooled biologic-naïve and biologic-experienced populations were used in the following occasions:[94]

- PsARC in PALACE 1-3, RAPID-PsA, FUTURE 2, and OPAL-Broaden
- PASI in PALACE 1-3, FUTURE 3-5, and OPAL-Broaden
- HAQ-DI change conditional on PsARC in PALACE 1-3
- ACR in OPAL-Broaden

The composition of biologic-experienced patients within these clinical trials is described in Table 39.

Table 39: Composition of biologic-experienced patients in pooled trials

Trial name	Treatment name	Prior biologic therapy, n (%)
FUTURE 2	SEC 300 mg	Prior TNFi: • 1: 16 (16.0) • 2 or 3: 17 (17.0)
	SEC 150 mg	Prior TNFi: • 1: 26 (26.0) • 2 or 3: 11 (11.0)
	SEC 75 mg PBO	Prior TNFi: • 1: 21 (21.2)

Trial name	Treatment name	Prior biologic therapy, n (%)
		• 2 or 3: 13 (13.1)
	PBO	Prior TNFi: • 1: 16 (16.3) • 2 or 3: 19 (19.4)
FUTURE 3	SEC 300 mg	44 (31.7)
	SEC 150 mg	44 (31.8)
	PBO	44 (32.1)
FUTURE 4	SEC 150 mg load	27 (23.9)
	SEC 150 mg non-load	27 (23.7)
	PBO	27 (23.9)
FUTURE 5	SEC 300 mg with loading dose	68 (30.7)
	SEC 150 mg with loading dose	65 (29.5)
	SEC 150 mg without loading dose	64 (28.8)
	PBO	98 (29.5)
OPAL Broaden	PBO	*Trial excluded patients with prior use of TNFi; however, a small proportion (1-3%) received non- TNFi bDMARDs before randomisation*
	TOFA 5 mg BID	
	TOFA 10 mg BID	
	ADA 40 mg Q2W	
PALACE 1	PBO	41 (24.4)
	APR 20 mg BID	37 (22.0)
	APR 30 mg BID	41 (24.4)
PALACE 2	PBO	23 (14.5)
	APR 20 mg BID	28 (17.2)
	APR 30 mg BID	23 (14.2)
PALACE 3	PBO	48 (28)
	APR 20 mg BD	50 (30)
	APR 30 mg BD	43 (26)
RAPID PSA	PBO	NR (19.1)
	CZP 200 mg Q2W	NR (22.5)
	CZP 400 mg Q4W	NR (17)

Key: ADA, adalimumab; APR, apremilast; BID, twice daily; bDMARD, biological disease-modifying anti-rheumatic drug. CZP, certolizumab; NR, not reported; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC, secukinumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib.
Source: NMA technical report.

A sensitivity analysis was conducted for the biologic-naïve NMAs, where trials using pooled data were excluded from the networks. No sensitivity analysis was undertaken for the biologic-experienced networks because none of the trials in the biologic-experienced networks had pooled populations.

Of note, the models consider placebo adjustments to take account of improvements in the placebo responses observed in RCTs over time. The trend of increasing

placebo response rates over time is not limited to PsA and has been observed in other conditions.[95-97] There are a number of explanations; one of which involves patients in more recent trials being treated earlier so have accrued less damage and are more likely to have a better prognosis, even if treated with placebo. Further details regarding the rationale for the choice of NMA model and sensitivity analyses is provided in Appendix D.1.3.

To assess the trend observed in the placebo arms, the time trends of the outcomes among placebo patients in the biologic-naïve and biologic-experienced populations were plotted (see Appendix D.1.3). For the biologic-naïve population, the binary and ordinal endpoints (i.e. PsARC, PASI and ACR) all had increasing placebo response rates over time. For the biologic-experienced population, it was difficult to draw a definitive conclusion about the time trend due to the small number of included trials in this evidence base. Therefore, for the base case analysis, placebo-adjusted effectiveness estimates were used to inform the outcomes for the biologic-naïve population only. The models with placebo response adjustment are consistent with the approach described in the NICE DSU Technical Support Document 3 (e.g. Program 6a).[98] For further explanation on the rational and methods for placebo-adjusted models, see Appendix D.1.3.

A total of 28 trials were considered in the NMA feasibility assessment. This included one Phase II trial, 22 Phase III trials, one Phase IIIb/IV trial, one Phase IV trial, and two trials without a phase specified. Most of the trials were placebo controlled while the SPIRIT-H2H, SELECT-PsA 1, SPIRIT-P1, and OPAL-Broaden trials included adalimumab as an active comparator arm. In total, 24 studies were included in the biologic-naïve NMA at Week 12 and seven in the biologic-experienced NMA at Week 12. For further information related to the feasibility assessment, see Appendix D.1.3.

Appendix D.1.3 provides full details of the SLR (including Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram) and the NMA methodology and study selection criteria.

B.2.9.3 Results

The trials included in the biologic-naïve and biologic-experienced networks had a wide range of sample sizes, with earlier trials showing a trend for smaller sample sizes compared with more recent trials. A comparison of patient demographics and baseline characteristics between trials indicated that patients with similar demographics but wide ranging disease durations and prior treatments were included across trials.

Results for the biologic-naïve and biologic-experienced NMAs at Week 12 informed the economic modelling for upadacitinib and are presented in Sections B.2.9.3.1 and B.2.9.3.2.

The results at Week 24 data were used to inform scenario analyses and are provided in Appendix D.1.3.

B.2.9.3.1 Biologic-naive population

A total of 24 trials were included in the biologic-naive NMA at Week 12. The treatment outcomes informed by each of these studies are summarised in Table 40.

Table 40: Summary of trials used to carry out the biologic-naive NMA

Trial	Treatments	PsARC	PASI	HAQ–DI/ PsARC	ACR
SELECT–PsA 1	• UPA 15 mg • ADA • PBO	✓	✓	✓	✓
Mease 2018	• ADA • PBO	–	✓ (75/90)	–	✓ (20/50/70)
ADEPT	• ADA • PBO	✓	✓ (50/75/90)	✓	✓ (20/50/70)
Genovese 2007	• ADA • PBO	✓	–	✓	✓ (20/50/70)
PALACE 1	• APR 30 mg • PBO	✓	✓ (50/75)	✓	✓ (20)
PALACE 2	• APR 30 mg • PBO	✓	✓ (50/75)	✓	✓ (20)
PALACE 3	• APR 30 mg • PBO	✓	✓ (50/75)	✓	✓ (20)

Trial	Treatments	PsARC	PASI	HAQ–DI/ PsARC	ACR
ACTIVE	• APR 30 mg • PBO	–	–	–	✓ (20/50/70)
RAPID–PsA	• CRT Q2W or Q4W • PBO	✓	✓ (50/75/90)	–	✓ (20/50/70)
Mease 2000	• ETN • PBO	✓	✓ (50/75)	✓	✓ (20/50/70)
Mease 2004	• ETN • PBO	✓	✓ (50/75)	✓	✓ (20/50/70)
GO–REVEAL	• GOL • PBO	✓	✓ (50/75/90)	✓	✓ (20/50/70)
IMPACT	• INF • PBO	✓	✓ (50/75/90)	✓	✓ (20/50/70)
IMPACT 2	• INF • PBO	✓	✓ (50/75/90)	✓	✓ (20/50/70)
SPIRIT–P1	• IXE Q2W • IXE Q4W • ADA • PBO	✓	✓ (50/75)	–	✓ (20/50/70)
SPIRIT–H2H	• IXE Q4W • ADA	–	✓ (75/90)	–	✓ (50)
FUTURE 2	• SEC 300 mg • SEC 150 mg • PBO	✓	✓ (75/90)	–	✓ (20)
FUTURE 3	• SEC 300 mg • SEC 150 mg • PBO	–	✓ (75/90)	–	✓ (20/50)
FUTURE 4	• SEC 150 mg • PBO	–	✓ (75/90)	–	✓ (20/50)
FUTURE 5	• SEC 300 mg • SEC 150 mg • PBO	–	✓ (75/90)	–	✓ (20/50/70)
CHOICE	• SEC 300 mg • SEC 150 mg • PBO	–	✓ (75/90)	–	✓ (20/50/70)
OPAL–Broaden	• TOF 5 mg • ADA • PBO	✓	✓ (75)	–	✓ (20/50/70)

Trial	Treatments	PsARC	PASI	HAQ–DI/ PsARC	ACR
PSUMMIT 1	• UST 45 mg • PBO	✓	✓ (50/75/90)	–	✓ (20/50/70)
PSUMMIT 2	• UST 45 mg • PBO	✓	✓ (75)	–	✓ (20/50/70)
PSUMMIT 1+2[a]	• UST 45 mg • PBO	–	–	✓	–

Key: ACR, American College of Rheumatology; ADA, adalimumab; APR, apremilast; CRT, certolizumab pegol; ETN, etanercept; HAQ–DI, Health Assessment Questionnaire Disability Index; GOL, golimumab; INF, infliximab; IXE, ixekizumab; NMA, network meta–analysis; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab.
Note: [a], For the PSUMMIT studies, HAQ–DI/PsARC is only reported for the pooled studies.
Source: NMA technical report.

In the biologic-naïve population, although the majority of the treatments were connected with placebo (or adalimumab) by only one trial, some connections were able to use data from multiple trials. The binary and ordinal endpoints (i.e. PsARC, PASI, and ACR) all had increasing placebo response rates over time in the biologic-naïve population. For HAQ-DI change, there was not a clear time trend either among PsARC responders or PsARC non-responders.[94] The feasibility assessment and networks of evidence for each of the outcome measures is provided in Appendix D.1.3.

In the PsARC model applying random-effects with placebo-response adjustment, upadacitinib 15 mg showed a significantly higher PsARC response rate than tofacitinib (odds ratio [OR] [redacted]; 95% credible interval [CrI]: [redacted], [redacted]) and apremilast (OR [redacted]; 95% CrI: [redacted], [redacted]).

In the PASI model applying random-effects with placebo-response adjustment, upadacitinib 15 mg was significantly higher than apremilast (OR for PASI75: [redacted]; 95% CrI: [redacted], [redacted]) and etanercept (OR for PASI75: [redacted]; 95% CrI: [redacted],[redacted]), and significantly lower than secukinumab 300 mg (OR for PASI75: [redacted]; 95% CrI: [redacted], [redacted]), ixekizumab once every 4 weeks (Q4W; OR for PASI75: [redacted]; 95% CrI: [redacted], [redacted]), and ixekizumab once every 2 weeks (Q2W; OR for PASI75: [redacted]; 95% CrI: [redacted], [redacted]). It is worth mentioning that secukinumab 300 mg recommends its use for severe plaque psoriasis or inadequate responders to TNFα inhibitors. [63]

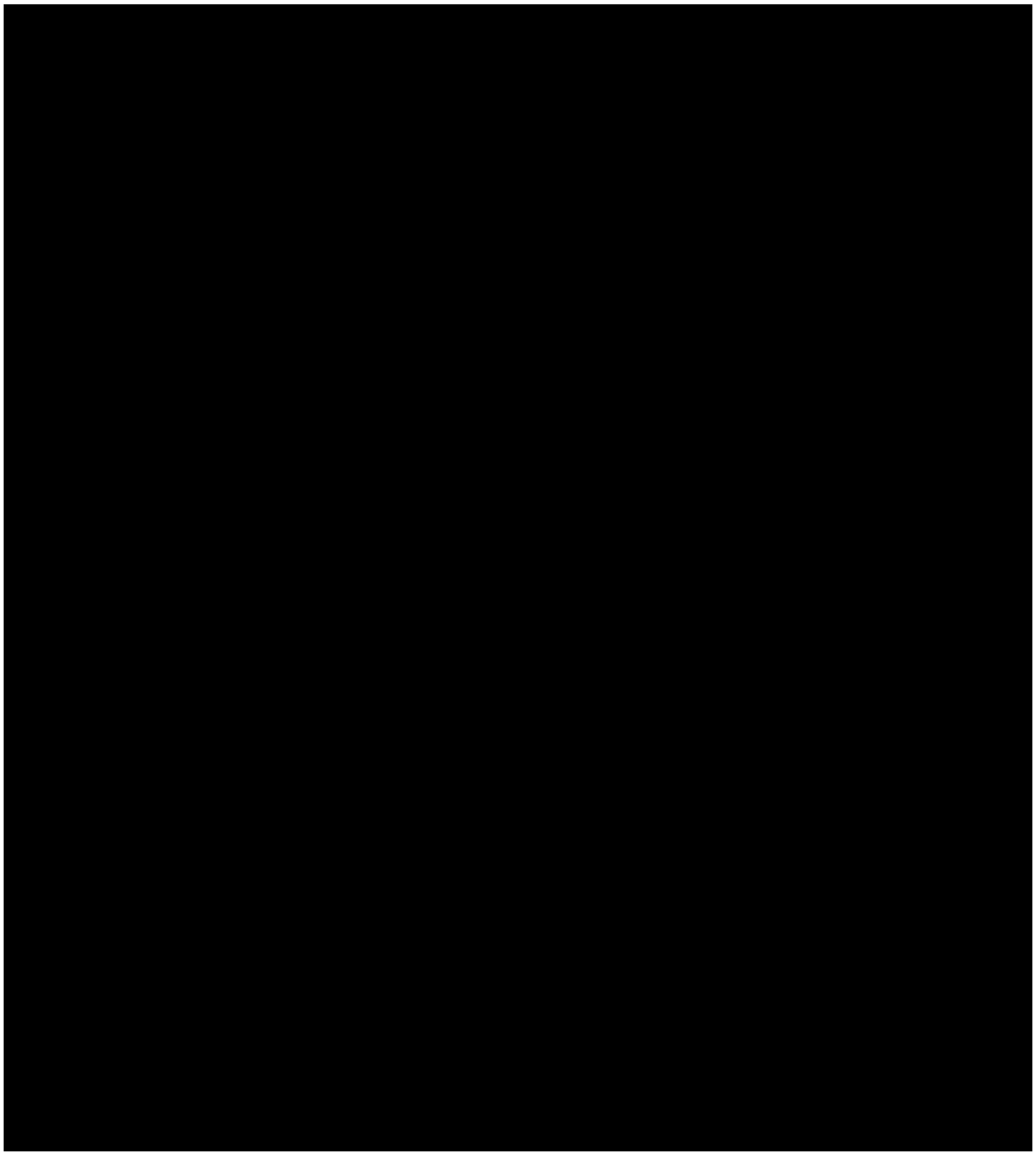
In the HAQ-DI conditional on PsARC model applying fixed-effects without placebo-response adjustment, there was a significantly larger reduction in HAQ-DI conditional on PsARC observed for upadacitinib 15 mg compared with apremilast (difference: [redacted]; 95% CrI: [redacted], [redacted]) and a significantly lower reduction in HAQ-DI compared with etanercept (difference: [redacted]; 95% CrI: [redacted], [redacted]).

In the ACR model applying random-effects with placebo-response adjustment, upadacitinib 15 mg showed a significantly higher ACR response rate than apremilast (OR for ACR20: [redacted]; 95% CrI: [redacted], [redacted]), ustekinumab (OR for ACR20: [redacted]; 95% CrI: [redacted], [redacted]), and secukinumab 150 mg (OR for ACR20: [redacted]; 95% CrI: [redacted], [redacted]).

Non-significant relative effectiveness findings for each outcome measure are available in Appendix D.1.3.

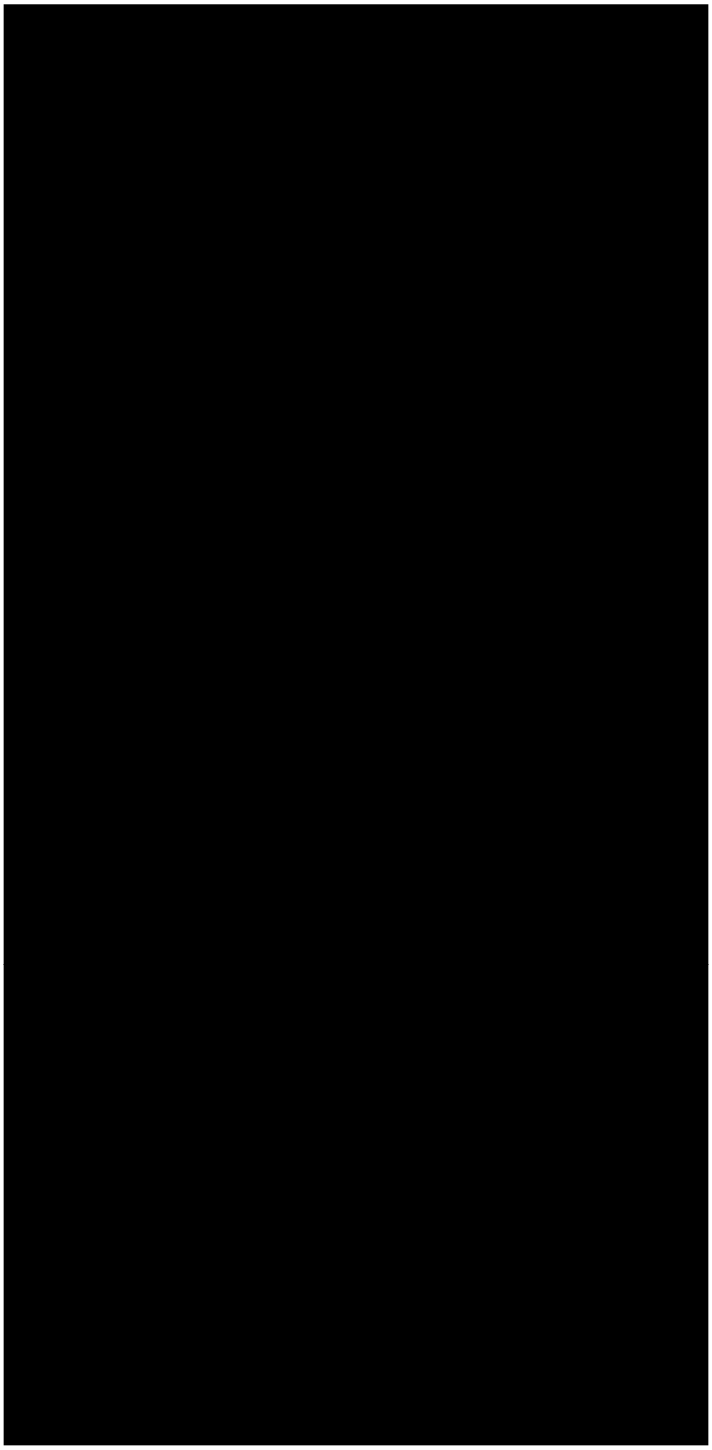
The estimated probabilities of achieving each outcome measure for upadacitinib 15 mg versus comparators in the biologic-naive population at Week 12 are presented in Figure 10 (PsARC), Figure 11 (PASI), Figure 12 (HAQ-DI), and Figure 13 (ACR). The absolute effect estimates for each comparator for each outcome measure are presented in Appendix D.1.3.

Figure 10: Estimated ORs (CrI) for upadacitinib 15 mg versus comparators for probability of achieving PsARC response (biologic-naïve NMA, Week 12)



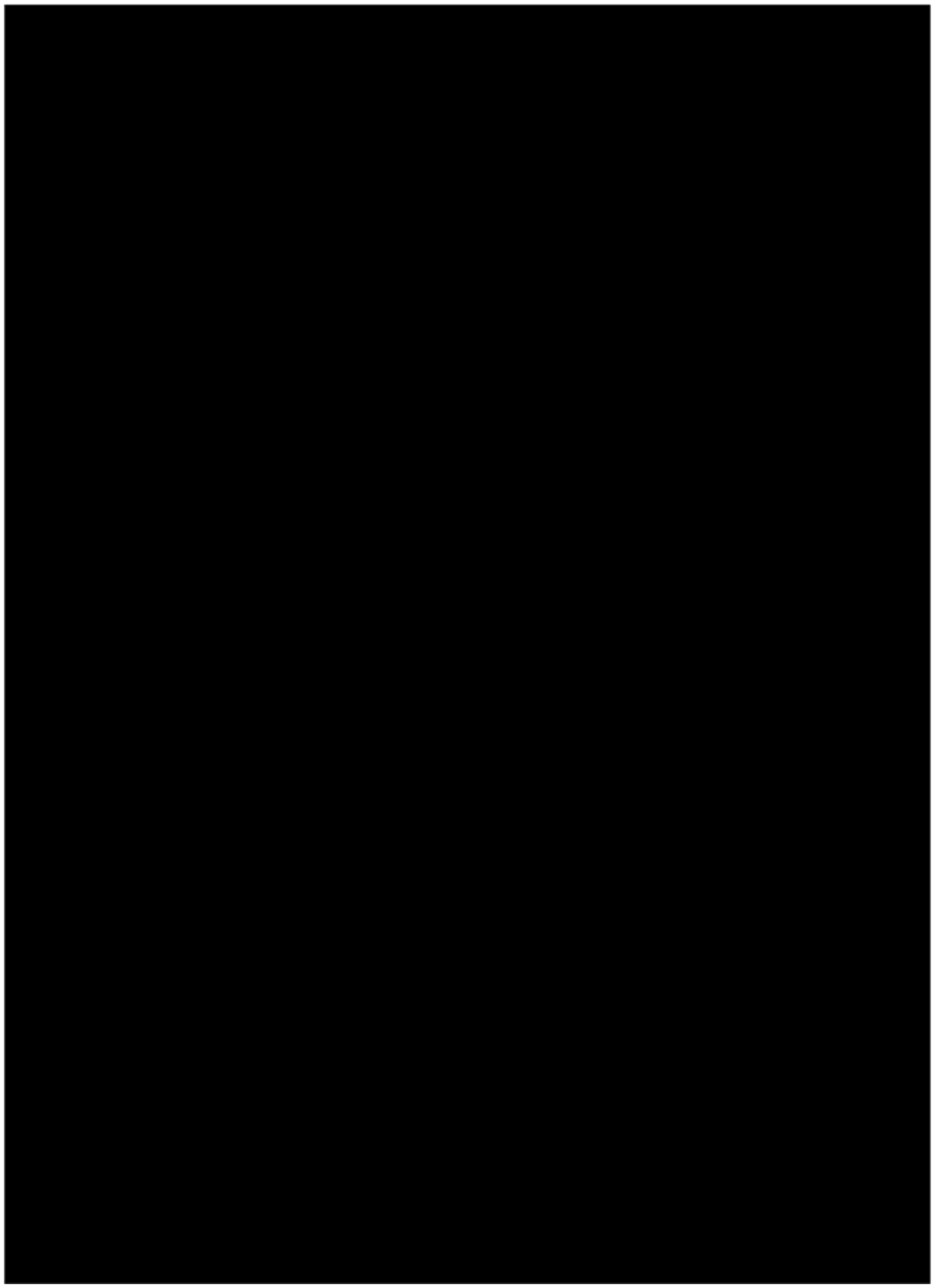
Key: CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PsARC, Psoriatic Arthritis Response Criteria; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying random-effects with placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 11: Estimated ORs (CrI) for upadacitinib 15 mg versus comparators for probability of achieving PASI response (biologic-naïve NMA, Week 12)



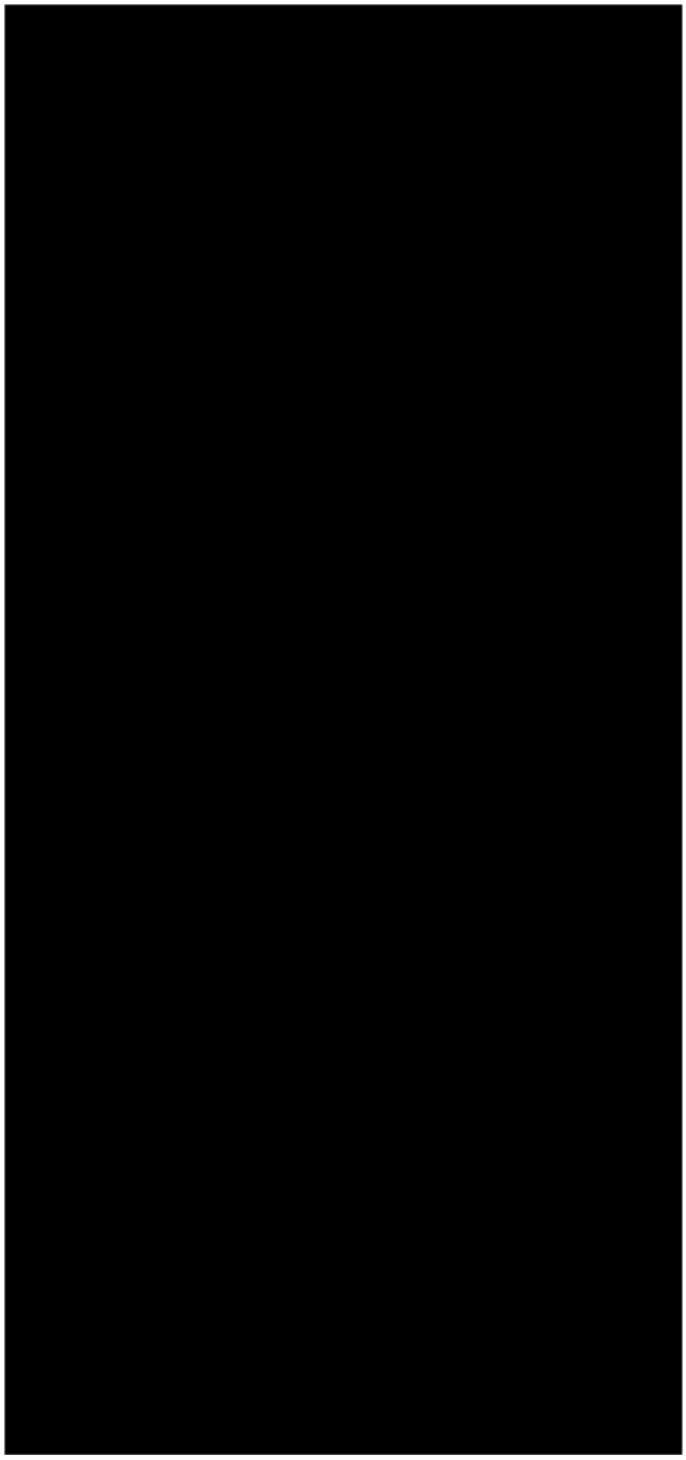
Key: CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PASI**,** Psoriasis Area and Severity Index; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying random-effects with placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 12: Estimated differences for upadacitinib 15 mg versus comparators in HAQ-DI (conditional on PsARC) change from baseline (biologic-naïve NMA, Week 12)



Key: HAQ-DI, Health Assessment Questionnaire Disability Index; NMA, network meta-analysis; PsARC, psoriatic arthritis response criteria; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying fixed-effects without placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 13: Estimated Ors (CrI) for upadacitinib 15 mg versus comparators for probability of achieving ACR response (biologic-naïve NMA, Week 12)



Key: ACR, American College of Rheumatology; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PASI**,** Psoriasis Area and Severity Index; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying random-effects with placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Overall, upadacitinib 15 mg showed broadly equivalent results compared to the current therapeutic options for treating biologic-naive PsA patients.

B.2.9.3.2 Biologic-experienced population

A total of seven trials were included in the biologic-experienced NMA at Week 12 (Table 41). Of note, the trial for certolizumab pegol (RAPID-PsA) was not included in the biologic-experienced networks, because it was the only trial that excluded patients with primary failure of a previous TNFα inhibitor. The exclusion was consistent with the recent NICE technology appraisals for secukinumab and certolizumab pegol, and tofacitinib.[1, 99]

Table 41: Summary of trials used to carry out the biologic-experienced NMA

Trial	Treatments	PsARC	PASI	HAQ–DI/ PsARC	ACR
SELECT–PsA 2	• UPA 15 mg • PBO	✓	✓ (50/75/90)	✓	✓ (20/50/70)
SPIRIT–P2	• IXE Q2W • IXE Q4W • PBO	✓	✓ (75/90)	–	✓ (20/50/70)
FUTURE 2	• SEC 300 mg • PBO	–	✓ (75/90)	–	✓ (20)
FUTURE 3	• SEC 300 mg • PBO	–	–	–	✓ (20/50)
FUTURE 5	• SEC 300 mg • PBO	–	–	–	✓ (20/50/70)
OPAL–Beyond	• TOF 5 mg • PBO	✓	✓ (75)	–	✓ (20/50/70)
PSUMMIT 2	• UST 45 mg • PBO	✓	✓ (75)	✓	✓ (20/50/70)

Key: ACR, American College of Rheumatology; HAQ–DI, Health Assessment Questionnaire Disability Index; IXE, ixekizumab; NMA, network meta–analysis; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; PBP, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC, secukinumab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab.
Source: NMA technical report.

The biologic-experienced networks were sparse, with the majority of the treatments connecting to placebo with only one trial. It was general difficult to draw definitive conclusions about the time trends of the outcomes among placebo patients due to the small number of biologic-experienced trials.[94] The feasibility assessment and networks of evidence for each of the outcome measures is provided in Appendix D.1.3.

In the PsARC model applying fixed-effects without placebo-response adjustment, upadacitinib 15 mg showed a significantly higher PsARC response rate than placebo (OR [redacted]; 95% CrI: [redacted], [redacted]); however, no statistically significant differences were observed between active treatments.

In the PASI model applying fixed-effects without placebo-response adjustment, upadacitinib 15 mg was significantly higher than tofacitinib (OR for PASI75: [redacted]; 95% CrI: [redacted], [redacted]).

In the HAD-DI conditional on PsARC model applying fixed-effects without placebo-response adjustment, no statistically significant differences were observed between upadacitinib and comparators.

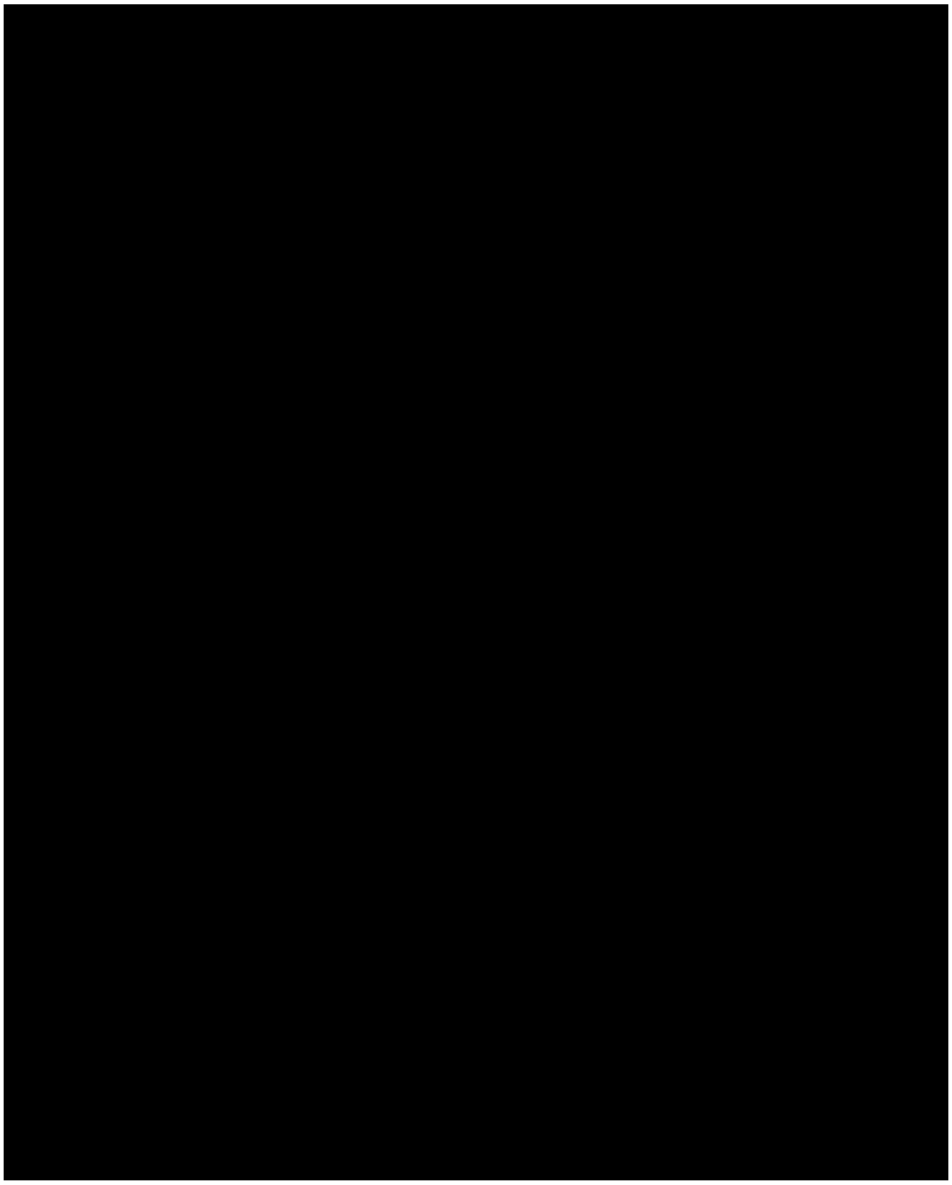
In the ACR model applying fixed-effects without placebo-response adjustment, upadacitinib 15 mg showed a significantly higher ACR response rate than placebo (OR for ACR20: [redacted]; 95% CrI: [redacted], [redacted]); however, no statistically significant differences were observed between active treatments (with the exception of upadacitinib 30 mg which has not been submitted for regulatory filing).

Non-significant relative effectiveness findings for each outcome measure are available in Appendix D.1.3. The estimated probabilities of achieving each outcome measure for upadacitinib 15 mg versus comparators in the biologic-experienced population at Week 12 are presented in Figure 14 (PsARC), Figure 15 (PASI), Figure 16 (HAQ-DI), and Figure 17 (ACR). The absolute effect estimates for each comparator for each outcome measure are presented in Appendix D.1.3.

Figure 14: Estimated ORs (CrI) for upadacitinib 15 mg versus comparators for probability of achieving PsARC response (biologic-experienced NMA, Week 12)

Key: CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PsARC, Psoriatic Arthritis Response Criteria; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying fixed-effects without placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 15: Estimated ORs (CrI) for upadacitinib 15 mg versus comparators for probability of achieving PASI response (biologic-experienced NMA, Week 12)

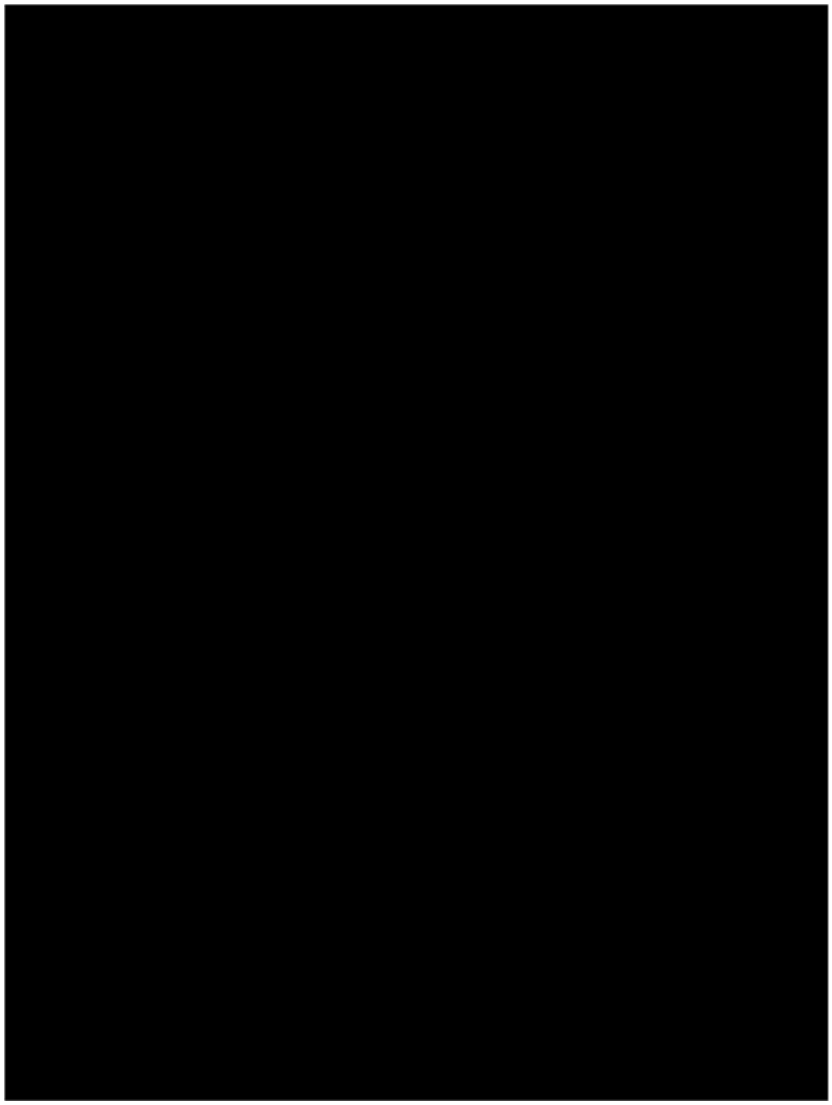


Key: CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PASI**,** Psoriasis Area and Severity Index; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying fixed-effects without placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 16: Estimated differences for upadacitinib 15 mg versus comparators in HAQ-DI (conditional on PsARC) change from baseline (biologic-experienced NMA, Week 12)

Key: HAQ-DI, Health Assessment Questionnaire Disability Index; NMA, network meta-analysis; PsARC, psoriatic arthritis response criteria; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying fixed-effects without placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Figure 17: Estimated ORs (CrI) for upadacitinib 15 mg versus comparators for probability of achieving ACR response (biologic-experienced NMA, Week 12)



Key: ACR, American College of Rheumatology; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; PASI**,** Psoriasis Area and Severity Index; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
Note: modelled applying fixed-effects without placebo-response adjustment.
*denotes a significant difference in treatment effect.
Source: NMA technical report.

Overall, upadacitinib 15 mg showed broadly equivalent results compared to the current therapeutic options for treating biologic-experienced PsA patients. Both 15 mg and 30 mg doses of upadacitinib had the highest probability of achieving a PsARC response versus other therapeutic options (although the 30 mg dose is not included in the regulatory filing).

These results are concordant with the exploratory measure of MDA response within the biologic-experienced NMA, for which upadacitinib 15 mg showed broadly

equivalent results compared to current therapeutic options for treating biologic-experienced PsA patients. For further details of the MDA response biologic-experienced NMA analysis and results, see Appendix D.1.3.

B.2.9.4 Uncertainties in the indirect treatment comparisons

A feasibility assessment was conducted to ascertain any between-trial heterogeneity along three dimensions:

- Trial design
- Patient characteristics
- Use of outcome data

A comparison of patient demographics and baseline characteristics between trials indicated that patients with similar demographics but wide ranging disease durations and prior treatments were included across trials. Similarly, a comparison of patients' disease characteristics across trials suggested that patients had varying degrees of concomitant plaque psoriasis and disease activity. With the exception of the EXCEED and ACTIVE trials, most studies permitted the concomitant use of csDMARDs during the trial period. There were differences observed in concomitant therapies used, for which the impact on outcomes could not be assessed. The clinical heterogeneity observed between trials in terms of disease duration and prior treatments supports the use of a random effect analysis within the biologic-naïve NMAs.

For the biologic-experienced population, the networks were sparse. While there may be cross-trial heterogeneities in treatment contrasts, the small number of trials made it infeasible to precisely estimate the level of such heterogeneities. Therefore, fixed effects models were deemed most appropriate in this scenario; however, it should be noted that where limited data are available the fixed effects analyses may underestimate uncertainty.

For biologic-naïve populations, heterogeneity was assessed using random-effects models with and without placebo-response adjustment for the NMAs at Week 12. The results suggested that there were between-trial heterogeneities in treatment contrasts for PsARC, PASI and ACR, but not for HAQ-DI change conditional on

PsARC. For PsARC, PASI and ACR, part of the heterogeneity was explained by the between-trial differences in placebo response rate. The results suggested that a high placebo response rate was associated with a low treatment contrast between the active treatment and placebo. However, after adjusting for placebo response rate in the models, some heterogeneity remained. It was difficult to identify the specific variables explaining the remaining heterogeneities, as many covariates were not assessed or reported uniformly across all trials. This aspect is true of all NMAs, and is also why a random effects analysis was used – as it assumes that there is some clinical heterogeneity between studies and that differences between trials are more than sampling variation.

Despite the above limitations (which are addressed where data allows), the analysis used the available data to produce an ITC in line with NICE guidance and was based on data from high-quality randomised trials, to estimate the relative efficacy of upadacitinib versus therapeutic options for PsA, and is appropriate to support inform decision making.

B.2.10. Adverse reactions

B.2.10.1 SELECT-PsA 1

B.2.10.1.1 Treatment exposure and subsequent therapy

At the Week 24 analysis, the mean duration of study drug exposure was similar between treatment arms.[78] The mean (standard deviation [SD]) duration of treatment was [redacted] days for upadacitinib 15 mg, [redacted] days for placebo, and [redacted] days for adalimumab.

B.2.10.1.2 Adverse events

The observed safety profile for upadacitinib in SELECT-PsA 1 was generally consistent with that observed in the rheumatoid arthritis clinical studies and SELECT-PsA 2. The rates of serious adverse events (AEs), severe AEs and AEs that resulted in drug discontinuation were comparable between the upadacitinib 15 mg and the placebo groups (Table 42).[78]

Table 42: Summary of adverse events up to Week 24 (SELECT-PsA 1, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 429)	Adalimumab 40 mg (N = 429)	Placebo (N = 423)
Any AE	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]
Any severe AE	[redacted]	[redacted]	[redacted]
Any AE with reasonable possibility of being related to study drug	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Occurring ≤ 30 days (70 days for ADA) after last dose	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; AE, adverse event; SAE, serious adverse event; SAS, safety analysis set.
Source: SELECT-PsA 1 clinical study report.[78]

Common adverse events

Up to Week 24, the System Organ Class (SOC) with the highest percentage of patients with treatment-emergent adverse events (TEAEs) was infections and infestations for patients in the upadacitinib, adalimumab, and placebo groups.[78] Among the upadacitinib and adalimumab groups, the percentages of patients with the most frequently reported TEAEs were generally comparable between the treatment groups, with the exception of increased blood creatine phosphokinase, which was higher for upadacitinib 15 mg (Table 43).

Table 43: TEAEs reported in ≥ 5% of patients in any treatment group up to Week 24 (SELECT-PsA 1, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 429)	Adalimumab 40mg (N = 429)	Placebo (N = 423)
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOW, every other week; TEAE, treatment-emergent adverse events.
Source: SELECT-PsA 1 clinical study report.[78]

The most frequently reported TEAEs considered by the investigator to have a reasonable possibility of being related to study drug in the upadacitinib 15 mg arm were increased blood creatine phosphokinase, upper respiratory tract infection, increased alanine aminotransferase, increased aspartate aminotransferase, leukopenia, and urinary tract infection.[78] See Appendix F for further details regarding these events.

Treatment-emergent AESIs up to Week 24

The numbers of adverse events of special interest (AESI) were comparable between the placebo and upadacitinib 15 mg groups, except for hepatic disorder and creatine phosphokinase elevation, where upadacitinib had higher rates compared with placebo.[78]

The rates of hepatic disorders were higher in the upadacitinib group than in the placebo group, but lower than in the adalimumab group.[78] Lower rates of herpes zoster, creatine phosphokinase elevation and lymphopenia were observed in patients treated with adalimumab compared with those treated with upadacitinib. No active tuberculosis, lymphoma or gastrointestinal perforation was reported in any treatment group.

Major adverse cardiovascular events (MACEs) and venous thromboembolisms (VTEs) were observed in the placebo and adalimumab groups, but not in the upadacitinib group (Table 44).[78]

Table 44: Summary of TEAE of special interest up to Week 24 (SELECT-PsA 1, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 429)	Adalimumab 40mg (N = 429)	Placebo (N = 423)
Any serious infection	[redacted]	[redacted]	[redacted]
Any opportunistic infection excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Any herpes zoster	[redacted]	[redacted]	[redacted]
Any active TB	[redacted]	[redacted]	[redacted]
Any malignancy	[redacted]	[redacted]	[redacted]
Any NMSC	[redacted]	[redacted]	[redacted]
Any malignancy other than NMSC	[redacted]	[redacted]	[redacted]
Any lymphoma	[redacted]	[redacted]	[redacted]
Any hepatic disorder	[redacted]	[redacted]	[redacted]
Any adjudicated GI perforation	[redacted]	[redacted]	[redacted]
Any anaemia	[redacted]	[redacted]	[redacted]
Any neutropenia	[redacted]	[redacted]	[redacted]
Any lymphopenia	[redacted]	[redacted]	[redacted]
Any CPK elevation	[redacted]	[redacted]	[redacted]
Any renal dysfunction	[redacted]	[redacted]	[redacted]
Any adjudicated MACE[a]	[redacted]	[redacted]	[redacted]
Any adjudicated VTE[b]	[redacted]	[redacted]	[redacted]

Key: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; SAS, safety analysis set; TB, tuberculosis; VTE, venous thromboembolism.
Notes: [a], MACE is defined as cardiovascular death (includes fatal acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular haemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke; [b], VTE includes deep vein thrombosis and pulmonary embolism.
Source: SELECT-PsA 1 clinical study report.[78]

Treatment-emergent adverse events leading to treatment discontinuation

Up to Week 24, the percentage of AEs leading to discontinuation was comparable between the upadacitinib 15 mg and placebo groups, and higher for adalimumab (Table 45).[78]

Table 45: TEAEs leading to discontinuation in ≥ 2 patients in any treatment group, up to Week 24 (SELECT-PsA 1, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 429)	Adalimumab 40mg (N = 429)	Placebo (N = 423)
Any adverse event	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOW, every other week; TEAE, treatment-emergent adverse event.
Source: SELECT-PsA 1 clinical study report.[78]

B.2.10.1.3 Deaths

Up to Week 24, [redacted] was reported in the placebo arm and no deaths were reported in the upadacitinib or adalimumab arms.[78]

B.2.10.2 SELECT-PsA 2

B.2.10.2.1 Treatment exposure and subsequent therapy

At the Week 24 analysis, the mean duration of study drug exposure was similar between treatment arms.[79] The mean (SD) duration of treatment was [redacted] days for upadacitinib 15 mg and [redacted] days for placebo.

B.2.10.2.2 Adverse events

The safety profile for upadacitinib in SELECT-PsA 2 was consistent with that seen in previous clinical studies across indications, with no new safety signals detected. The proportions of patients with serious AEs, severe AEs, and AEs leading to study drug discontinuation were numerically higher with upadacitinib 15 mg than with placebo (Table 46).[79]

Table 46: Summary of adverse events up to Week 24 (SELECT-PsA 2, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 211)	Placebo (N = 212)
Any AE	135 (64.0)	139 (65.6)
Any SAE	12 (5.7)	4 (1.9)
Any AE leading to discontinuation of study drug	15 (7.1)	11 (5.2)
Any severe AE	[redacted]	[redacted]
Any AE with reasonable possibility of being related to study drug	[redacted]	[redacted]
Deaths	0	1 (0.5)

Key: AE, adverse event; SAE, serious adverse event; SAS, safety analysis set.
Source: SELECT-PsA 2 clinical study report[79] and Mease et al 2020[83]

Common adverse events

Up to Week 24, the most frequently reported TEAEs (≥ 5% of patients) in any treatment group were upper respiratory tract infection, nasopharyngitis, urinary tract infection, diarrhea, blood creatine phosphokinase increased, bronchitis, psoriatic arthropathy, influenza, and nausea.[79] The percentages of patients with the most frequently reported TEAEs were generally comparable between placebo and upadacitinib 15 mg groups, with the exception of a higher rate of nasopharyngitis and diarrhea in the placebo arm and a higher rate of bronchitis and influenza in the upadacitinib 15 mg arm (Table 47).

Table 47: TEAEs reported in ≥ 5% of patients in any treatment group up to Week 24 (SELECT-PsA 2, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 211)	Placebo (N = 212)
Upper respiratory tract infection	13 (6.2)	10 (4.7)
Nasopharyngitis	10 (4.7)	17 (8.0)
Bronchitis	10 (4.7)	5 (2.4)
Psoriatic arthropathy	10 (4.7)	11 (5.2)
Urinary tract infection	9 (4.3)	12 (5.7)
Influenza	8 (3.8)	3 (1.4)
Diarrhoea	5 (2.4)	12 (5.7)
Nausea	4 (1.9)	7 (3.3)
Blood CPK increased	4 (1.9)	4 (1.9)

Key: CPK, creatine phosphokinase.
Source: Mease et al 2020[83]

The most frequently reported TEAEs considered by the investigator to have a reasonable possibility of being related to the study in the upadacitinib 15 mg arm were urinary tract infection and bronchitis.[79] See Appendix F for further details regarding these events.

Treatment-emergent AESIs up to Week 24

The number of events was low for the majority of AESIs and the percentages of patients with these events were generally comparable between the placebo and upadacitinib 15 mg groups. There was one death in the placebo group, one VTE event in the upadacitinib 15 mg group, and one non-fatal MACE in the upadacitinib 15 mg group (Table 48).[83]

Table 48: Summary of TEAE of special interest up to Week 24 (SELECT-PsA 2, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 211)	Placebo (N = 212)
Any serious infection	1 (0.5)	1 (0.5)
Any opportunistic infection excluding TB and herpes zoster	0	0
Any herpes zoster	3 (1.4)	2 (0.9)
Any active TB	0	0
Any malignancy	3 (1.4)	0
Any NMSC	1 (0.5)	0
Any malignancy other than NMSC	2 (0.9)	0
Any lymphoma	1 (0.5)	0
Any hepatic disorder	4 (1.9)	3 (1.4)
Any anaemia	4 (1.9)	2 (0.9)
Any neutropenia	2 (0.9)	1 (0.5)
Any lymphopenia	2 (0.9)	0
Any CPK elevation	4 (1.9)	4 (1.9)
Any renal dysfunction	0	1 (0.5)
Any adjudicated MACE[a]	1 (0.5)	
Any adjudicated VTE[b]	1 (0.5)	

Key: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; SAS, safety analysis set; TB, tuberculosis; VTE, venous thromboembolism
Notes: [a], MACE is defined as cardiovascular death (includes fatal acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular haemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke; [b], VTE includes deep vein thrombosis and pulmonary embolism.
Source: Mease et al 2020[83]

Treatment-emergent adverse events leading to treatment discontinuation

Up to Week 24, the percentages of AEs leading to discontinuation were comparable between the upadacitinib 15 mg and placebo groups (Table 49).[79]

Table 49: TEAEs leading to discontinuation in ≥ 2 patients in any treatment group, up to Week 24 (SELECT-PsA 2, SAS)

Patients, n (%)	Upadacitinib 15 mg (N = 211)	Placebo (N = 212)
Any adverse event	[redacted]	[redacted]
Psoriatic arthropathy	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]

Key: TEAE, treatment-emergent adverse event.
Source: SELECT-PsA 2 clinical study report.[79]

B.2.10.2.3 Deaths

Up to Week 24, one death was reported in the placebo arm and no deaths were reported in the upadacitinib arms.[83]

B.2.10.3 Integrated safety analysis

An integrated safety analysis, including patients who received ≥ 1 dose of study drug from SELECT-PsA 1 and SELECT-PsA 2, is presented in Table 50. The rates of TEAEs, SAEs, and AEs leading to study drug discontinuation were similar between upadacitinib, placebo and adalimumab arms.

Table 50: Integrated analysis of TEAEs through Week 24 (SELECT-PsA 1 and SELECT-PsA 2)

Event, n (%)	PBO (N=635)	UPA 15 mg (N=640)	ADA 40 mg (N=429)

AEs	391 (61.6)	422 (65.9)	278 (64.8)
Serious AEs	17 (2.7)	26 (4.1)	16 (3.7)
AEs leading to discontinuation	24 (3.8)	28 (4.4)	22 (5.1)
Deaths	2 (0.3)	0	0
AESIs			
Infection	213 (33.5)	240 (37.5)	146 (34.0)
Serious infection	5 (0.8)	6 (0.9)	3 (0.7)
Opportunistic infection	0	1 (0.2)	0
Herpes Zoster	5 (0.8)	7 (1.1)	0
Active tuberculosis	0	0	0
Non-melanoma skin cancer	1 (0.2)	1 (0.2)	0
Malignancy other than NMSC	0	3 (0.5)	3 (0.7)
MACE (adjudicated)	1 (0.2)	1 (0.2)	2 (0.5)
VTE (adjudicated)	1 (0.2)	1 (0.2)	2 (0.5)
Gastrointestinal perforation (adjudicated)	0	0	0
Hepatic disorder	19 (3.0)	43 (6.7)	67 (15.6)
Anemia	6 (0.9)	7 (1.1)	1 (0.2)
Neutropenia	2 (0.8)	6 (0.9)	10 (2.3)
Lymphopenia	5 (0.8)	10 (3.5)	1 (0.5)
CPK elevation	10 (1.6)	42 (6.6)	24 (5.6)
Renal dysfunction	2 (0.3)	0	0

Key: ADA, adalimumab; AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; EOW, every other week; MACE, major adverse cardiovascular events; NMSC; non-melanoma skin cancer; PBO, placebo; QD, once daily; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism; UPA, upadacitinib.
Source: Burmester, 2020[100]

B.2.11. Ongoing studies

There are no ongoing studies of upadacitinib in PsA. However, Period 2 of the SELECT-PsA 1 and SELECT-PsA 2 trials are ongoing and are anticipated to provide evidence for the longer-term use of upadacitinib; results are not expected to be available in time to inform this appraisal.

B.2.12. Innovation

Patients with inadequate responses to ≥ 2 csDMARDs currently have several TNFα inhibitor or IL inhibitor treatment options. However, in a complex disease such as PsA, there may be multiple dysregulated cytokines, and therefore blockading one cytokine alone may not inhibit all pathogenic pathways. The JAK tyrosine kinases, which include JAK1, JAK2, JAK3 and TYK2, are intracellular molecules involved in signalling transduction of key cytokines implicated in the complex pathophysiology of PsA.

Upadacitinib, as a selective and reversible JAK inhibitor, preferentially inhibits signalling by JAK1 or JAK1/3, which directly and indirectly mediates the systemic inflammation of PsA, therefore maximising inhibition of inflammatory disease activity.[6] Selectivity for JAK1, versus other JAK subtypes, provides a degree of PsA disease specificity that differentiates upadacitinib from tofacitinib – a non-selective inhibitor of JAK1 and JAK3, and the only JAK inhibitor currently approved for use in PsA patients in the UK.[55] Upadacitinib provides several benefits versus tofacitinib, namely:[6, 77]

- Upadacitinib 15 mg is suitable for use across age groups, including patients aged over 65 years
- Upadacitinib 15 mg does not require dose adjustment to mitigate safety concerns
- Upadacitinib 15 mg offers the flexibility of monotherapy

Furthermore, there is emerging evidence to show that JAK inhibitor response is not compromised by prior JAK inhibitor exposure. In rheumatoid arthritis patients discontinuing their first JAK inhibitor due to inefficacy or side effects, there was no loss of response with the second JAK inhibitor.[101] Owing to the chronic and progressive nature of disease, most patients with PsA are expected to become nonresponsive or intolerant to treatment over time,[16] and adding another JAK inhibitor to the clinician's armamentarium fulfils an important unmet need for additional treatment options.

Another therapeutic class used in the ≥ 2 csDMARDs setting includes IL-17 inhibitors. IL-17 inhibitors are associated with high levels of skin clearance in PsA

patients, although are also associated with gastro-intestinal side effects that restrict their use and exclude patients with a predisposition to inflammatory bowel disease.[102] The safety profile of upadacitinib 15 mg does not require such restrictions, thereby providing a treatment option to a broader patient population.[6]

Upadacitinib has a fast onset of action, with patients achieving ACR20 as early as 2 weeks from treatment initiation, resulting in rapid improvement in painful joint count and functional impairment.[78, 79] The oral administration route of upadacitinib provides additional benefit in achieving rapid improvements, as oral availability removes the requirement for in-hospital treatment and injection training, which would otherwise be required for subcutaneously administered PsA therapies. This has important implications for optimising treatment adherence and persistence,[69] and is particularly valuable in the current COVID-19 pandemic as it reduces the risk of infection via close contact. Additionally, the BSR COVID-19 guidance recommends initiating vulnerable patients on JAK inhibitors, given they have a shorter half-life and a rapid wash out compared to other biologics.[75]

PsA remains a treatment challenge due to the heterogenous nature of the disease and treatment goals remain unmet, as many patients experience residual pain and functional impairment with current treatment options. Few treatment options are able to offer meaningful improvement across the many musculoskeletal and skin manifestations for patients, without sacrificing on key manifestations like axial disease, enthesitis, and dactylitis.

In the SELECT-PsA 1 and SELECT-PsA 2 trials, upadacitinib 15 mg demonstrated efficacy across the spectrum of relevant disease domains, including axial disease, enthesitis and dactylitis, which translated to improvements in fatigue and pain. Of particular note is the ability of upadacitinib to address axial disease, which extends beyond PsA to axial spondyloarthritis patients,[103] exemplifying the broad efficacy of upadacitinib across the spectrum of spondyloarthritic diseases.[103] As such, upadacitinib may play an important role in preventing structural damage and preserving functional mobility of the axial skeleton which would otherwise have a devastating impact on patient HRQL.[104]

The ability of upadacitinib to target several of the multifactorial symptoms of PsA is a prominent advantage, as it minimises the treatments otherwise required for patients to address this heterogeneous disease.[78, 79]

Upadacitinib has a well-characterised, acceptable safety profile in the PsA population, contributing to its positive benefit/risk profile in these patients. It alters the course of disease for PsA patients, which translates to significant improvements in physical function and disability – and provides an additional option to the clinician's armamentarium to manage this lifelong, relapsing and remitting disease.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence

Upadacitinib is a fast-acting, orally available treatment for PsA in patients with inadequate responses to both csDMARDs and bDMARDs. It inhibits structural damage to joints, prevents progression and development of extra-articular manifestations and axial disease, and is associated with meaningful improvements in physical function and ability to conduct daily activities. Importantly, it improves HRQL while demonstrating an acceptable safety profile.

As a composite measure that captures improvement in tender and swollen joints, patient and physician global assessment, functional ability and pain, the ACR20 is a reliable and impactful measure of disease activity and treatment benefit in PsA.[81] In as quickly as 2 weeks, patients treated with upadacitinib demonstrate an ACR20 response.[78, 79] At Week 12, both trials met their primary endpoint and together demonstrated a statistically significant improvement of ACR20 response with upadacitinib compared with placebo, and a numerically greater advantage compared with adalimumab in biologic naïve patients (SELECT-PsA 1). In both SELECT-PsA 1 and SELECT-PsA 2, the results for the ranked secondary endpoints were consistent with those of the primary analysis, with better efficacy for upadacitinib versus placebo observed for all measures (Table 12).[78, 79] These measures demonstrate the benefit of upadacitinib for addressing clinically relevant manifestations of PsA, and therefore achieving key treatment goals such as preventing joint damage, stopping swelling, reducing pain and improving HRQL.[12]

The core goal of treatment is to minimise disease activity, with MDA response acting as a surrogate marker in clinical trials to define patients whose disease state meets pre-defined, established criteria for 'minimal activity'.[13] As a composite measure, MDA takes into account multiple domains of this heterogeneous disease, such physical assessments of joint and skin involvement, and patient reported pain and health disability. In both SELECT-PsA 1 and SELECT-PsA 2, upadacitinib 15 mg was associated with a significantly higher proportion of patients achieving MDA compared with placebo.[78, 79] In biologic-naïve patients in SELECT-PsA 1, upadacitinib 15 mg was associated with a numerically higher proportion of patients achieving MDA compared with adalimumab. Results of the biologic-experienced NMA demonstrated similar findings, with broadly equivalent efficacy in terms of MDA achieved with upadacitinib 15 mg compared with current therapeutic options in PsA.

SELECT-PsA 1 is one of the few trials in PsA to provide direct comparative evidence to biological therapies. Although not formally assessed in the hierarchical statistical testing structure, SELECT-PsA 1 demonstrated nominally significant benefit for patients receiving upadacitinib 15 mg compared with adalimumab in outcome measures including:[78]

- ACR20 at Week 24
- HAQ-DI at Week 12
- BASDAI at Week 24
- ASDAS at Week 24
- PsARC at Weeks 20 and 24 (the only disease activity measure developed specifically for PsA)
- EQ-5D-5L at Week 24[78]

Although ITC evidence portrays upadacitinib 15 mg as broadly equivalent to current therapeutic options for treating biologic-naive and biological-experienced PsA patients, the direct evidence from SELECT-PsA 1 points to improvements versus standard of care in some key outcomes.

In both SELECT-PsA 1 and SELECT-PsA 2, upadacitinib demonstrated a consistent safety profile, as observed in other indications, with no new safety signals.[78, 79]

Upadacitinib has an established and acceptable tolerability profile while providing the simplicity of one dose, one pill, once a day.

B.2.13.2 Strengths and limitations of the clinical evidence base

While SELECT-PsA 1 and SELECT-PsA 2 were representative of trial designs and patient populations commonly used in PsA, there were aspects of the trials that may not be considered representative of patients anticipated to receive upadacitinib in the UK. SELECT-PsA 1 and SELECT-PsA 2 included patients with one prior csDMARD, whereas the prescribing of biologics to patients in the UK is restricted to those who have had an inadequate response to ≥ 2 csDMARDs. Given the similar efficacy for upadacitinib in subgroups of patients with one versus two prior csDMARDs (see Section B.2.7.1), the treatment benefit observed in these trials is expected to translate to the UK population. The prior csDMARD most frequently used was methotrexate; which aligns with previous clinical trials, UK clinical practice, and previous NICE appraisals in PsA.[1, 82]

SELECT-PsA 1 is one of the few trials in PsA to provide head-to-head evidence for biological therapies. In addition to direct comparative evidence, NMAs were conducted in line with precedent from previous appraisals that further confirmed the broadly equivalent benefit of upadacitinib in biologic-naïve and biologic-experienced populations (see Section B.2.9).

The rates of response in the placebo arms of SELECT-PsA 1 and SELECT PsA-2 were high, which may impact comparative estimates of the treatment effect. The trend of increasing placebo response rates over time is not limited to PsA and has been observed in other conditions.[95-97] There are a numbers of explanations; one of which involves patients in more recent trials being treated earlier so have accrued less damage and are more likely to have a better prognosis, even if treated with placebo. To prevent dilution of the treatment effect, in line with previous appraisals, placebo effects were adjusted in the NMA.

Overall, the SELECT-PsA 1 and SELECT-PsA 2 clinical trial programme represents the largest clinical trial programme in PsA to date and provides an appropriate base to inform the assessment of clinical and cost effectiveness of upadacitinib for the

treatment of PsA. As SELECT-PsA 1 and SELECT-PsA 2 are both high-quality studies, conducted in accordance with ethical principles of Good Clinical Practice, they meet the quality assessment criteria indicative of reliable internal validity (see Section B.2.5). Together, SELECT-PsA 1 and SELECT-PsA 2 demonstrate the efficacy of upadacitinib in both csDMARD-IR and bDMARD-IR patients, with meaningful magnitudes of responses in clinically relevant manifestations of PsA.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search for existing economic evaluations in moderate to severe PsA did not identify any previous cost-effectiveness studies for upadacitinib in this population. The search strategy was originally performed on 6 September 2019 and subsequently updated twice: first on 26 May 2020 and second on 3 September 2020. Full details of these searches and the findings are reported in Appendix G. Overall, the review identified 55 studies from 63 publications eligible for inclusion in the cost-effectiveness review. Nineteen studies from 25 publications were for the UK setting and of those, eight were NICE technology appraisals (TAs).

Table 51 summarises key components of the three most recent NICE TAs[1, 5, 82]; throughout the remainder of Section B.3 we draw lessons from these, in the spirit of incremental evidence development and consistency across NICE evaluations.

Table 51: Summary list of the three most recent published cost-effectiveness studies

Study	Year	Summary of model	Summary of NMA	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA543 (tofacitinib)[1]	2018	Markov cohort model with 3-monthly cycles consisting of trial periods, continued trial periods and BSC Subpopulation: 2: bDMARDs naïve 3: prior-bDMARDs 4. Contraindicated to TNFα inhibitor	Two networks: biologic-naïve and biologic-experienced. Overall population data used for some comparators: in the biologic-naïve network ~50% (CZP) ~20% (SEC) 14- 30% (APR) had prior bDMARDs Where data were not available from a primary publication, they were extracted from the TA445 AG report	Biologic-naïve 47.9 Biologic-experienced 50	Incremental QALYs vs BSC **bDMARDs naïve** TOF: 2.52 APR: 2.02 ADA: 2.67 CZP: 2.89 ETAN: 3.20 SEC: 2.85 GOL: 2.9 INF: 3.26 **prior-bDMARDs** TOF: 1.30 UST: 1.42 SEC: 1.60 **TNFα inhibitor contraindicated:** TOF: 1.14 UST: 1.33 SEC: 1.62	Incremental costs vs BSC **bDMARDs naïve** TOF: £32,822 APR: £39,434 ADA: £47,275 CZP: £49,490 ETAN: £50,598 SEC: £51,143 GOL: £53,774 INF: £69,389 **prior-bDMARDs** TOF: £11,732 UST: £26,709 SEC: £54,206 **TNFα inhibitor contraindicated:** TOF: £8,930 UST: £24,979 SEC: £30,153	Incremental QALYs vs BSC **bDMARDs naïve** TOF: £13,029 APR: £19,555 ADA: £17,701 CZP: £17,145 ETAN: £15,799 SEC: £17,931 GOL: £18,507 INF: £21,270 **prior-bDMARDs** TOF: £9,001 UST: £18,761 SEC: £33,914 **TNFα inhibitor contraindicated:** TOF: £7,825 UST: £18,837 SEC: £18,557

Study	Year	Summary of model	Summary of NMA	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA537 (ixekizumab)[82]	2018	A Markov cohort model with patients in three health states: • Trial period • Continued treatment period • Receiving BSC	Two networks: biologic-naïve and biologic-experienced. HAQ-DI results from pooled population (not stratified by prior biologic use). Overall population data used for some comparators: in the biologic-naïve network ~50% (CZP) ~20% (SEC) 14- 30% (APR) had prior bDMARDs As change from baseline HAQ-DI conditional on response was not publicly available for CZP, the value for golimumab has been used instead.	Biologic-naïve 49.5 Biologic-experienced 51.9	**bDMARD-naïve, no psoriasis sub population** BSC: 8.09 APR→ UST→ BSC: 9.49 CRT→ UST→ BSC: 9.67 SEC→ UST→ BSC: 9.78 ADA→ UST→ BSC: 9.71 ETN→ UST→ BSC: 10.02 GOL→ UST→ BSC: 9.90 IXE→ UST→ BSC: 9.69 INF→ UST→ BSC: 10.12 **bDMARD-naïve, mild-to-moderate psoriasis subpopulation** BSC: 7.74 APR→ UST→ BSC: 9.16 CRT→ UST→ BSC: 9.34	**bDMARD-naïve, no psoriasis sub population** BSC: £54,046 APR→ UST→ BSC: £93,347 CRT→ UST→ BSC: £99,866 SEC→ UST→ BSC: £100,241 ADA→ UST→ BSC: £101,322 ETN→ UST→ BSC: £103,692 GOL→ UST→ BSC: £108,195 IXE→ UST→ BSC £116,010 INF→ UST→ BSC: £127,297 **bDMARD-naïve, mild-to-moderate psoriasis subpopulation** BSC: £70,006 APR→ UST→ BSC: £105,446 CRT→ UST→ BSC: £111,375	ICER/QALY IXE sequence vs comparator **bDMARD-naïve, no psoriasis subpopulation** BSC: £38,750 APR→ UST→ BSC: £109,534 CRT→ UST→ BSC: £636,928 SEC→ UST→ BSC: IXE dominated ADA→ UST→ BSC: IXE dominated ETN→ UST → BSC: IXE dominated GOL→ UST→ BSC: IXE dominated INF→ UST→ BSC: £26,593 **bDMARD-naïve, mild-to-moderate-psoriasis subpopulation** BSC: £35,316 APR→ UST→ BSC: £99,733 CRT→ UST→ BSC: £431,727

Study	Year	Summary of model	Summary of NMA	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					SEC→ UST→ BSC: 9.47 ADA→ UST→ BSC: 9.39 ETN→ UST→ BSC: 9.69 GOL→ UST→ BSC: 9.59 IXE Q4W→ UST→ BSC: 9.38 INF→ UST→ BSC: 9.82 **bDMARD-naïve, moderate-to-severe psoriasis subpopulation** BSC: 6.21 APR→ UST→ BSC: 7.70 CRT→ UST→ BSC: 7.90 ADA→ UST→ BSC: 7.97 ETN→ UST→ BSC: 8.24 GOL→ UST→ BSC: 8.23 IXI Q2W→ UST→ BSC: 8.11	SEC→ UST→ BSC: £111,743 ADA→ UST→ BSC: £112,849 ETN→ UST→ BSC: £114,657 GOL→ UST→ BSC: £118,987 IXE Q4W→ UST→ BSC: £127,777 INF→ UST→ BSC: £138,072 **bDMARD-naïve, moderate-to-severe psoriasis subpopulation** BSC: £99,884 APR→ UST→ BSC: £127,576 CRT→ UST→ BSC: £132,373 ADA→ UST→ BSC: £133,882 ETN→ UST→ BSC: £134,567 GOL→ UST→ BSC: £138,550 IXI Q2W→ UST→ BSC: £155,459	SEC→ UST→ BSC: IXE dominated ADA→ UST→ BSC: IXE dominated ETN→ UST→ BSC: iXE dominated GOL→ UST→ BSC: IXE dominated INF→ UST→ BSC: £23,230 **bDMARD-naïve, moderate-to-severe psoriasis subpopulation** BSC: £29,170 APR→ UST→ BSC: £67,096 CRT→ UST→ BSC: £109,062 ADA→ UST→ BSC: £155,110 ETN→ UST→ BSC: IXE sequence dominated GOL→ UST→ BSC: IXE sequence dominated SEC→ UST→ BSC: SEC sequence dominated

Study	Year	Summary of model	Summary of NMA	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					SEC→ UST→ BSC: 7.97 INF→ UST→ BSC: 8.51 **bDMARD-experienced, no psoriasis subpopulation** BSC: 7.38 UST: 8.24 IXE Q4W: 8.21 **bDMARD-experienced, mild-to-moderate-psoriasis subpopulation** BSC: 7.06 UST: 7.97 IXE Q4W: 7.93 **bDMARD-experienced, moderate-to-severe psoriasis subpopulation** BSC: 2.26 UST: 3.21 IXE Q4W: 3.24	SEC→ UST→ BSC: £155,532 INF→ UST→ BSC: £157,603 **bDMARD-experienced, no psoriasis subpopulation** BSC: £55,942 UST: £82,143 IXE Q4W: £93,369 **bDMARD-experienced, mild-to-moderate psoriasis sub population** BSC: £70,271 UST: £94,133 IXE Q4W: £105,562 **bDMARD-experienced, moderate-to-severe psoriasis subpopulation** BSC: £99,618 UST: £118,915 IXE Q4W: £135,063	INF→ UST→ BSC: £5,335 **bDMARD-experienced, no psoriasis subpopulation** BSC: £45,092 UST: IXE sequence dominated **bDMARD-experienced, mild-to-moderate-psoriasis subpopulation** BSC: £40,344 UST: IXE sequence dominated **bDMARD-experienced, moderate-to-severe psoriasis sub population** BSC: £36,197 UST: £557,092

Study	Year	Summary of model	Summary of NMA	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA445 (certolizumab pegol and secukinumab)[5]	2017	A two-part Markov cohort model: • Initial response period • Post-response period	Two networks: biologic-naïve and biologic-experienced.	47	**Subpopulation 1 (one prior DMARD)** BSC: 5.312 CZP: 8.377 SEC 300 mg: 8.524 **Subpopulation 2 (≥2 prior DMARD)** BSC: 5.312 CZP: 7.226 300 mg of SEC: 7.379 ADA: 7.411 GOL: 7.637 ETN: 7.719 INF: 7.890 **Subpopulation 3 (biologic-experienced):** BSC: 5.312 UST: 6.334 300 mg of SEC: 6.632	**Subpopulation 1 (one prior DMARD)** BSC: £95,965 CZP: £159,951 SEC 300 mg: £179,692 **Subpopulation 2 (≥2 prior DMARD)** BSC: £95,965 CZP: £137,240 SEC 300 mg: £157,086 ADA: £138,109 GOL: £142,850 ETN: £144,585 INF: £167,126 **Subpopulation 3 (biologic-experienced):** BSC: £95,965 UST: £118,127 300 mg of SEC: £143,534	**Subpopulation 1 (one prior DMARD)** Pairwise ICER/QALY CZP vs BSC: £20,870 SEC 300 mg vs BSC: £26,064 SEC 300 mg vs CZP: £134,783 **Subpopulation 2 (≥2 prior DMARD)** Pairwise ICER/QALY CZP vs BSC: £21,564 SEC 300 mg vs BSC: £29,569 ADA vs BSC: £20,074 GOL vs BSC: £20,161 ETN vs BSC: £20,197 INF vs BSC: £27,599 **Subpopulation 3 (biologic-experienced):** ICER/QALY SEC 300 mg vs BSC: £21,684 UST vs BSC: £36,013

Key: ADA, adalimumab; APR, apremilast; bDMARD, biological disease modifying antirheumatic drug; BSC, best supportive care; CRT, certolizumab; CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; QALYs, quality-adjusted life years; SEC, secukinumab; TNFα, tumour necrosis factor-alpha; TOF, tofacitinib; UST, ustekinumab; vs, versus.

B.3.2. Economic analysis

The systematic literature review presented in Section B.3.1 did not identify an economic analysis that evaluated the cost-effectiveness of upadacitinib in PsA. Therefore, a de novo economic analysis was developed to assess the cost-effectiveness of upadacitinib versus other recommended therapies for the treatment of active PsA (precise modelled populations are described below in Section B.3.2.1). This model is based on the second revision of the 'York Model' used in NICE TA445[5], which was developed by the Centre for Reviews and Dissemination and Centre for Health Economics at the University of York. This model also formed the basis of the two most recent PsA submissions (NICE TA537 [ixekizumab] and NICE TA543 [tofacitinib])[1, 82] in terms of patient population, the structure, inputs, and assumptions used throughout; where possible, the company has built on this precedent and taken into consideration evidence review group (ERG) and committee critique from these previous appraisals. The Markov structure captures patients' transitions through a maximum of two active treatment lines, followed by best supportive care (BSC), with death as the absorbing state.

B.3.2.1 Patient population

As detailed in Section B.1.1, the anticipated marketing authorisation for upadacitinib 15 mg is '[redacted] The BSR guidelines and previous NICE TA guidance recommend that patients should have two csDMARDs before receiving advanced therapies.[1, 53, 82] In alignment with this guidance, which is assumed to reflect clinical practice in the National Health Service (NHS) in England and Wales, the population who have had one csDMARD is not considered in this submission. The proposed position in the treatment pathway is therefore narrower than the anticipated marketing authorisation and final NICE scope, and reflects the subpopulations that have received positive recommendations from NICE in previous technology appraisals.

The following subpopulations were considered in the economic analyses:

1. People with active PsA whose disease has not responded adequately to at least two csDMARDs
2. People with active PsA whose disease has not responded adequately to csDMARDs and one or more TNFα inhibitors
3. People with active PsA in whom TNFα inhibitors are contraindicated or not tolerated

As described in Section B.2.3, both the SELECT-PsA 1 and SELECT-PsA 2 trials enrolled patients who were diagnosed with three or more tender joints and three or more swollen joints, had active plaque psoriasis or a documented history of plaque psoriasis and met the CASPAR criteria for diagnosis of PsA. Specifically, SELECT-PsA 1 investigated the safety and efficacy of upadacitinib versus adalimumab and placebo in adult patients with active PsA who have a history of inadequate response to at least one csDMARD. SELECT-PsA 2 investigated the safety and efficacy of upadacitinib versus placebo in adult patients with active PsA who have a history of inadequate response to at least one bDMARD.

The SELECT-PsA 1 trial population includes patients who are not considered in our decision problem: those who have been treated with one csDMARD. This was also true of the NMA network informing the biologic-naïve population, as noted in Section B.2.9.3.1. In the final appraisal determination (FAD) for TA537, this issue was raised by the committee; however, the clinical experts noted that in their experience, the efficacy of a biological therapy does not differ between those who have had one or two previous csDMARDs.[82] On balance, SELECT-PsA 1 patients are assumed to be reflective of Population 1.

The SELECT-PsA 2 trial population is assumed to be reflective of Population 2. As detailed in Section B.2.7.2, a post hoc analysis was performed to assess prior bDMARD exposure on upadacitinib efficacy, finding that upadacitinib 15 mg demonstrated generally consistent efficacy in patients with inadequate response to one or multiple prior bDMARDs.[93] Given the general consistency in efficacy, small sample sizes from which this analysis is based on, and lack of evidence to inform data for the comparators, this subgroup analysis of patients with prior bDMARD use is not modelled separately.

For Population 3, clinician feedback sought by AbbVie from an advisory board on 22 May 2020 suggested it is reasonable to assume these patients have the same efficacy as the biologic-naïve population.[4] SELECT PsA-1 patients are therefore assumed to be reflective of Population 3, as well as Population 1, in alignment with previous appraisals.

Each of the three subpopulations is further stratified by presence or severity of concomitant psoriasis: no psoriasis (BSA<3%), mild-to-moderate psoriasis (BSA≥3% and PASI≤10), and moderate-to-severe psoriasis (BSA>3% and Psoriasis Area and Severity Index (PASI) >10), thus comprising a total of nine subgroups of interest. These subgroups are aligned with the subgroups included in two of the most recent relevant appraisals, TA537 and TA445.[5, 82] In TA543, however, psoriasis subgroups were modelled together by calculating a weighted average PASI score for the total population; this was flagged as a limitation by the ERG, with one of the key reasons being that the severity of psoriasis is necessary for determining the appropriate dose of secukinumab for the comparator arm.

Based on the pooled full analysis set populations from the SELECT PsA-1 and SELECT PsA-2 trials, patients entering the model had a mean age of [redacted] years and a mean weight of [redacted]kg; female patients comprised [redacted]% of the population. As noted in Sections B.2.3.1.2 and B.2.3.2.2, feedback from UK clinicians indicated that the baseline characteristics of patients in SELECT-PsA 1 were broadly generalisable to patients expected to receive upadacitinib in the UK.[4]

As discussed further in Section B.3.2.2, patients entering the model are also defined by their baseline PASI and HAQ-DI scores which represent the psoriasis and arthritis components of PsA, respectively. Mean PASI and HAQ-DI scores at baseline, as reported in the SELECT PsA-1 and SELECT PsA-2 trials, representing the nine subgroups of interest are shown in Table 52. When comparing to the baseline scores reported in the three most recent PsA appraisals, TA445, TA537 and TA543, the baseline PASI scores from the SELECT PsA-1 and SELECT PsA-2 trials for the no psoriasis subgroup are higher; in previous appraisals, these have been reported as zero.[1, 5, 82] Scores of between 0 and 2 would generally be considered as “no psoriasis”; in a clinical study of PsA patients, it would be difficult to find many

patients with a PASI score of 0 as there is typically always some level or redness or induration that would drive the score up by few points. This is supported by clinical opinion provided in TA445 where it was suggested that "about 50% of patients that receive biologic treatment have mild or minimal concomitant psoriasis (less than 3% BSA or a PASI score of less than 2.5)".[5] For the mild-to-moderate and moderate-to-severe baseline PASI scores, these fall between the scores reported in TA445, TA537 and TA543. Baseline HAQ-DI scores are similar to those reported in the three recent appraisals. The baseline scores from the SELECT PsA-1 and SELECT PsA-2 trials are assumed to be reflective of patients prior to initiating upadacitinib or another bDMARD/tsDMARD comparator included in the economic model.

Table 52: Baseline PASI and HAQ-DI scores by target population and severity of concomitant psoriasis

Psoriasis severity	Biologic-naïve (Population 1)[a]	Biologic-experienced (Population 2)[b]	TNFα inhibitor-contraindicated (Population 3)[c]
No psoriasis	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]
Mild-to-moderate psoriasis	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]
Moderate-to-severe psoriasis	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]	Baseline PASI: [redacted] Baseline HAQ-DI: [redacted]

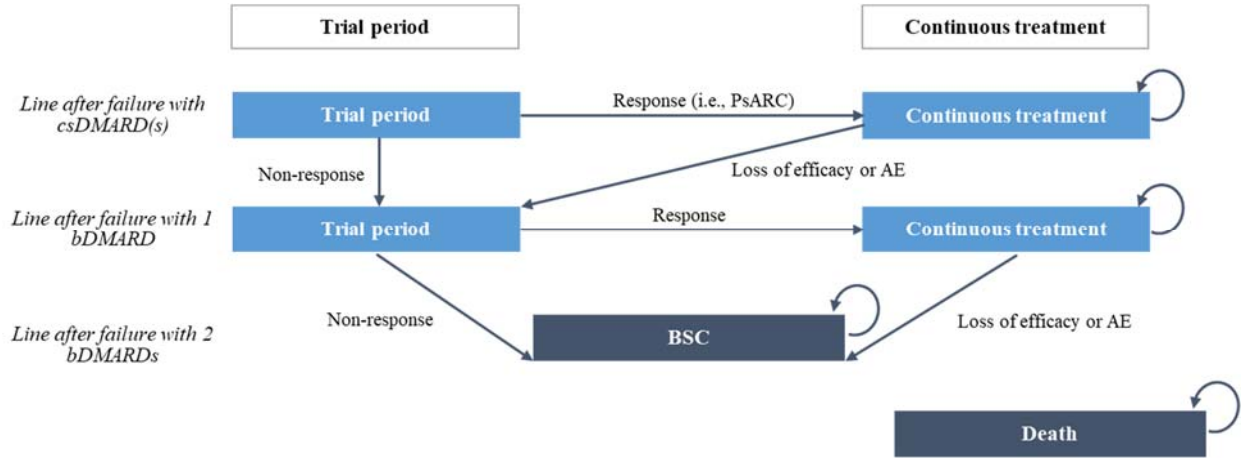
Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index.
Notes: [a] Source: SELECT-PsA 1; [b] source: SELECT-PsA 2; [c] assumed equal to SELECT-PsA 1

B.3.2.2 Model structure

The de novo model was developed in Microsoft Excel 2016® as a Markov cohort model to assess whether patients respond to treatment or not during an initial trial period, and the need to move to the next treatment option. The model closely follows the precedent set by the second revision of the York Model, used in TA445, which is a widely accepted framework for modelling PsA[1, 5, 82], and is designed to capture

costs and health outcomes associated with both the joint and skin component of PsA. Figure 18 provides a state transition diagram illustrating the model structure.

Figure 18: Model structure



Key: BSC, best supportive care; DMARD, disease-modifying antirheumatic drug; bDMARD, biologic DMARD; csDMARD, conventional systemic DMARD; PsARC, Psoriatic Arthritis Response Criteria.
Notes: Transitions to death may occur from any health state. Arrows to death are omitted from the diagram for simplicity. Each trial period consists of three 4-week tunnel states.

Altogether, the Markov structure captures patients' transitions through a maximum of two active treatment lines followed by BSC, with death as the absorbing state.

As shown in Figure 18, the following mutually exclusive treatment-related states in the Markov model are defined to track patients' treatment status and survival over time:

- Line after failure with two csDMARDs: Trial period
- Line after failure with two csDMARDs: Continuous treatment period
- Line after failure with one bDMARD (and/or tsDMARD): Trial period
- Line after failure with one bDMARD (and/or tsDMARD): Continuous treatment period
- BSC
- Death

At model entry, the patients' starting state depends on the population being evaluated. Patients in the biologic-naïve and TNFα inhibitor-contraindicated populations enter the model at the beginning of the trial period in the line after failure

with two csDMARDs. Patients in the biologic-experienced population enter the model in the trial period of the line after failure with one bDMARD.

Within each treatment-related state, patients' health status is modelled using HAQ-DI scores to represent the arthritis component of PsA and PASI 50/75/90 response to represent the psoriasis component. PsARC response determines the proportion of patients who transition from the trial period to the continuous treatment period, in line with clinical practice, as detailed in Section B.3.3.1. Utility values and disease management costs in each treatment-related state are calculated as a function of HAQ-DI and PASI response outcomes, as described in Sections B.3.4 and B.3.5, respectively.

Additional details on each treatment-related state are provided below.

B.3.2.2.1 Trial period

Each line of therapy begins with an initial trial period of 12 weeks, in accordance with the second revision of the York Model (TA445)[5], and is modelled as a series of three 4-week tunnel states. This 12-week period is assumed to be consistent with the time of response assessment conducted in NHS England clinical practice, as per NICE guidance and clinical expert opinion.[4] To assess the impact of this time point, a 24-week trial period has been tested in a scenario analysis (Section B.3.3.1 provides further detail).

Patients are assumed to remain on treatment for the entirety of the trial period unless death occurs. At the end of the trial period, PASI 50/75/90 and treatment response, defined according to the PsARC, are assessed. Patients also experience a change from baseline in their HAQ-DI score, which is conditioned on PsARC response.

Patients who achieve response transition to the continuous treatment period and continue to receive the same treatment. Patients who do not achieve treatment response are assumed to discontinue at the end of the trial period and enter the initial trial period for the next line of treatment.

B.3.2.2.2 Continuous treatment period

During the continuous treatment period of a given line of therapy, patients who met the PsARC response criterion, assessed at the end of the trial period, are assumed to continue receiving the same therapy until discontinuation due to any cause (e.g. AEs, loss of response). Within this state, HAQ-DI score and PASI 50/75/90 response probabilities are therefore estimated conditional on achievement of PsARC response. Consistent with the assumption applied in TA445[5], and other previous appraisals in PsA (as summarised in Table 53), patients who achieve PsARC response maintain the same HAQ-DI improvement and level of PASI response during the period of time that they remain on treatment.

To account for gradual loss of efficacy or tolerability over time, an annual risk of any-cause discontinuation is applied within the continuous treatment period, as discussed in Section B.3.3.4.2. As is also discussed, alternative discontinuation rates by treatment line, based on clinical opinion, are explored as scenario analyses.

Upon discontinuation, patients are assumed to revert to their baseline HAQ-DI and PASI scores, and switch to the next line of active therapy (or transition to BSC after the last active treatment in the sequence).

B.3.2.2.3 Best supportive care

Patients transition to the BSC state if they do not achieve the treatment response threshold with the last active treatment line, or once they discontinue the continuous treatment phase with the last active therapy for any reason. BSC represents a mixture of csDMARDs and supportive medications (e.g. nonsteroidal anti-inflammatory drugs, corticosteroids and palliative care). Patients who enter the BSC state remain there until death or the end of the modelled timeframe.

Upon transitioning to BSC, patients' HAQ-DI and PASI scores are assumed to revert to baseline levels in alignment with previous submissions.[1, 5, 82, 105, 106] In subsequent cycles spent in the BSC state, PASI score is assumed to remain constant until death, while the HAQ-DI score is assumed to progressively worsen (increase), in-line with the natural history of untreated disease, until the maximum HAQ-DI score of 3 is reached.[5]

B.3.2.2.4 Death

Death is the absorbing state in the model. Patients may transition to the death state from any of the aforementioned states. Treatments for PsA are assumed to have no effect on mortality risk. Mortality is determined by general population all-cause mortality rates, adjusted for excess mortality associated with PsA. In each model cycle, death is assumed to occur with equal probability from any other state in the model.

B.3.2.2.5 General model settings

The analysis perspective is that of the NHS and Personal Social Services (PSS) in England for costs, and direct health effects on individual patients for outcomes. This is consistent with the NICE reference case.[107]

The cycle length was 4 weeks; this was sufficiently short while also allowing trial periods of 12 weeks (three cycles) and 24 weeks (six cycles) to be easily modelled. Given the short cycle length, a half-cycle correction was not applied to any cost or health outcomes.

A discount rate of 3.5% per annum is applied to costs and quality-adjusted life years (QALYs), as also specified by the NICE reference case.[107] The time horizon in the base case was set to 48.5 years (i.e. 100 minus the starting age of the cohort) in order to comprehensively capture all relevant differences in costs and benefits between the comparator sequences.

Table 53 presents features of the current economic analysis and a comparison with previous NICE technology appraisals for PsA.

Table 53: Features of the economic analyses

Factor	Previous appraisals							Current appraisal	
	TA313 UST	TA220 GOL	TA199 2011 York Model	TA445 2016 York Model	TA433 APR	TA543 TOF	TA537 IXE	Chosen values	Justification
Perspective	UK NHS PSS perspective								Alignment with NICE reference case
Time horizon	52 years	40 years						48.2 years (i.e. 100 years minus the starting age of the cohort)	Lifetime horizon in alignment with NICE reference case and previous appraisals
Treatment waning effect	**On-treatment:** PsARC response, HAQ-DI improvement and PASI response maintained **Off-treatment:** PsARC response is lost and HAQ-DI and PASI scores revert to baseline. If the patient discontinues active treatment and goes on to receive BSC, HAQ-DI worsens over time, in line with natural history progression								Alignment with previous appraisals
Source of utilities	York Model equation used in base case: EQ-5D utility = 0.897 – 0.298*HAQ – 0.004*PASI						Same York function with regression coefficients estimated from SPIRIT trial data	Same York function with regression coefficients estimated from SELECT PsA trial data	Scenario analyses applied regression coefficients from the York Model equation
Source of costs	Drug costs: BNF and MIMS Administration costs: PSSRU Unit Costs of Health and Social Care, NHS reference costs Monitoring costs: NHS reference costs HAQ-DI-related costs: Kobelt et al (2002) PASI-related costs: Hartman et al (2002); Poyner et al (1999)								Alignment with NICE reference case and previous appraisals (TA445, TA543 and TA537)

Key: APR, apremilast; BNF, British National Formulary; BSC, best supportive care; GOL, golimumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; ICER, incremental cost-effectiveness ratio; IXE, ixekizumab; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; PSS, personal social services; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; TOF, tofacitinib; UST, ustekinumab.

B.3.2.3 Intervention technology and comparators

Upadacitinib, the intervention technology under evaluation, is implemented in the model as per the expected marketing authorisation, anticipated in [redacted], and is reflective of the decision problem described in Section B.1.1.

Comparator treatments include those recommended by NICE for use in adult patients with active PsA. Specifically, the comparators of interest are split by the following three populations:

- For people whose disease has not responded adequately to two or more prior csDMARDs (i.e. adalimumab, apremilast [Otezla®], certolizumab pegol [Cimzia®], etanercept, golimumab [Simponi®], ixekizumab [Taltz®], infliximab, secukinumab [Cosentyx®] and tofacitinib [Xeljanz®])[1, 5, 82, 105, 108, 109]
- For those whose disease has not responded adequately to csDMARDs and one or more TNF-alpha inhibitors (i.e. certolizumab pegol, ixekizumab, secukinumab, tofacitinib, ustekinumab [Stelara®] and BSC)[1, 2, 5, 82]
- For people in whom TNF-alpha inhibitors are contraindicated or not tolerated (i.e. ixekizumab, secukinumab, tofacitinib, ustekinumab and BSC)[1, 2, 5, 82]

As detailed in Section B.1.3, although various targeted treatments are available in current practice, additional options are necessary to manage the disease over the patient's lifetime, given the expectation that patients eventually become non-responsive. The comparators were modelled according to licensed dosing schedules (Table 54).

For all treatments, PsARC response assessment was assumed to occur after an initial trial period of 12 weeks, consistent with recommendations from the BSR[53] and with NHS England clinical practice.[4] As shown in Table 54, the assumption of a 12-week trial period differed from the NICE recommended timing of response assessment for certain treatments. Despite these differences, a uniform 12-week trial period was used to allow for a more balanced, interpretable comparison of upadacitinib versus the included comparators, in line with the approach used in the TA445.[5] This approach also takes into account criticism given by the ERG for TA537;

the ERG stated that the use of different response time points in the NMA for the different treatments was a potential limitation of the analysis.[82]

An alternative response assessment time point of 24 weeks, for upadacitinib and all comparators, is tested as a scenario (Section B.3.8.3). The aim of this scenario was primarily to assess whether the longer time to assessment resulted in notable differences in treatment response rates (i.e. to what extent did the probability of response increase or decrease over this additional 12-week period). In addition, the exploration of a 24-week response time point was suggested by experts at the advisory board for consideration in the economic model.[4]

Table 54: Dosing schedules and timing of response assessment

Treatment	Dosing schedule	Week of response assessment in model		Week of response assessment per NICE recommendations[107]
		Base case	Scenario	
Upadacitinib	15 mg daily	12	24	-
Adalimumab	40 mg EOW	12	24	12
Apremilast	Initial titration schedule (Week 0–2), 30 mg twice daily thereafter	12	24	16
Certolizumab pegol	400 mg at Week 0, 2 and 4, and 200 mg Q2W thereafter	12	24	12
Etanercept	25 mg BIW or 50 mg QW	12	24	12
Golimumab	50 mg monthly or 100 mg monthly (if >100 kg and no adequate clinical response to 50 mg after 3 or 4 doses)	12	24	12
Infliximab	5 mg/kg at Week 0, 2 and 6, and Q8W thereafter	12	24	12
Ixekizumab	160 mg at Week 0 and 80 mg Q4W thereafter	12	24	16
Secukinumab	150 or 300 mg at Week 0, 1, 2, 3 and 4, and monthly thereafter	12	24	16
Tofacitinib	5 mg twice daily	12	24	12
Ustekinumab	45 mg at Week 0 and 4, and Q12W thereafter (90 mg may be used if >100 kg)	12	24	24

Key: BIW, twice a week; EOW, every other week; NICE, National Institute for Health and Care Excellence; QW: once weekly; Q2W: once every 2 weeks; Q4W: once every 4 weeks; Q8W: once every 8 weeks; Q12W: once every 12 weeks; TNFα, tumour necrosis factor alpha.

Further details on the dosing schedules of each treatment is provided in Section B.3.5.1, Table 69.

B.3.2.4 Treatment sequences

The NICE pathway for managing peripheral spondyloarthritis in adults and BSR guidance recommends switching between treatments in patients with an inadequate response or loss of response to a bDMARD (Section B.1.3).[53, 55] The base case for the biologic-naïve population therefore considered treatment sequences comprising two lines of therapy followed by BSC (Table 55). In each treatment sequence evaluated in the biologic-naïve population, the line of therapy after failure of two csDMARDs is occupied by upadacitinib or one of the comparators recommended by NICE for use in this position.

Treatment sequences in the biologic-experienced population comprised one line of therapy, starting from the line after failure of one bDMARD, followed by BSC (Table 55). The line of therapy after failure of one bDMARD was occupied by upadacitinib or one of the comparators recommended by NICE to treat patients who have an inadequate response or loss of response to prior TNFα inhibitor therapy. Of note, certolizumab pegol is recommended by NICE for use in patients who were previously treated with TNFα inhibitor therapy but who experienced inadequate response after the first 12 weeks of treatment (i.e. secondary non-responders to TNFα inhibitor), representing only a subset of the overall biologic-experienced population.[99] Because the RAPID-PsA trial of certolizumab pegol among biologic-experienced patients excluded primary non-responders to TNFα inhibitor therapy[110], certolizumab pegol was not evaluated as a comparator in the biologic-experienced population as it was not deemed comparable to the other included trials.

In the TNFα inhibitor-contraindicated population, treatment sequences comprised one line of therapy (starting from the line after failure of two csDMARDs) followed by BSC (Table 55). For this population, each treatment sequence began with upadacitinib or a comparator recommended by NICE for use in patients for whom TNFα inhibitor is contraindicated but would otherwise be considered.

Table 55: Comparator sequences – base case

Sequence	After failure of two csDMARDs	After failure of one biologic	BSC
Biologic-naïve population			
Upadacitinib sequence	Upadacitinib 15 mg	Ustekinumab	BSC
Adalimumab sequence	Adalimumab	Ustekinumab	BSC
Apremilast sequence	Apremilast	Ustekinumab	BSC
Certolizumab pegol sequence	Certolizumab pegol	Ustekinumab	BSC
Etanercept sequence	Etanercept	Ustekinumab	BSC
Golimumab sequence	Golimumab	Ustekinumab	BSC
Infliximab sequence	Infliximab	Ustekinumab	BSC
Ixekizumab sequence	Ixekizumab	Ustekinumab	BSC
Secukinumab sequence	Secukinumab 150 or 300 mg	Ustekinumab	BSC
Tofacitinib sequence	Tofacitinib	Ustekinumab	BSC
Biologic-experienced population			
Upadacitinib sequence		Upadacitinib 15 mg	BSC
Ixekizumab sequence		Ixekizumab	BSC
Secukinumab sequence		Secukinumab 300 mg	BSC
Tofacitinib sequence		Tofacitinib	BSC
Ustekinumab sequence		Ustekinumab	BSC
BSC sequence			BSC
TNFα inhibitor-contraindicated population			
Upadacitinib sequence	Upadacitinib 15 mg	Skip to BSC	BSC
Ixekizumab sequence	Ixekizumab	Skip to BSC	BSC
Secukinumab sequence	Secukinumab 150 or 300 mg	Skip to BSC	BSC
Tofacitinib sequence	Tofacitinib	Skip to BSC	BSC
Ustekinumab sequence	Ustekinumab	Skip to BSC	BSC
BSC sequence			BSC

Key: BSC, best supportive care; DMARD, disease-modifying antirheumatic drug; bDMARD, biologic DMARD; csDMARD, conventional systemic DMARD; TNFα, tumour necrosis factor alpha.

Alternative and longer treatment sequences are possible in clinical practice. However, implementing additional lines of therapy in the model is either not viable or highly limited by the constraints of the evidence base. In clinical practice treatment sequencing represents a complex process where treatment history, patient characteristics and current options available within the therapeutic arsenal influence the choice, and likely the effectiveness, of subsequent treatments. This was noted in the advisory board held on 22 May 2020, where the feedback was that patients would receive more than two lines of active treatment in NHS England clinical practice and there is variability of the subsequent treatment choice.[4] However, given

the data constraints to capture all potential scenarios, that approach would lead to a large number of possible treatment sequences for each population and as such a pragmatic approach was taken.

Furthermore, the base-case treatment sequences considered in this economic model are consistent with those presented in TA445 and other recent NICE appraisals,[1, 5, 82] and this approach therefore increases consistency and transparency across appraisals. Additionally, in the biologic-naïve population having a common treatment as second line implies a level playing field, while modelling multiple active treatment lines would also require evidence on any degradation effect in the long term, and this evidence is flawed.

The base-case treatment sequences for the biologic-naïve population and the bio-experienced population have a common ground of pragmatism that has proved to be useful in previous reimbursement processes by eliciting the overall effect of the introduction of the new intervention for treating PsA, and therefore it has been implemented in this economic evaluation.

B.3.3. Clinical parameters and variables

Measures of treatment effectiveness in the base case model include PsARC response, HAQ-DI score and PASI 50/75/90 response. Other than the comparison to adalimumab in SELECT PsA-1, no other studies were identified through the SLR that investigated upadacitinib in comparison with bDMARDs, tsDMARDs or csDMARDs in patients with moderate to severe PsA. Therefore, an indirect treatment comparison in the form of an NMA was conducted.

Treatment-specific effectiveness inputs were obtained from the NMAs, as detailed in Section B.2.8 and B.2.9, and are varied by line of therapy within the economic model. Specifically, NMA results for the biologic-naïve population were used in the line after failure of two csDMARDs, while NMA results for the biologic-experienced population were used in the lines of therapy after failure of one or more bDMARD(s). For the population with active PsA in whom TNFα inhibitors are contraindicated or not tolerated, NMA results for the biologic-naïve population were also used; as

discussed in Section B.3.2.1, clinical experts deemed this an appropriate estimation.[4]

B.3.3.1 Psoriatic Arthritis Response Criteria response

NICE Guideline 65 (NG65)[111] and BSR guidelines[53] for PsA define response as the achievement of an adequate response using the PsARC, i.e. an improvement in at least two of the four PsARC criteria (one of which must include joint tenderness or swelling score) with no worsening in any of the four criteria.[56] A detailed description of the PsARC criteria is provided in Section B.2.6.2.3. PsARC is a widely reported efficacy endpoint in clinical trials and has been adopted as the base case response criterion for treatment continuation in all previous NICE appraisals in PsA.[1, 5, 82, 105, 106, 108, 109]

The economic model therefore assumed that patients must achieve PsARC response to transition to continuous treatment at a given line of therapy. The transition from the trial period to the continuous treatment period was modelled according to the NMA-based probability of PsARC response for the specific treatment received. Non-responders discontinue treatment and may receive a subsequent line of therapy (1st bDMARD/tsDMARD, 2nd bDMARD/tsDMARD or BSC). Patients who receive a subsequent bDMARD or tsDMARD are assessed again for PsARC response at the end of the trial period.

As discussed in Section B.2.9, 17 trials (including SELECT PsA-1) were included in the biologic-naïve NMA and reported PsARC response, and four trials (including SELECT PsA-2) were included in the biologic-experienced NMA and reported PsARC response. The PsARC response probabilities at 12 weeks summary results, by comparator therapy, are presented in Table 56 for the biologic-naïve and biologic-experienced populations. Specifically, for the biologic-naïve NMA, a random effects model with placebo-response adjustment was implemented in the base case, while for the biologic-experienced population, a fixed-effects model was implemented due to the sparsity of the networks (as discussed in Appendix D [D.1.3.2]).

These results were used in the base-case economic model to determine treatment response at the end of the trial period. The PsARC response probabilities at 24 weeks, tested as a model scenario, are presented in Appendix D.

Table 56: Base-case estimates of PsARC response probabilities (posterior median [95% CrI]) by treatment and population

Treatment	Biologic-naïve and TNFα inhibitor contraindicated populations	Biologic-experienced population
Upadacitinib 15 mg	[redacted]	[redacted]
Adalimumab	[redacted]	–
Apremilast	[redacted]	–
Certolizumab pegol	[redacted]	–
Etanercept	[redacted]	–
Golimumab	[redacted]	–
Infliximab	[redacted]	–
Ixekizumab	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	–
Secukinumab 300 mg[a]	[redacted]	68.6% (41.0%, 88.0%)
Tofacitinib	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

Key: PsARC, Psoriatic Arthritis Response Criteria; TNFα, tumour necrosis factor alpha.

Notes: [a] The probability of PsARC response for secukinumab 300 mg in the biologic-experienced population is extracted from the NMA results reported in TA445. For all other treatments, the values displayed above are from the *de novo* NMAs of PsARC response.
Biologic-naïve (and TNFα inhibitor contraindicated) patients with concomitant moderate-to-severe plaque psoriasis are assumed to receive the 300 mg dosage, while those with no psoriasis or mild-to-moderate psoriasis are assumed to receive the 150 mg dosage. For biologic-experienced patients, all are assumed to receive the 300 mg dosage.

For secukinumab 300 mg in the biologic-experienced population, summary-level trial results for PsARC were unavailable for inclusion in the NMA and were redacted in TA445; the probability of PsARC response and corresponding 95% credible interval (CrI) for this treatment was therefore extracted from the NMA results reported in TA445 (i.e. 68.6%; 95% CrI: 41.0%, 88.0%).[5] The efficacy estimate for the secukinumab differs with the dose received: 150 or 300 mg. It is assumed that biologic-naïve (and TNFα inhibitor contraindicated) patients with concomitant moderate-to-severe plaque psoriasis will receive the 300 mg dosage, while those with no psoriasis or mild-to-moderate psoriasis will receive the 150 mg dosage.[63] For biologic-experienced patients, all are assumed to receive the 300 mg dosage.

B.3.3.2 HAQ-DI change conditional on Psoriatic Arthritis Response Criteria response

Treatment efficacy with respect to the arthritis component of PsA is modelled based on improvement in HAQ-DI score from baseline to the end of the trial period. As described in Section B.2.9, separate NMAs were conducted to estimate changes in HAQ-DI conditional on PsARC response status, for each treatment. Twelve trials reporting HAQ-DI conditional on PsARC response were included in the biologic-naïve NMA (including SELECT PsA-1), and two trials were included in the biologic-experienced NMA (SELECT PsA-2 and PSUMMIT 2). Fixed effects models were selected for both populations. The summary results, by comparator therapy, are presented in Table 57 for the biologic-naïve and biologic-experienced populations.

Treatments that could not be included in the de novo NMAs (certolizumab pegol, ixekizumab, secukinumab, and tofacitinib) were instead populated using the approach described in Section B.3.3.2.1.

Table 57: Base-case estimates of ΔHAQ-DI conditional on PsARC response and non-response (posterior median [95% CrI]) by treatment and population

Treatment	Biologic-naïve and TNFi-contraindicated populations		Biologic-experienced population	
	ΔHAQ-DI | PsARC response	*ΔHAQ-DI | PsARC non-response*	*ΔHAQ-DI | PsARC response*	*ΔHAQ-DI | PsARC non-response*
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	–	–
Apremilast	[redacted]	[redacted]	–	–
Certolizumab pegol[a]	[redacted]	[redacted]	–	–
Etanercept	[redacted]	[redacted]	–	–
Golimumab	[redacted]	[redacted]	–	–
Infliximab	[redacted]	[redacted]	–	–
Ixekizumab[a]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg[a]	[redacted]	[redacted]	–	–

Secukinumab 300 mg[a]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib[a]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; PsARC, Psoriatic Arthritis Response Criteria; TNFi, tumour necrosis factor alpha inhibitor.
Notes: [a] Changes in HAQ-DI conditional on PsARC are imputed using the approach described in the Section B.3.3.2.1.
Biologic-naïve (and TNFα inhibitor contraindicated) patients with concomitant moderate-to-severe plaque psoriasis are assumed to receive the 300 mg dosage, while those with no psoriasis or mild-to-moderate psoriasis are assumed to receive the 150 mg dosage. For biologic-experienced patients, all are assumed to receive the 300 mg dosage.

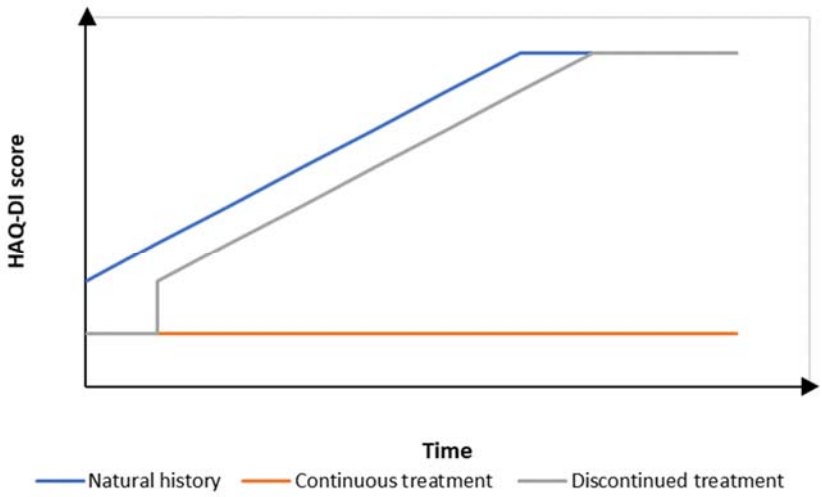
During each trial period, treated patients include both PsARC responders and non-responders. All patients are assumed to experience an improvement in baseline HAQ-DI score; this is specific to each treatment and conditional on achieving a PsARC response. PsARC responders experience a greater change from baseline HAQ-DI than PsARC non-responders. By the end of the trial period, the expected change in HAQ-DI with a given treatment is calculated as the average of the change from baseline HAQ-DI for PsARC responders, and the change from baseline HAQ-DI for PsARC non-responders, weighted respectively by the probability of PsARC response and non-response estimated for that treatment.

During the continuous treatment period, it is assumed that PsARC responders maintain their improvement in HAQ-DI as long as they are on treatment, as depicted in Figure 19 (orange line). For non-responders who did not achieve PsARC response at the end of the trial period, and responders who discontinue treatment during the continued treatment period, the HAQ-DI score is assumed to revert to baseline. When a patient goes on to receive a subsequent active treatment, they experience the corresponding improvement in HAQ-DI score conditional on PsARC response for that treatment.

When patients discontinue from active treatment and receive BSC, HAQ-DI is assumed to revert to baseline and subsequently progress in line with the natural history of PsA. This is shown in Figure 19 (grey line). The annual progression (increase) in a HAQ-DI score per year was 0.072, until the maximum HAQ-DI score of 3 is reached (this is depicted where the blue and grey lines plateau). This rate of progression was reported in Rodgers et al. (2011) (TA199)[112] and is based on a re-

analysis of data from the Norfolk Arthritis Register (NOAR) study[113], focusing specifically on patients with uncontrolled inflammatory polyarthritis (i.e. with three tender joints and three swollen joints) who had previously received two or more DMARDs. This rate of progression to reflect natural history of the disease was also used in previous submissions, as outlined in Table 53.

Figure 19: Illustration of HAQ-DI score progression over time



Key: HAQ-DI, Health Assessment Questionnaire-Disability Index.

The source used to inform the rate of disease progression on BSC was discussed in the advisory board on 22 May 2020.[4] Although it was noted that the NOAR study has limitations (i.e. it is a single-centre observational study), it was considered unlikely that there are better sources available, largely due to the fact that taking patients off all DMARDs and treating them with BSC is clinically implausible. Furthermore, the use of the placebo arm data for modelling progression on BSC is problematic given the issue of the observed placebo creep, as discussed in Section B.2.13.2.

In a given model cycle, a patient's absolute HAQ-DI score is calculated as the sum of the baseline HAQ-DI score and the change in HAQ-DI score from baseline, corresponding to their treatment-related state.

The resulting HAQ-DI scores enter into regression equations that determine patients' utility (Section B.3.4.5) and arthritis-related disease management costs (Section B.3.5.2.1) within the same model cycle. As discussed in these sections, during the trial period, the model assumed a linear improvement of the HAQ-DI change.

In TA445 (and prior to this, TA199) the assessment group proposed an adjustment to account for the perceived expectation effect, which assumed that the HAQ-DI change in placebo was attributable to the clinical trial setting and would not be seen in clinical practice.[5, 109]

Table 58 lists recent technology appraisals in PsA and whether any corrections or discounting to the clinical inputs were made for estimating costs and benefits. Implementation of the expectation effect correction is inconsistent across recent appraisals and no corrections were included in TA537, TA543 and the ongoing guselkumab technology appraisal. In TA445, the expectation effect was considered to be uncertain and may not be reproducible in clinical practice.[5]

Table 58: Inclusion of expectation effect correction in recent TAs

Technology appraisal	Inclusion	Method	Applicability in the base case
Secukinumab and certolizumab pegol [TA445][5]	Yes	The mean change in HAQ-DI across the placebo arms of the RCTs was discontinued from the change in HAQ-DI for patients using biologics	Yes
Ixekizumab [TA537][82]	No	NR	No
Tofacitinib [TA543][1]	No	NR	No
Guselkumab [in progress; ID1658][114]	No	NR	No

Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; NR, not reported; RCT, Randomized clinical trial; TA, technology appraisal

The traditional definition of placebo expectation effect relies on the assumption that if one's expectation underlies the efficacy of placebo, one would expect a reduction or even an elimination of the placebo effect after revealing the nature of the placebo. Therefore, one could argue that the expectation effect discount should be applied in outcomes with short-term effect, for instance binary outcomes indicating whether or not patients respond to treatment, rather than its application in the long-term outcomes capturing disease progression over 30, 40 or 50 years.

Given the inconsistencies in previous appraisals, the discordance in literature and the fact that the adjustment is applied to a long-term outcome, this economic model did not apply the expectation effect correction in the base case. The impact of the expectation effect in the results is tested in a scenario analysis using TA445 methodology (e.g. deducting the change in HAQ-DI score in the placebo arms

weighted by the PsARC response in that arm, from the HAQ-DI score change in the treatment arm, Appendix M).

B.3.3.2.1 Imputation of missing HAQ-DI inputs

Summary-level trial results on changes in HAQ-DI conditional on PsARC response are not publicly available for several comparators, including certolizumab pegol, secukinumab, ixekizumab, and tofacitinib. Because it was not feasible to include these treatments in the NMAs of change in HAQ-DI conditional on PsARC response status, alternative sources and assumptions were used to impute missing HAQ-DI inputs for these treatments, similar to the approach taken in TA543.[1]

Specifically, for treatments with these inputs missing that were evaluated in TA445 or another previously published NMA study (Ruyssen-Witrand et al. 2020[115]), point estimates and 95% CrIs were extracted from the NMA results reported in those sources (Table 59 and Table 60).

For the remaining treatments, missing HAQ-DI change conditional on PsARC response inputs were imputed. Summary-level trial results for the overall (i.e. unconditional) change in HAQ-DI from baseline to week 12 were used in conjunction with the estimated association between the changes in HAQ-DI conditional on PsARC response status. The following steps were performed:

1. Using pooled patient-level data from all randomisation arms of the SELECT-PsA 1 and SELECT-PsA 2 trials, a generalised linear mixed-effects model was fitted to obtain an estimate of the association between change in HAQ-DI and a dichotomous indicator for PsARC response status for patient *i* at visit *j* (Equation 1). The regression analysis was conducted using data from all post-baseline visits in which patients had observed values for both HAQ-DI and PsARC response status, and included patient-level random effects to account for correlation between repeated measurements for the same individual. In this regression equation, β1 provides an estimate of the difference in the change in HAQ-DI for a patient with PsARC response versus a patient without PsARC response. The resulting estimate of β1 was -0.217 (standard error [SE]: 0.005).

Equation 1: Regression model of change in HAQ-DI as a function of PsARC response

$$\Delta HAQ\text{-}DI_{ij} = Intercept + \beta 1 \times PsARC_{ij} + \varepsilon$$

2. Using this estimate of β1, the following relationship between change in HAQ-DI for PsARC response and change in HAQ-DI for PsARC non-response was assumed for each treatment *t* with missing values of these inputs (Equation 2):

Equation 2: Assumed relationship between change in HAQ-DI for PsARC response and change in HAQ-DI for PsARC non-response

$$\Delta HAQ\text{-}DI_{ij}|PsARC\ response_{\ t} = \Delta HAQ\text{-}DI_{ij}|PsARC\ non\text{-}response_{\ t} + \beta 1$$

3. For each treatment *t*, an estimate of the overall (i.e. unconditional) ΔHAQ-DI and the corresponding SE was extracted from a relevant trial publication in each target population (Table 59 and Table 60). Because the weighted average of ΔHAQ-DI|PsARC response$_t$ and ΔHAQ-DI|PsARC non-response$_t$ must equal ΔHAQ-DI$_t$, the relationship presented in Equation 3 was used. In this equation, the probability of PsARC response for treatment *t* (PsARC$_t$) was populated using NMA results for PsARC:

Equation 3: Relationship between change in HAQ-DI for PsARC response, change in HAQ-DI for PsARC non-response, and overall change in HAQ-DI

$$\Delta HAQ\text{-}DI_t = PsARC_t \times \Delta HAQ\text{-}DI_{ij}|PsARC\ response_{\ t} + (1 - PsARC_t) \times \Delta HAQ\text{-}DI_{ij}|PsARC\ non\text{-}response_{\ t}$$

4. With two equations and two unknown variables, estimates of ΔHAQ-DI|PsARC response and ΔHAQ-DI|PsARC non-response were obtained by solving Equation 2 and Equation 3. The resulting estimates of change in HAQ-DI conditional on PsARC response and non-response differ by β1 and compile to a weighted average of change in HAQ-DI to match the overall change in HAQ-DI result extracted from the corresponding trial publication.

Final values used in the model after imputation are presented in Table 61.

Table 59: Sources used to populate missing HAQ-DI inputs in biologic-naïve and TNFα inhibitor contraindicated populations

Treatments with missing HAQ-DI inputs	HAQ-DI change for PsARC responders	HAQ-DI change for PsARC non-responders	Unconditional change in HAQ-DI	Source
	est. (95% CrI)	est. (95% CrI)	est. (SE)	
Certolizumab pegol	-0.470 (-0.558, -0.370)	-0.118 (-0.196, -0.021)	NA	TA445[5]
Ixekizumab	-0.610 (-0.800, -0.420)	0.000 (-0.200, 0.200)	NA	Ruyssen-Witrand et al. (2020)[115]
Secukinumab 150 mg	-0.435 (-0.557, -0.294)	-0.085 (-0.228, 0.057)	NA	TA445[5]
Secukinumab 300 mg	-0.509 (-0.658, -0.378)	-0.078 (-0.205, 0.062)	NA	TA445[5]
Tofacitinib	NR	NR	-0.350 (0.050)	Mease et al. (2017)[116], week 12

Key: CrI, credible interval; est, estimate; HAQ-DI, Health Assessment Questionnaire-Disability Index; NA, not applicable; NR, not reported; PsARC, Psoriatic Arthritis Response Criteria; SE, standard error; TNFα, tumour necrosis factor-alpha.

Table 60: Sources used to populate missing HAQ-DI inputs in biologic-experienced population

Treatments with missing HAQ-DI inputs	HAQ-DI change for PsARC responders	HAQ-DI change for PsARC non-responders	Unconditional change in HAQ-DI	Source
	est. (95% CrI)	est. (95% CrI)	est. (SE)	
Ixekizumab	NR	NR	-0.600 (0.100)	Nash et al. (2017)[117], week 12
Secukinumab 300 mg	-0.385 (-0.624, -0.145)	-0.430 (-0.880, 0.014)	NA	TA445[5]
Tofacitinib	NR	NR	-0.390 (0.050)	Gladman et al. (2017)[118], week 12

Key: CrI, credible interval; est, estimate; HAQ-DI, Health Assessment Questionnaire-Disability Index; NA, not applicable; NR, not reported; PsARC, Psoriatic Arthritis Response Criteria; SE, standard error.

Table 61: Estimates of change in HAQ-DI conditional on PsARC response status for treatments not included in the de novo NMAs

Treatment	Biologic-naïve and TNFα inhibitor contraindicated populations		Biologic-experienced population	
	HAQ-DI change for PsARC responders	HAQ-DI change for PsARC non-responders	HAQ-DI change for PsARC responders	HAQ-DI change for PsARC non-responders
Certolizumab pegol	[redacted]	[redacted]	-	-
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	-	-
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; PsARC, Psoriatic Arthritis Response Criteria; TNFα, tumour necrosis factor-alpha.
Notes: Biologic-naïve (and TNFα inhibitor contraindicated) patients with concomitant moderate-to-severe plaque psoriasis are assumed to receive the 300 mg dosage, while those with no psoriasis or mild-to-moderate psoriasis are assumed to receive the 150 mg dosage. For biologic-experienced patients, all are assumed to receive the 300 mg dosage.

B.3.3.3 Psoriasis Area and Severity Index response

The effect of treatment on the psoriasis component of PsA is represented by probabilities of PASI 50, 75 and 90 response, i.e. the proportions of patients achieving ≥50%, ≥75% and ≥90% relative improvement in PASI scores from baseline, respectively. PASI response probabilities for the trial period were obtained through NMAs. As discussed in Section B.2.9, 22 trials (including SELECT PsA-1) were included in the PASI biologic-naïve NMA (PASI 50, 75, and 90 were reported in 12, 22, and 13 trials, respectively), and five trials (including SELECT PsA-2) were included in the PASI biologic-experienced NMA (PASI 50, 75, and 90 were reported in 1, 5, and 3 trials, respectively). A random-effects model with placebo-response adjustment was selected for the biologic-naïve NMA, while a fixed effects model was selected for the biologic-experienced NMA. All treatments could be included in the NMAs. The summary results, by comparator therapy, are presented in Table 62 for the biologic-naïve and biologic-experienced populations.

The PASI response for the secukinumab 150 mg comparator was used to inform the efficacy estimates for the biologic-naïve and TNFα inhibitor contraindicated populations with no concomitant psoriasis or mild-to-moderate psoriasis. It is assumed that biologic-experienced and biologic-naïve patients with concomitant

moderate-to-severe plaque psoriasis will receive the 300 mg dosage, as per the SmPC.[63]

Table 62: Base-case estimates of PASI 50/75/90 response probabilities (posterior median [95% CrI]) by treatment and population

	Biologic-naïve and TNFα inhibitor contraindicated populations			Biologic-experienced population		
Treatment	**PASI 50**	**PASI75**	**PASI 90**	**PASI 50**	**PASI75**	**PASI 90**
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	–	–	–
Apremilast	[redacted]	[redacted]	[redacted]	–	–	–
Certolizumab pegol	[redacted]	[redacted]	[redacted]	–	–	–
Etanercept	[redacted]	[redacted]	[redacted]	–	–	–
Golimumab	[redacted]	[redacted]	[redacted]	–	–	–
Infliximab	[redacted]	[redacted]	[redacted]	–	–	–
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	–	–	–
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PASI, Psoriasis Area and Severity Index; TNFα, tumour necrosis factor alpha.
Notes: Biologic-naïve (and TNFα inhibitor contraindicated) patients with concomitant moderate-to-severe plaque psoriasis are assumed to receive the 300 mg dosage, while those with no psoriasis or mild-to-moderate psoriasis are assumed to receive the 150 mg dosage. For biologic-experienced patients, all are assumed to receive the 300 mg dosage.

During the continuous treatment period, PASI response probabilities are conditioned on PsARC response. Following the approach described in Rodgers et al. (2011) (TA199)[112], and subsequently used in TA445[5], TA537[82] and TA543[1], the joint probability of achieving both PsARC and PASI75 response with a given treatment was approximated using the marginal probabilities of PsARC response and PASI75 response (as estimated from the NMA) in conjunction with the Pearson correlation coefficient between these two binary outcomes (Table 63). The base-case value of the correlation coefficient was set equal to 0.436 (SE: 0.112), as reported in Rodgers et al., based on an analysis of patient-level data from the ADEPT trial of adalimumab.[112, 119] The conditional probabilities of PASI75 response among PsARC responders and non-responders were then calculated by dividing the joint probabilities (a and b [Table 63]) by the marginal probabilities of PsARC response and non-response, respectively.

Table 63: Conditional probabilities of PASI75 response among PsARC responders and non-responders

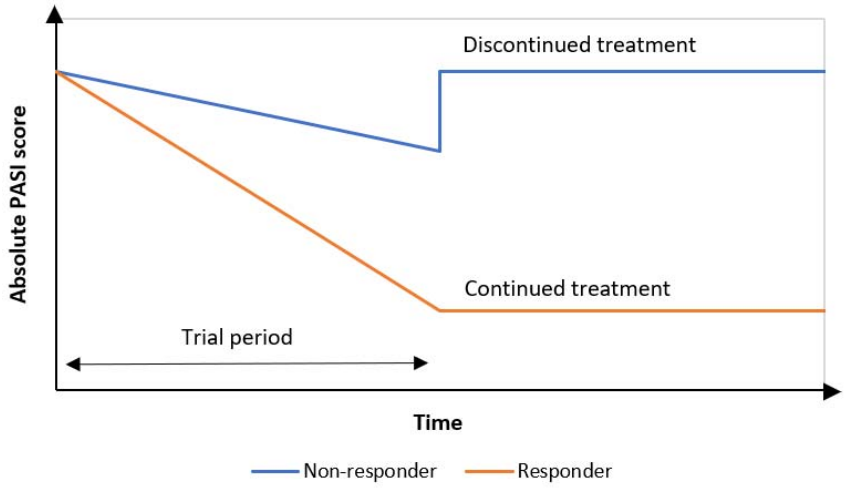
Joint probabilities of PASI75 response and PsARC response	**Joint probabilities of PASI75 response and PsARC non-response**
(a) = $\rho \times SQRT[PsARC_t \times PASI75_t \times (1 - PsARC_t) \times (1 - PASI75_t)] + PsARC_t \times PASI75_t$ Where: ρ is the Pearson correlation coefficient between PsARC and PASI75 response; $PsARC_t$ and $PASI75_t$ are the probabilities of PsARC and PASI75 response, respectively, for treatment t, as estimated in the NMA	(b) = $PASI75_t$ - (a)
Key: NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.	

The conditional probabilities of PASI 50 response among PsARC responders and non-responders were then calculated. This is based on the assumption that the ratio of PASI 50–74 to PASI <75 responders is the same among PsARC responders and non-responders as in the overall population. Similarly, the conditional probabilities of PASI 90 response among PsARC responders and non-responders were calculated

with the assumption that the ratio of PASI 90 to PASI75 responders is the same among PsARC responders and non-responders as in the overall population.

As in TA445[5] (and previous PsA appraisals; see Table 52), patients were assumed to maintain their level of PASI response for the duration of time that they remained on continuous treatment. Upon discontinuation due to any cause, patients were assumed to lose response and revert to their baseline PASI scores at the point of initiating the next treatment in the sequence. PASI scores are assumed to remain constant in subsequent cycles spent in the BSC state. The change in PASI score throughout the model duration is depicted in Figure 20.

Figure 20: Change in PASI score for responders and non-responders



Key: Psoriasis Area and Severity Index

In a given model cycle, a patient's PASI score (as a continuous measure) is approximated using baseline PASI score and probabilities of PASI 50–74, 75–89, and 90–100 response. These are assumed to correspond to 50%, 75% and 90% reductions from baseline PASI scores, respectively. The resulting PASI score enters into regression equations that determine utility (Section B.3.4.5). Additionally, the probability of a PASI75 response, along with the baseline distribution of plaque psoriasis severity (i.e. moderate-to-severe, mild-to-moderate, or no psoriasis), determines psoriasis-related disease management costs (Section B.3.5.2.1) in each model cycle.

Consistent with the assumption used for HAQ-DI change during the trial period, a linear improvement in PASI, from baseline to the start of the continuous treatment period, is assumed. As described in Sections B.3.4.5 and Section B.3.5.2.1, this linear improvement was applied directly to the utility values and disease management costs, respectively, rather than to the PASI (and HAQ-DI) values.

B.3.3.4 Transition probabilities

As described in Section B.1.3.1, PsA is a chronic and progressive inflammatory disease. For patients not receiving biologic therapies, this is characterised by a worsening in HAQ-DI score over time, reflecting the decrease in functional capability as the arthritis component of the disease progresses. However, the PASI score is assumed to remain constant over time as the psoriasis element is not considered to be progressive. These assumptions are applied in the model to reflect the natural history of the disease.

For the patients who are PsARC responders and remain on biologic therapy, both the PASI score and HAQ-DI score are assumed to be maintained for the duration of time that the patient remains on continuous treatment. The model also considers the risk of treatment discontinuation, following the first cycle of the model, due to AEs and loss of efficacy. This probability of discontinuing treatment is assumed to be independent of HAQ-DI and PASI score in the model, relevant for all comparators and is constant over time, as discussed in Section B.3.3.4.2.

Movement between health states, capturing patients' progression from line of treatment to the next, are represented as transition probabilities. These are described below.

B.3.3.4.1 Trial period

After initiating treatment in the trial period, patients transition to the next state in the tunnel unless they die within the temporary state. At the end of the trial period, an assessment of whether patients have achieved PsARC response determines their transition to the continuous treatment period or to the trial period for the next treatment. The transition from the trial period to the continuous treatment period was, therefore, modelled according to the NMA-based probability of PsARC response for

the specific treatment received. This is as estimated in the NMA of PsARC in the biologic-naïve population (in the line of therapy after failure of two csDMARDs) or the biologic-experienced population (in the lines of therapy after one bDMARD failure). Patients who did not respond were assumed to transition to the next line of therapy in the sequence (or to BSC after non-response to the last line of therapy).

For the biologic-naïve population, when patients discontinue and move onto the next line of treatment the effectiveness of the next treatment line is derived from the biologic-experienced network of the NMA. This was done to reflect the differences in efficacy between lines of therapy; no adjustment to account for treatment effect degradation as patients move on to subsequent lines of therapy was therefore necessary given this is captured in the NMA effect estimates.

For the biologic-experienced population, the base-case model assumes that upon treatment discontinuation the subsequent line of treatment is BSC; therefore, as discussed previously, baseline effectiveness is assumed.

B.3.3.4.2 Continuous treatment period

Patients who achieve a PsARC response enter the continuous treatment period and remain in this state until discontinuation due to any cause. Within this state, an all-cause discontinuation rate was applied to account for gradual loss of efficacy or tolerability in the long-term. Based on a meta-analysis of registry data from multiple countries[109, 112], the base case assumed that patients discontinue continuous treatment at a constant annual hazard rate of 0.165, uniform across treatments and lines of therapy. This assumption was consistent with the York Model (TA199 and TA445)[5, 109], and subsequent recent PsA submissions.[1, 82]

The annual hazard of discontinuation was converted into a 4-week discontinuation probability, based on an assumption of constant hazards. The resulting probability of discontinuation per 4-week cycle was applied in each model cycle as the transition probability from each continuous treatment therapy state to the next active line of treatment in the sequence (or to the BSC state following discontinuation of the last treatment line).

Clinical opinion, sought from the advisory board held on 22 May 2020, was that patients tend to remain on treatment increasingly less with each subsequent line, and that discontinuation rates would be higher in the biologic-experienced non-responders versus the biologic-naïve non-responders. Therefore, a scenario was modelled to adjust the discontinuation rates using hazard ratios (HRs) derived from the literature. Specifically, targeted searches identified a publication by Gabay et al. (2015)[120] which assessed the impact of the number of previous bDMARDs on treatment discontinuation using data from a Swiss rheumatoid arthritis registry. This study reported that the number of previously used bDMARDs was a negative predictor of bDMARD retention. No relevant studies were identified for PsA, therefore the impact of bDMARD line in rheumatoid arthritis was considered to be a reasonable proxy.

The discontinuation rate is only applied to the active treatment states. For the biologic-naïve population (line after failure with two csDMARDs), it is assumed that the 0.165 hazard rate applies. For patients who subsequently enter the line after failure with one bDMARD state (and for biologic-experienced patients who enter at this line), the statistically significant HR of 1.24 (95% CI: 1.09, 1.41, P-value<0.05), which represented 1 vs 0 previous bDMARDs, reported in Gabay et al. (2015)[120] is applied to adjust the discontinuation rate in this scenario.

Alternatively, an additional scenario analysis is tested whereby a different source is used to determine the annual hazard of discontinuation. The results of this, and the scenario exploring different discontinuation rates by treatment line, are presented in Section B.3.8.3.

B.3.3.4.3 Mortality

Age- and gender-dependent national mortality rates were obtained from the Office for National Statistics (ONS) National Life Tables for England and Wales (2017–19).[121] PsA appears to be associated with excess mortality risk relative to the general public. Therefore, national mortality rates were adjusted using a standardised mortality ratio (SMR) of 1.05. This SMR was used by the Evidence Review Group in TA537[82], based on the 1996–2004 cut of data published in Ali et al. (2007).[122]

An alternative SMR of 1.36 is assessed as a scenario; this was derived from the same study but using data between the period between 1978 and 2004, and was used in the previous recent PsA NICE appraisals. In TA537, the ERG preferred to adopt the SMR of 1.05 in their base case given it is based on more recent data and the SMR appears to have declined over time.

Patients can transition from any treatment state to the death state. To model mortality within the model cohort, the mortality rate at each age was calculated as a weighted average of SMR-adjusted, gender-specific mortality rates using the proportion of females across the SELECT-PsA 1 and SELECT-PsA 2 trials in Cycle 0 and accounting for changes over time in the gender distribution of the cohort. PsA treatment was assumed to have no effect on life expectancy.

B.3.4. Measurement and valuation of health effects

As discussed in Section B.1.3, the multiple manifestations of PsA cause a combination of physical and psychological symptoms that contribute to significant reductions in HRQL and ability to carry out daily activities. PsA patients experience decreased physical function, social isolation, less work productivity and lower life satisfaction compared with the general population.[11]

In accordance with the NICE reference case, health effects in the economic evaluation are expressed in terms of QALYs, which account for both HRQL and life expectancy. Valuation of health effects for each treatment sequence in the model was based on the utility calculated as a function of concurrent HAQ-DI and PASI scores, consistent with previous PsA appraisals (Table 53). The utility corresponding to a given set of HAQ-DI and PASI scores was assumed to be the same irrespective of treatment.

B.3.4.1 Health-related quality of life data from clinical trials

The EQ-5D-5L questionnaire was administered to patients in the SELECT-PsA 1 and SELECT-PsA 2 trials at baseline, Week 12, Week 24, Week 36 and Week 52. A summary of the EQ-5D-5L observations by treatment arm is presented in Table 64 for SELECT PsA 1 and Table 65 for SELECT PsA 2.

Table 64: Summary of EQ-5D-5L observations by treatment, SELECT PsA 1

Treatment	Patients in FAS population	Patients in analysis (%)[a]		Observations / records[a]	Mean number of observations / records per patient[a]
All	1,704	1,704	(100.0%)	6,582	3.86
Placebo	423	423	(100.0%)	1,606	3.80
Adalimumab	429	429	(100.0%)	1,665	3.88
Upadacitinib 15 mg	429	429	(100.0%)	1,670	3.89
Upadacitinib 30 mg	423	423	(100.0%)	1,641	3.88

Key: EQ-5D-5L, EuroQol-Five Dimensions-Five Levels; FAS, full analysis set
Note: [a] Sample sizes represent the number of unique patients and patient-visits included in the regression analyses of utility as a function of HAQ-DI and PASI scores within the SELECT-PsA 1 and SELECT-PsA 2 trials. The repeated-measures regression analyses included all patient-visits in which the patient had non-missing EQ-5D-5L responses and concurrent HAQ-DI and PASI scores available.

Table 65: Summary of EQ-5D-5L observations by treatment, SELECT PsA 2

Treatment	Patients in FAS population	Patients in analysis (%)[a]		Observations / records[a]	Mean number of observations / records per patient[a]
All	641	638	(99.5%)	2,495	3.91
Placebo	212	210	(99.1%)	787	3.75
Upadacitinib 15 mg	211	210	(99.5%)	848	4.04
Upadacitinib 30 mg	218	218	(100.0%)	860	3.94

Key: EQ-5D-5L, EuroQol-Five Dimensions-Five Levels; FAS, full analysis set
Note: [a] Sample sizes represent the number of unique patients and patient-visits included in the regression analyses of utility as a function of HAQ-DI and PASI scores within the SELECT-PsA 1 and SELECT-PsA 2 trials. The repeated-measures regression analyses included all patient-visits in which the patient had non-missing EQ-5D-5L responses and concurrent HAQ-DI and PASI scores available.

Data from these evaluations were analysed to derive base-case utility functions for implementation in the economic model. Regression analyses were conducted using repeated measurements of EQ-5D-5L from the trials, pooling across all treatment arms, as per Equation 4.

Equation 4: EQ-5D-5L regression equation

$$EQ\text{-}5D\text{-}5L = \alpha + \beta 1 \times HAQ\text{-}DI + \beta 2 \times PASI + \varepsilon$$

Generalised linear mixed-effects models (with individual-level random effects) were used to account for the correlation among repeated measures for the same individual. The dependent variable of each model was the observed EQ-5D-5L index

score at each visit (i.e. Week 0, 12, 24, 36 and 52). In accordance with the NICE position statement, updated in October 2019, on the EQ-5D-5L valuation set, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK EQ-5D-3L value set using the crosswalk developed by van Hout et al. (2012).[123, 124] Independent variables in the regression models included continuous HAQ-DI and PASI scores at each visit.

Separate regression models were fitted using SELECT-PsA 1 trial data for biologic-naïve patients and SELECT-PsA 2 trial data for biologic-experienced patients (Table 66). The analytical sample for the base-case regression models included a total of 1,704 patients (6,582 patient visits) in SELECT-PsA 1 and 638 patients (2,495 patient visits) in SELECT-PsA 2 with EQ-5D-5L, HAQ-DI and PASI measurements concurrently available.

Table 66: Base-case EQ-5D-5L utility equations derived from SELECT-PsA 1 and SELECT-PsA 2 trial data by subpopulation

Independent variable	Biologic-naïve and TNFα inhibitor-contraindicated: SELECT-PsA 1 trial data			Biologic-experienced: SELECT-PsA 2 trial data		
	coefficient	(SE)	p-value	coefficient	(SE)	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ-5D-5L, EuroQol-5D five level; HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index; SE, standard error; TNFα, tumour necrosis factor alpha.

In each target population, additional analyses were conducted using a regression model fitted using pooled data from both the SELECT-PsA 1 and SELECT-PsA 2 trials (combined biologic-naïve and -experienced population); or utility regression coefficients obtained from the York Model[5] (Table 67). These were tested in the economic model as alternative scenarios, the results of which are presented in Section B.3.8.3.

Table 67: Alternative utility equations used in scenario analyses

Independent variable	Pooled SELECT-PsA 1 and SELECT-PsA 2 trial data			York Model (TA199/TA445)	
	N=2,342; 9,077 patient visits				
	coefficient	(SE)	p-value	coefficient	(SE)
Intercept	[redacted]	[redacted]	[redacted]	0.897	(0.006)
HAQ-DI	[redacted]	[redacted]	[redacted]	-0.298	(0.006)
PASI	[redacted]	[redacted]	[redacted]	-0.004	(0.0003)

Key: HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index; SE, standard error.

B.3.4.2 Mapping

As described in Section B.3.4.1, the EQ-5D-5L questionnaire was administered to patients in the SELECT-PsA 1 and SELECT-PsA 2 trials. As also described in Section B.3.4.1 and consistent with the latest (October 2019) NICE guidance on this matter[123], the van Hout et al. algorithm was used to estimate EQ-5D-3L equivalent utility values from the EQ-5D-5L questionnaire data.[124]

B.3.4.3 Health-related quality of life studies

A systematic search for HRQL evidence in patients with moderate-to-severe PsA was performed alongside the search for economic studies reported in Section B.3.1. It comprised an original search on 9 September 2019, with subsequent updates on 26 May 2020 and 3 September 2020, and is reported in full in Appendix H.

A total of 72 studies from 78 publications were included in this review. Of these, 28 studies from 34 publications reported UK specific data. All except two of the studies used EQ-5D to derive utility values; one reported SF-6D utility values and one mapped the SF-36 to EQ-5D. Reporting levels varied between publications, limiting the comparability of these results. In various studies it was unclear whether the utility values derived were valued using a UK value set.

Eight studies reported utility values for biologic therapies. Of these, only one (Hatswell et al., 2014) reported separate utility values by biologic-naïve or biologic-experienced status for patients randomised to receive either ustekinumab or

placebo. The study found that for patients who were TNFα inhibitor-naïve, utility from baseline to Week 24 improved by 0.04 in the placebo arm and 0.11 in the ustekinumab arm. For the TNFα inhibitor-experienced population, this improvement was 0.06 and 0.13 for the placebo and ustekinumab arms, respectively. Of the other studies reporting the mean change in EQ-5D utility values for biologic therapies, mean change ranged from 0.07–0.30. However, this differs dependent on factors such as patient characteristics, response status and time point at which utility is measured. All these studies show an improvement in HRQL following treatment but differences in how these are reported make it difficult to draw firm conclusions.

Based on the review of cost-effectiveness studies, the model followed the approach of TA445 (in addition to all the previously published NICE technology appraisals) by modelling utility as a function of HAQ-DI and PASI. As the studies identified in the HRQL review reported only health state utility values, these were not used to inform the model.

B.3.4.4 Adverse reactions

As discussed in Section B.2.9, in SELECT PsA-1, the rates of serious AEs, severe AEs and AEs that resulted in drug discontinuation were comparable between the upadacitinib 15 mg and the placebo groups. In SELECT PsA-2, the proportions of patients with serious AEs, severe AEs, and AEs leading to study drug discontinuation were numerically higher with upadacitinib 15 mg than with placebo. Of note, the safety profile of upadacitinib in both the biologic-naïve and biologic-experienced populations was consistent with that seen in previous clinical studies across indications, with no new safety signals detected.

The HRQL and cost impact of AEs was not modelled in this economic evaluation due to the uncertainty around the estimation of these parameters. This approach is consistent with previous submissions, including the 2016 York Model, TA445[1, 5, 82], where it was argued that the major impact of AEs is captured in the treatment discontinuation rates (Section B.3.3.4.2). Moreover, the impact of AEs on the model results was expected to be small given the infrequency of malignant AEs and the acute nature of serious infections.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

As discussed previously, patients' HRQL was defined as a function of HAQ-DI and PASI scores. Table 66 in Section B.3.4.1 summarises the utility functions used in the base-case analysis for each target population. The resulting utility values, by population and treatment arm, are presented in Table 68.

EQ-5D-5L responses were collected, alongside efficacy measurements in the SELECT-PsA 1 and SELECT-PsA 2 trials, and mapped onto the UK EQ-5D-3L value set using the crosswalk developed by van Hout et al. (2012). Base-case utility functions were estimated through primary analyses of data from the SELECT-PsA 1 and SELECT-PsA 2 trials among all patients in the full analysis set populations with concurrent EQ-5D-5L, HAQ-DI and PASI measurements available.

States in the Markov model were defined by treatment status (i.e. trial period and continuous treatment period by line of therapy, then BSC) and death. In the base case, utility gains were assumed to linearly increase during each trial period to account for gradual improvement in HAQ-DI and PASI scores during the 12 weeks following the initiation of a new treatment line. This assumption was supported by the clinical and health economics experts attending the 22 May 2020 advisory board.[4] Alternative assumptions of zero or immediate utility gains during each trial period were considered in scenario analyses (Section B.3.8.3). Because patients transition to the continuous treatment period of a treatment line only if they achieved PsARC response in the trial period, patients' utility in the continuous treatment period was calculated based on HAQ-DI and PASI scores conditional on PsARC. As discussed previously, HAQ-DI and PASI scores were assumed to be maintained while patients remain on continuous treatment. On transitioning to BSC, HAQ-DI and PASI scores reverted to baseline levels. In subsequent cycles where patients remained on BSC, HAQ-DI was assumed to progress linearly according to the natural history of PsA, while PASI scores remained constant. Capturing ageing trends in utility was expected to have minimal impact, given the assumption of no treatment-specific effect on life expectancy, and was therefore not applied.

Table 68: Summary of utility values used for cost-effectiveness analysis

Treatment	Utility value: trial period			Utility value: continuous period		
	No psoriasis	Mild-moderate psoriasis	Moderate-severe psoriasis	No psoriasis	Mild-moderate psoriasis	Moderate-severe psoriasis
Biologic-naïve population						
Baseline	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced population						
Baseline	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitor-contraindicated population						
Baseline	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: N/A, not applicable; TNFα, tumour necrosis factor alpha.						

B.3.5. Cost and healthcare resource use identification, measurement and valuation

A systematic search for published cost and healthcare resource identification, measurement and valuation data in moderate-to-severe PsA was run alongside the searches for economic evaluation and HRQL data noted in Sections B.3.1 and B.3.4. As reported in Appendix I, the original search run on 3 September 2019 was updated on 21 May 2020 and again on 2 September 2020.

The model considered costs and resource use associated with:

- Drug acquisition and administration
- Routine monitoring
- Arthritis- and psoriasis-related healthcare resource use
- Management of AEs

Unit costs were obtained from the 2018–19 NHS Reference Costs, Monthly Index of Medical Specialties (MIMS), Personal Social Services Research Unit (PSSRU) and other published and publicly available sources.[125-127] Where applicable, cost inputs were inflation-adjusted from their original reporting year to 2019 pound sterling (GBP) using the Office for National Statistics' Consumer Price Index for Health.[128]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition cost

Drug acquisition costs were calculated in the model as a function of unit drug costs and dosing schedules for the included treatments (Table 69 and Table 70). Dosing schedules were based on the SELECT-PsA 1 and SELECT-PsA 2 trial protocols[78, 79] for upadacitinib and EMA labelling[63-66, 77, 129-133] for comparators (Table 69). Methotrexate was assumed to be received concomitantly by a proportion of patients during treatment with bDMARDs/tsDMARDs; this proportion was based on feedback from a questionnaire completed by four clinical experts attending the 22 May 2020 advisory board.[4] Given each expert provided different estimates, reflecting the variations in NHS England clinical practice, the mean proportion was calculated for use in the model. For the upadacitinib arm, the proportions of concomitant

methotrexate were derived from the SELECT-PsA 1 and 2 trials. Scenario analyses were conducted to assess the impact of assuming no patients received concomitant methotrexate, and following the assumption used by the UCB submission reported in TA445, where it was assumed that 58% of all patients, regardless of treatment, received concomitant methotrexate.[5] For patients receiving concomitant methotrexate, a weekly dosage of 7.5 mg was assumed based on the starting dosage recommended by the EMA.[134]

Unit drug costs for branded and biosimilar agents were retrieved from MIMS and the electronic market information tool (eMIT) for methotrexate (Table 70).[126, 135] Equivalent efficacy was assumed for biosimilar and branded formulations of the same agent; therefore, the base case conservatively assumed biosimilar pricing for treatments that had biosimilars available at the time of this submission (i.e. etanercept, adalimumab and infliximab). For each of these treatments, the list price associated with the least expensive biosimilar was used. A separate acquisition cost was not applied to BSC and therefore the cost of BSC is assumed to be entirely captured in terms of health state costs. For adalimumab, a unit price of [redacted], equating to an annual price of [redacted] per patient, was used in line with the Commercial Medicines Unit price; this was recommended by NICE during the Decision Problem Meeting for this appraisal held on 24th September 2020.

The acquisition cost of upadacitinib at list price is £805.56 per 28 pack of 15 mg tablets (£10,508 per patient per year). A Patient Access Scheme (PAS) discount of [redacted]% on the list price, has been submitted and is used in the model base case; this results in an annual cost of [redacted] per patient per year.

Tofacitinib, secukinumab, ixekizumab and apremilast have been recommended by NICE under confidential PAS discounts that apply a percentage reduction to the list price.[55] The base case uses list prices for these treatments. Certolizumab pegol is subject to a PAS requiring that the first three months of treatment be provided for free.[55] This PAS for certolizumab pegol is reflected in the calculation of drug acquisition costs for this treatment during the trial period (Table 70). Golimumab was recommended by NICE under a PAS that set the price of the 100 mg dose equal to

that of the 50 mg dose.[55] Ustekinumab is available at the 90 mg dose for the same price as that of the 45 mg dose.

Weight-based dosing requirements for infliximab were calculated using the mean baseline weight of patients in the SELECT-PsA 1 and SELECT-PsA 2 trials (87.0 kg), with the assumption of no vial-sharing.

Table 69: Drug dosing schedules

Treatment	Description of dosing schedule	
	Trial period	**Continuous treatment period**
Upadacitinib 15 mg	15 mg daily	15 mg daily
Adalimumab	40 mg EOW	40 mg EOW
Apremilast[a]	Initial titration schedule (Week 0–2), 30 mg twice daily thereafter	30 mg twice daily
Certolizumab pegol	400 mg at Week 0, 2 and 4, and 200 mg Q2W thereafter	200 mg Q2W
Etanercept	25 mg twice weekly	25 mg twice weekly
Golimumab	50 mg monthly	50 mg monthly
Infliximab	5 mg/kg at Week 0, 2, 6, and Q8W thereafter	5 mg/kg Q8W
Ixekizumab	160 mg at Week 0 and 80 mg Q4W thereafter	80 mg Q4W
Secukinumab 150 mg[b]	150 mg at Week 0, 1, 2, 3, 4 and monthly thereafter	150 mg monthly
Secukinumab 300 mg[c]	300 mg at Week 0, 1, 2, 3, 4 and monthly thereafter	300 mg monthly
Tofacitinib	5 mg twice daily	5 mg twice daily
Ustekinumab	45 mg at week 0, 4 and Q12W thereafter	45 mg Q12W

Key: EMA, European Medicines Agency; EOW, every other week; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; Q#W: once every # weeks; TNFα, tumour necrosis factor alpha.
Notes: [a] Scheduled dosages of apremilast during Weeks 0–2 are covered by the 690 mg starter pack and consist of 10 mg on Day 1, 10 mg twice on Day 2, 10 mg and 20 mg on Day 3, 20 mg twice on Day 4, 20 mg and 30 mg on Day 5, and 30 mg twice daily on Day 6–14; [b] In the biologic-naïve and TNFα inhibitor-contraindicated populations, dosing requirements for secukinumab were based on the NICE and EMA recommendations that patients with concurrent moderate-to-severe plaque psoriasis receive the 300 mg dosage, while those with mild-to-moderate or no plaque psoriasis receive the 150 mg dosage. [c] In the biologic-experienced population, 300 mg dosing of secukinumab was assumed based on NICE and EMA recommendations.

Table 70: Drug acquisition costs

Treatment	Unit drug costs[a]		Cost of starter pack (if applicable)[b]		Total units required		PAS discount (%)		Proportion receiving methotrexate in combination	Drug cost per 4-week cycle (£), including concomitant methotrexate	
	Cost per unit (£)	Strength per unit (mg)	Cost per starter pack (£)	Strength per starter pack (mg)	Trial period (excluding starter pack)[b]	Continuous treatment period (annual)[c]	Trial period[d]	Continuous treatment period		Trial period	Continuous treatment period
Upadacitinib 15 mg (biologic-naïve and TNFα inhibitor contraindicated or not tolerated populations)	[redacted]	15	–	–	84.0	364.0	–	–	70%	[redacted]	[redacted]
Upadacitinib 15 mg (biologic-experienced population)	[redacted]	15	–	–	84.0	364.0	–	–	39%	[redacted]	[redacted]
Adalimumab	[redacted]	40	–	–	6.0	26.0	–	–	64%	[redacted]	[redacted]
Apremilast[a]	9.82	30	265.18	690	126.0	728.0	–	–	5%	546.75	550.03
Certolizumab pegol	357.50	200	–	–	9.0	26.0	100.0%	–	32%	0.17	715.17
Etanercept	82.00	25	–	–	24.0	104.0	–	–	49%	643.76	643.76
Golimumab	762.97	50	–	–	3.0	12.0	–	–	45%	763.21	704.52
Infliximab	377.00	100	–	–	15.0	32.5	–	–	70%	1,885.37	942.87
Ixekizumab	1,125.00	80	–	–	4.0	13.0	–	–	28%	1,500.14	1,125.14
Secukinumab 150 mg[e]	609.39	150	–	–	6.0	15.0	–	–	40%	1,218.99	562.72
Secukinumab 300 mg[e]	609.39	150	–	–	12.0	24.0	–	–	40%	2,437.77	1,125.24
Tofacitinib	12.32	5	–	–	168.0	728.0	–	–	63%	690.36	690.36
Ustekinumab	2,147.00	45	–	–	2.0	4.3	–	–	20%	1,431.44	715.77
Methotrexate (when used in combination)	0.04	2.5	–	–	N/A	156	–	–	N/A	0.53	0.53

Key: N/A, not applicable; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme.
Notes: Biosimilar pricing is used for etanercept, adalimumab and infliximab based on list prices for etanercept (Benepali®/Erelzi®), adalimumab (Hulio®) and infliximab (Flixabi®);
[a] Scheduled dosages of apremilast during Weeks 0–2 are covered by the 690 mg starter pack and consist of 10 mg on Day 1, 10 mg twice on Day 2, 10 mg and 20 mg on Day 3, 20 mg twice on Day 4, 20 mg and 30 mg on Day 5 and 30 mg twice daily on Day 6–14;

[b] Total units in the trial period include dosages (other than the starter pack) scheduled within the interval [0, t) weeks, where t is the end of the trial period for a given treatment.(If a dosage is schedule at Week t, that dosage is not counted as it is allocated to the continuous treatment period);
[c] Annual units in the continuous treatment period include dosages scheduled per year starting after the trial period.
[d] NICE recommended certolizumab pegol with a PAS that covers 100% of costs during the first 12 weeks of treatment (TA537 and TA543).
[e] In the biologic-naïve and TNFα inhibitor-contraindicated populations, dosing requirements for secukinumab were based on the NICE and EMA recommendations that patients with concurrent moderate-to-severe plaque psoriasis receive the 300 mg dosage, while those with mild-to-moderate or no plaque psoriasis receive the 150 mg dosage. In the biologic-experienced population, 300 mg dosing of secukinumab was assumed based on NICE and EMA recommendations.

B.3.5.1.2 Drug administration cost

Drug administration costs were dependent on the route of administration for each treatment. For drugs administered by subcutaneous self-injection, administration costs accounted for the cost of a single 1-hour nurse training session for self-administration during the trial period, consistent with other recent NICE submissions.[1, 82] No further administration costs were applied in the continuous treatment period for these treatments.

For infliximab (an intravenous therapy), the unit cost of an outpatient intravenous infusion was applied per scheduled administration (i.e. three times during the 12-week trial period and an average of 6.5 times annually during the continuous treatment period). Unit costs of drug administration were obtained from 2019 PSSRU Unit Costs of Health and Social Care and the 2018–19 NHS Reference Costs (Table 71).[125, 136]

For orally administered drugs, no administration cost was assumed.

Table 71: Drug administration cost

Route	Unit cost per administration (£)	Source
Subcutaneous	42.00	PSSRU, Unit Costs of Health and Social Care 2019, Nurse (GP practice), wage cost per hour
Intravenous	183.54	NHS Reference Cost 2018-2019, SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance), Outpatient
Oral	0.00	Assumption based on TA543 and 537
Key: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.		

B.3.5.1.3 Monitoring costs

Monitoring requirements during treatment were based on the TA445[5, 137], which aligned with guideline recommendations from the BSR[53] (Table 72). Monitoring services included routine outpatient visits and laboratory tests.

Table 72: Frequency of treatment monitoring during the trial and continuous treatment periods for each drug

Test	Frequency of monitoring services	
	Trial period	Continuous treatment (annual)
Rheumatologist visit	2	0
Full blood count	2	2
Liver function test		
Urea and electrolyte		
ESR		
Chest X-ray	1	0
TB Heaf test		
ANA test		
ds DNA test		

Key: ANA, antinuclear antibody; ds DNA test, double strand DNA test; ESR, erythrocyte sedimentation rate; TB, tuberculosis.
Notes: Frequency of test was assumed the same for all treatments, based on the York Model.

To confirm that these monitoring services are reflective of current NHS England clinical practice, Table 72 was validated with clinical experts at the 22 May 2020 advisory board.[4] Based on this feedback, changes were made to the tests and frequency of tests required; specifically:

- The frequency of rheumatologist visits, full blood count, liver function and urea and electrolyte tests have increased
- C-reactive protein tests are assumed to be done in place of erythrocyte sedimentation rate
- T-spot and quantiferon tests are assumed to be done in place of the tuberculosis Heaf test
- Double stranded DNA test is assumed not to be done in clinical practice

This is summarised below in Table 73.

Table 73: Frequency of treatment monitoring during the trial and continuous treatment periods for each drug based on expert opinion

Test	Frequency of monitoring services	
	Trial period	Continuous treatment (annual)
Rheumatologist visit	4	2
Full blood count	8	4
Liver function test	8	4
Urea and electrolyte	8	4
CRP[a]	2	2
Chest X-ray	1	0
T spot / quantiferon	1	0
ANA test	1	0
ds DNA test	0	0

Key: ANA, antinuclear antibody; ds DNA test, double strand DNA test; ESR, erythrocyte sedimentation rate; TB, tuberculosis.
Notes: Frequency of test was assumed the same for all treatments, based on the York Model.
[a] No estimates of CRP test frequency were provided by the clinical experts; therefore, the model assumes the same frequency as ESR reported in the York model.

Unit costs for each resource were obtained from the 2018–19 NHS Reference Costs or, for services without a corresponding reference code, from the original York Model (Table 74).[112, 136] The costs of a T spot (£55) and quantiferon test (£45) were reported in NICE clinical guideline 117, which derived the costs from Pooran et al, 2010. The mean cost of the two tests was used, and this was inflated from 2010 to a 2019 cost year, based on inflation indices reported in the Unit Costs for Health and Social Care.[125]

Table 74: Unit costs of treatment monitoring

Service	Unit cost per service (£)	Sources
Rheumatologist visit	143.49	NHS Reference Cost 2018-2019, WF01A (Service code: 410; Rheumatology), CL
Full blood count	2.79	NHS Reference Cost 2018-2019, DAPS05 (Haematology), DAPS
Liver function test	1.10	NHS Reference Cost 2018-2019, DAPS04 (Clinical biochemistry), DAPS
Urea & electrolyte	1.10	NHS Reference Cost 2018-2019, DAPS04 (Clinical biochemistry), DAPS
CRP	2.79	NHS Reference Cost 2018-2019, DAPS05 (Haematology), DAPS
Chest X-Ray	30.59	NHS Reference Cost 2018-2019, DAPF (Direct Access Plain Film), DADS

Service	Unit cost per service (£)	Sources
T spot / quantiferon	58.24	NICE CG117, Cost Effectiveness Analysis of Interferon Gamma Release Assay (IGRA) Testing for Latent Tuberculosis, Appendix 6
ANA test	2.79	NHS Reference Cost 2018-2019, DAPS05 (Haematology), DAPS
ds DNA test	2.79	NHS Reference Cost 2018-2019, DAPS05 (Haematology), DAPS
Key: ANA, antinuclear antibody; ds DNA test, double strand DNA test; ESR, erythrocyte sedimentation rate; TB, tuberculosis.		

A scenario analysis was tested to apply the additional cost of a dermatologist visit for patients with moderate-to-severe psoriasis. Consistent with the resource use reported in TA574, certolizumab pegol for treating moderate to severe plaque psoriasis[138], an annual frequency of two visits per year in the continuous treatment health state is applied. For the initial trial period, it is also assumed that patients with moderate-to-severe psoriasis will require two dermatologist visits. In addition, the use of the treatment monitoring frequencies from TA445 (Table 72) were also tested as a scenario analysis. The results of these scenarios are presented in Section B.3.8.3.

Table 75: Unit costs of dermatologist visit: scenario analysis

Service	Unit cost per service (£)	Sources
Dermatologist visit	120.14	NHS Reference Cost 2018-2019, DAPS05 (Haematology), DAPS

B.3.5.2 Health state unit costs and resource use

Health state costs are based on HAQ-DI and PASI scores, as per previous NICE submissions (including TA445 and TA543).[1, 5] The method used in most previous submissions estimates arthritis-related costs linked to HAQ-DI score and psoriasis-related costs linked to PASI75 response status. As per the approach used to quantify utility gains during the trial period, in the base case, arthritis- and psoriasis-related management costs were assumed to linearly decrease during each trial period to account for gradual improvement in HAQ-DI and PASI scores during the 12 weeks following the initiation of a new treatment line. Alternative assumptions of zero or

immediate HAQ-DI and PASI score improvement during each trial period were considered in scenario analyses.

B.3.5.2.1 Costs associated with HAQ-DI

Following the approach used in multiple prior NICE submissions[1, 5, 82], arthritis-related resource use costs are estimated using a regression published by Bansback et al. (2006), which used resource use values from a study by Kobelt et al. (2002).[139, 140]

The study by Kobelt et al. used data from a UK cohort that included over 900 patients with rheumatoid arthritis and at least 5-years of follow up in the 1980s and 1990s. Treatment during this time period pre-dated the introduction of biologic therapies, mainly comprising csDMARDs (sulfasalazine and methotrexate). Health resource utilisation was collected throughout the study, or via cross-sectional survey in the case of medical visits, with unit costs obtained from hospital accounting and official price lists. Costs were reported for six health states, defined based on HAQ-DI, with the worst health state ≥2.6 and the best health state ≤0.6.

The linear regression model fitted by Bansback et al. estimated total direct healthcare costs (including both medical and pharmacy costs) as a function of HAQ-DI score, as per the below equation:

$$Annual\ healthcare\ costs = \alpha + \beta 1 \times HAQ\text{-}DI + \mathcal{E}$$

Values for the intercept and coefficient were obtained from the most recent prior submission in this indication (TA543) and inflated to 2019 GBP (Table 76).[1, 128] Costs for medications have been estimated to amount to 15% of the total cost.[112] Except in the BSC state, healthcare costs during treatment included a 15% reduction to prevent double-counting of drug acquisition costs, modelled separately (Section B.3.5.1). For BSC, this reduction is not applied in order to incorporate the costs of supportive medicines in this state, consistent with the approach used in TA445.[5]

Table 76: Arthritis-related resource use costs per 4-week cycle as a function of HAQ-DI score

Including medications (£)	Excluding medications (£)

Intercept	HAQ-DI coefficient	Intercept	HAQ-DI coefficient
149.79	43.69	123.16	37.14
Key: HAQ-DI, Health Assessment Questionnaire-Disability Index. **Notes:** Intercept and HAQ-DI coefficient are converted from direct annual costs to 4-week costs.			

B.3.5.2.2 Costs related to Psoriasis Area and Severity Index

The psoriasis element of disease management costs have been linked to PASI response in prior submissions (e.g. TA445, TA199)[5, 109], based on evidence from a Dutch study by Hartman et al. (2002) among patients with psoriasis treated with DMARDs.[141] The Hartman et al. estimation grouped patients according to the severity of their psoriasis at baseline. Patients without psoriasis at baseline had no cost attributed. Costs for patients with controlled psoriasis (defined by PASI75 response achievement) were estimated based on the cost of a patient in remission; while costs for patients with uncontrolled psoriasis (i.e. PASI75 non-response) were assumed to undergo one course of ultraviolet B treatment annually, including a cost for one initial treatment and one follow-up.

Values for psoriasis-related costs were taken from the most recent submission (TA543) and inflated to 2019 (Table 77).[1, 128]

Table 77: Psoriasis-related resource use cost by PASI75 response status and baseline severity of plaque psoriasis

Treatment outcome	4-week cost (£)		
	No psoriasis	Mild-to-moderate psoriasis	Moderate-to-severe psoriasis
Controlled psoriasis (with PASI75 response)	0.00	5.75	5.75
Uncontrolled psoriasis (without PASI75 response)	0.00	71.15	203.37
Key: PASI, Psoriasis Area and Severity Index.			

B.3.5.3 Miscellaneous unit costs and resource use

No other costs are considered.

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

B.3.6.1 Summary of base case analysis inputs

A summary of the variables included in the model, their base case values, and the measurement of uncertainty and distribution is tabulated in Appendix N.

B.3.6.2 Assumptions

Table 78 summarising the key model assumption will be updated and presented here.

Table 78: Key model assumptions

Assumption	Justification
A lifetime time horizon was used.	A lifetime horizon was used to capture all differences in costs and outcomes for all patients.
The base case for the biologic-naïve population considered treatment sequences comprising two lines of therapy followed by BSC. Following the failure of the first bDMARD/tsDMARD, patients are assumed to receive treatment with ustekinumab. Treatment sequences in the biologic-experienced population comprised one line of therapy, starting from the line after failure of one bDMARD, followed by BSC.	A common subsequent-line treatment algorithm was maintained across the specified sequences to avoid confounding by efficacy of subsequent line treatments. It is acknowledged that alternative sequences and additional treatment lines are possible in clinical practice, however, due to the uncertainties around what these sequences would be and what the treatment degradation effect would be, additional lines of treatment were not modelled. The base-case treatment sequences considered in this economic model are consistent with those presented in TA445 and other recent NICE appraisals.
PsARC response for secukinumab in the biologic-experienced population was based on NMA results reported in TA445[5].	In the case of secukinumab, summary-level trial results for PsARC in the biologic-experienced population were unavailable for inclusion in the de novo NMA as they were not in the public domain (and redacted in TA445). Therefore, the PsARC response estimate for use in the model was extracted from the NMA results reported in TA445[5]. This approach was taken in the absence of an alternative, to ensure a comparison against secukinumab in the biologic-experienced population was presented. Furthermore, the same approach was taken in TA543.[1]
HAQ-DI change conditional on PsARC response for certolizumab pegol, ixekizumab, secukinumab, and tofacitinib were populated with data from TA445[5], a NMA study[115], and summary-level trial results[116-118].	Due to paucity of data, these treatments could not be included in the de novo NMAs and were populated using the approach described in Section B.3.3.2.1. This approach was taken in the absence of an alternative, to ensure a comparison against these treatments was presented. Furthermore, a similar approach was taken in TA543.[1]
The model base case did not account for the expectation effect.	Although previous literature suggests that expectation effects should be corrected in the disease progression outcome (HAQ-DI) this adjustment is counterintuitive to the nature of expectation itself, which should vanish over

	time. Given the literature is inconclusive on this matter, adjustments in economic models are exploratory rather than the base case. A scenario analysis was therefore tested to adjust for the expectation effect by discounting the mean change in HAQ-DI across the placebo arms of the randomised controlled trials from the change in HAQ-DI for patients using biologics, in line with approaches used in previous appraisals[1, 5, 82].
Responder patients maintain the improvement in HAQ-DI and PASI scores achieved by the end of the trial period throughout the continued treatment period until discontinuation from treatment.	This assumption is applied uniformly across all comparators and is consistent with previous NICE appraisals in PsA[1, 5, 82].
A constant annual discontinuation rate of 0.165 is applied on a cyclical basis to all patients on active treatment in the continued treatment period.	Clinical experts at an advisory board suggested that the proportion of patients discontinuing treatment increased with each subsequent line of treatment[4], therefore a scenario analysis was tested which assumed the discontinuation rate increased at subsequent lines. The constant rate across all treatment is consistent with previous appraisals[1, 5, 82].
HAQ-DI and PASI scores return to baseline levels upon discontinuation of biological treatment.	This is consistent with previous appraisals[1, 5, 82] and was validated with clinical experts at the 22 May 2020 advisory board.[4]
For patients who discontinue from active treatment and receive BSC, HAQ-DI is assumed to revert to baseline and subsequently progress in line with the natural history of PsA; PASI also reverts to baseline PASI and remains constant in subsequent cycles spend in the BSC state.	This is consistent with previous appraisals[1, 5, 82].
For the population with active PsA in whom TNFα inhibitors are contraindicated or not tolerated, NMA results for the biologic-naïve population were also used.	TNFα inhibitor contraindicated patients are likely to be a combination of biologic-naïve and biologic-experienced patients. However, due to a lack of efficacy data specific to these patients, the base case analysis was undertaken using the biologic-naïve population. Clinician feedback gathered at an advisory board suggested that it is reasonable to assume the same efficacy as in the biologic-naïve population[4]. This is also consistent with TA543.[1]
An excess mortality risk associated with PsA was modelled for all comparators, by applying an SMR to the age- and gender-matched general population.	As there is no evidence to suggest that mortality differs between treatments, the increased mortality is not modified by treatment or treatment response. Given the assumption of excess mortality is applied to all arms, the impact on the results is minimal. The application of the same SMR for all arms was consistent with the approaches used in previous PsA NICE submissions, including TA445.[5] Furthermore, the SMR used (1.05) aligned with the ERG's preferences in In TA537.[82]
Key: BSC, best supportive care; HAQ-DI, Health Assessment Questionnaire-Disability Index; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria;	

B.3.7. Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

Table 79, Table 80 and Table 81 display base case cost-effectiveness results for the populations of interest:

- Biologic-naïve
- Biologic-experienced
- TNFα inhibitor-contraindicated

Each population is further stratified by psoriasis severity (no psoriasis, mild-to-moderate and moderate-to-severe).

All cost-effectiveness results presented, here and throughout the dossier, reflect the PAS price of £[redacted] per patient per year for upadacitinib. Time preference discounting, as described in Section B.3.2.2, is applied to all cost and QALY outcomes shown, but not life year estimates.

A comparison of clinical outcomes from the trial and model, and disaggregated cost and QALY results, are presented in Appendix J. Base-case results using the upadacitinib list price are included in Appendix P.

Biologic-naïve population base case results

The fully incremental analysis allows the calculation of incremental QALY gains and costs, along the list of treatment options ranked by ascending cost, starting with adalimumab as the cheapest comparator therapy. As summarised in Table 79, the results show that six of the comparators are dominated. Upadacitinib is associated with an incremental cost-effectiveness ratio (ICER) of just under £20,000/QALY in all psoriasis severity subgroups. For the two remaining comparators that were not dominated, etanercept and infliximab, their associated ICERs fall in the south-west quadrant; these treatments result in marginally greater incremental QALYs and are associated with comparatively high incremental costs compared with upadacitinib.

The pairwise results of the base case analysis for the biologic-naïve population in all psoriasis severity subgroups show that upadacitinib is dominant against five out of

nine comparators. For the comparisons where upadacitinib is not dominant, three result in ICERs falling in the south-west quadrant: etanercept, golimumab and infliximab. The cost-effectiveness planes, presented in Appendix O for the probabilistic analysis, demonstrate that the ICERs for upadacitinib versus each of these comparators largely fall below the willingness to pay (WTP) threshold line of £30,000. Furthermore, as demonstrated in Section B.3.8.1, the cost-effectiveness acceptability frontiers (CEAFs) show that, at a WTP threshold of £30,000, upadacitinib is the most economically preferred treatment option. The comparison of upadacitinib and adalimumab results in ICERs of below £20,000/QALY in all psoriasis severity subgroups.

Table 79: Base case results for biologic-naïve population

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£19,322
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£19,322	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£57,118	£57,118*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£229,092*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£365,044	£113,594*
Mild-to-moderate psoriasis							
Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£17,980
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£17,980	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£64,577	£64,577*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£274,601*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£271,574	£112,907*
Moderate-to-severe psoriasis							

Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£12,701
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£12,701	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£86,662	£86,662*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£353,052*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£110,772	£97,333*

Key: bDMARD, biological disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; QALYs, quality-adjusted life years; UPA, upadacitinib; vs, versus.
Note: Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence.

Biologic-experienced population base case results

As summarised in Table 80, the results of the fully incremental base-case analysis for the biologic-experienced population in all psoriasis severity subgroups show that only upadacitinib and ixekizumab are not dominated. Upadacitinib is associated with an ICER of below the £20,000/QALY WTP threshold in all subgroups, with particularly low ICERs of <£10,000/QALY for the biologic-experienced with mild-to-moderate and moderate-to-severe psoriasis subgroups. Ixekizumab was found to be more costly and more effective than upadacitinib (and BSC), resulting in a high south-west ICER; the higher south-west ICER implies better cost-effectiveness for the upadacitinib sequence.

Table 80: Base case results for biologic-experienced population

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£11,513
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£11,513	N/A
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Extended dominated	£424,592*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£194,345	£194,345*
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£416,712*
Mild-to-moderate psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£9,775
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£9,775	N/A
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Extended dominated	£788,986*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£191,874	£191,874*
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£384,703*
Moderate-to-severe psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£6,165
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£6,165	N/A
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£177,669	£177,669*
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£269,436*

Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; QALYs, quality-adjusted life years; UPA, upadacitinib; vs, versus.
Note: Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence.

TNFα inhibitor-contraindicated population base case results

As summarised in Table 81, the results of the fully incremental base-case analysis for the TNFα inhibitor-contraindicated population in all psoriasis severity subgroups show that upadacitinib is associated with an ICER of below £20,000/QALY (and below £10,000/QALY in the moderate-to-severe psoriasis subgroup) when compared with the cheapest option, BSC. All other comparators were found to be dominated, except secukinumab in the no psoriasis and mild-to-moderate psoriasis subgroups, where it was associated with a very high south-west ICER. Considering how high this south-west ICER is, this implies better cost-effectiveness for the upadacitinib sequence.

Table 81: Base case results for people in whom TNFα inhibitors are contraindicated or not tolerated

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£16,931
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£16,931	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£10,151,112	£10,151,112*
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Mild-to-moderate psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£10,492
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£10,492	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£6,330,422	£6,330,422
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant

Moderate-to-severe psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£8,809
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£8,809	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant

Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALYs, quality-adjusted life years; TNFα, tumour necrosis factor alpha; UPA, upadacitinib; vs, versus.
Note: South-west ICERs are denoted by an asterisk (*) and indicate that the UPA sequence is estimated to be both less costly and less effective than the specified comparator sequence. South-west ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs the UPA sequence.

B.3.8. Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To characterise uncertainty in the model results, a probabilistic sensitivity analysis (PSA) was undertaken in which key model parameters were simultaneously varied based on specified distributional assumptions over 1,000 model iterations; the mean PSA ICER appears robust to additional PSA draws, as illustrated within the cost-effectiveness model. The cost-effectiveness model allows the user to generate probabilistic results for any of the programmed settings options, including all scenario analyses reported in Section B.3.8.3.

A summary of the parameters and corresponding distributions considered in the PSA is presented in Appendix N. Where available, the standard error of a distribution was obtained from the same data source used to inform the base case input value. Otherwise, the standard error was assumed to be equal to 10% of the mean value if data on variability was not available.

A summary of the PSA results for all subpopulations is presented in Table 82. When compared with the deterministic results presented in Table 79, Table 80 and Table 81 (for the biologic-naïve, biologic-experienced and TNFα inhibitor-contraindicated populations, respectively), these appear to be a reasonable approximation of the mean PSA results, suggesting deterministic results are generally robust to uncertainty from parameter distributions.

Table 82: Mean PSA base case results

Technologies	Total costs (£)	Total QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic pairwise ICER of UPA vs comparator (£/QALY)
Biologic-naïve; no psoriasis					
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£19,731
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£56,930*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£223,360*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£112,315*
Biologic-naïve; mild-to-moderate psoriasis					
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£18,379
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£64,260*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£267,164*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£111,810*
Biologic-naïve; moderate-to- severe psoriasis					
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£13,067
Upadacitinib sequence	[redacted]	[redacted]	£0	0.00	N/A

Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£84,598*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£336,155*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£95,997*
Biologic-experienced; no psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£11,542
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£380,297*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£202,316*
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£396,832*
Biologic-experienced; mild-to-moderate psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£9,808
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£632,692*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£199,723*
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£373,411*
Biologic-experienced; moderate-to-severe psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£6,232
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£184,939*
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£278,711*

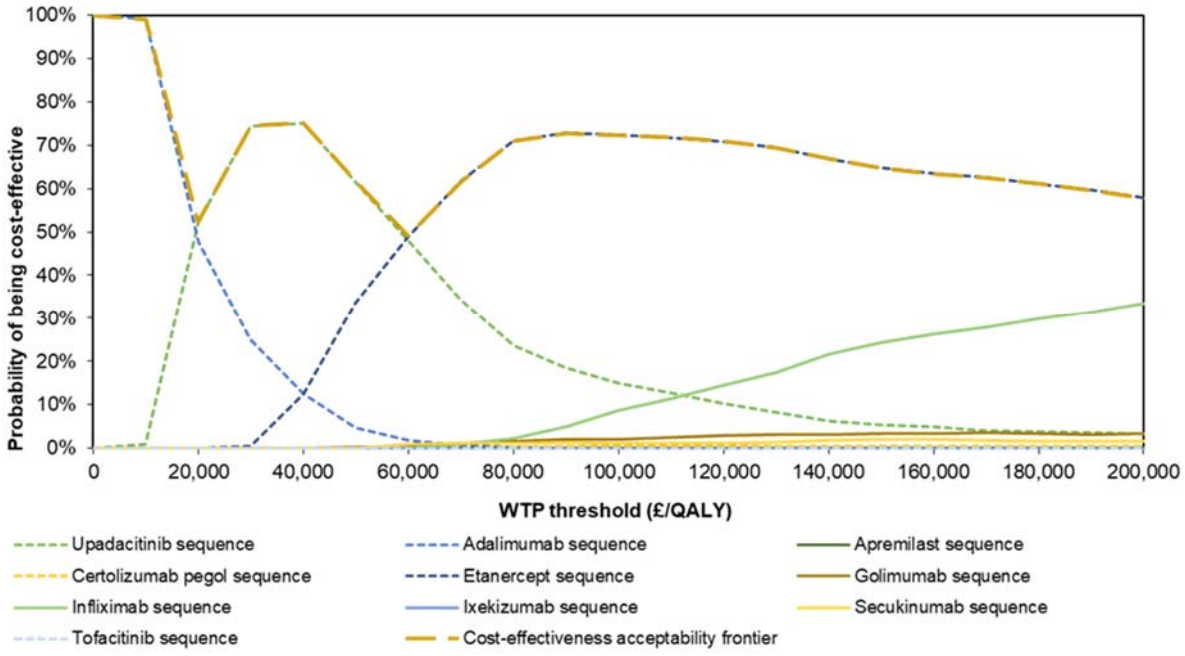
TNFα inhibitor contraindicated or not tolerated; no psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£17,057
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
TNFα inhibitor contraindicated or not tolerated; mild-to-moderate psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£10,496
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
TNFα inhibitor contraindicated or not tolerated; moderate-to-severe psoriasis					
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£8,774
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant

Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; TNFα, tumour necrosis factor alpha; vs, versus.
Notes: South-west ICERs are denoted by an asterisk (*) and indicate that the UPA sequence is estimated to be both less costly and less effective than the specified comparator sequence. South-west ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs the UPA sequence.

Graphical representations of the PSA results from the 1,000 model iterations are presented in Appendix O as scatterplots of incremental cost and QALY pairs on the cost-effectiveness plane for the upadacitinib sequence versus comparator sequences in each target population.

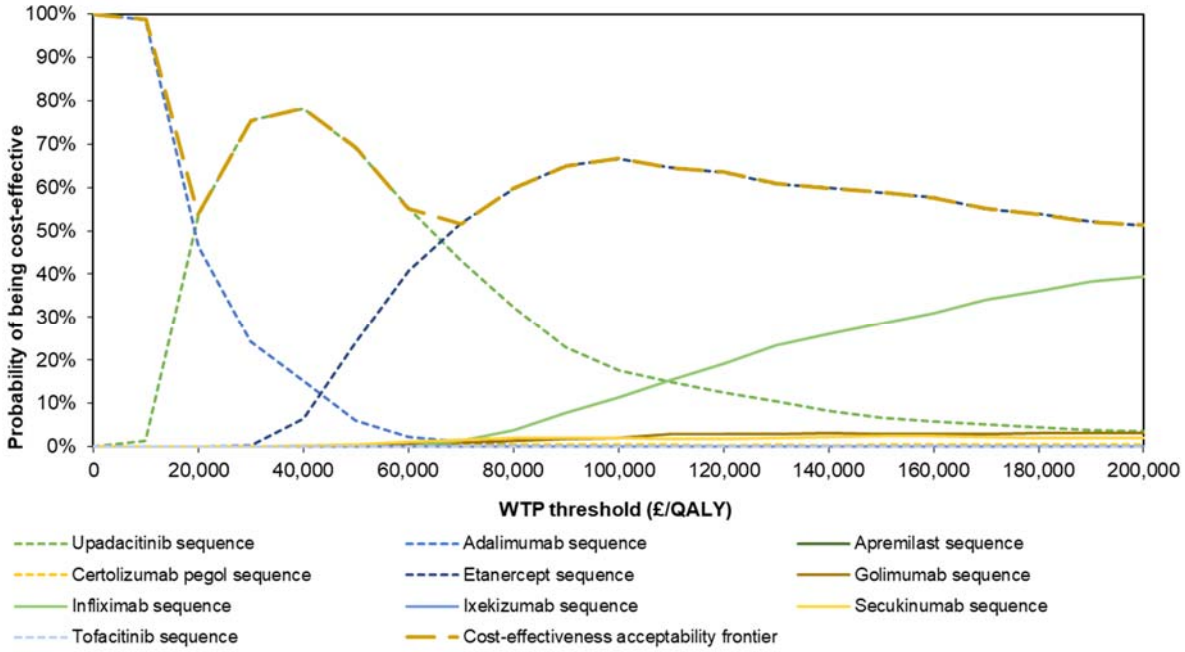
Cost-effectiveness acceptability curves (with CEAFs) for each subpopulation are presented for all treatment sequences in Figure 21 to Figure 29. For each subpopulation, these show that, at a WTP threshold of £30,000, upadacitinib is the most economically preferred treatment option.

Figure 21: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-naïve population with no psoriasis



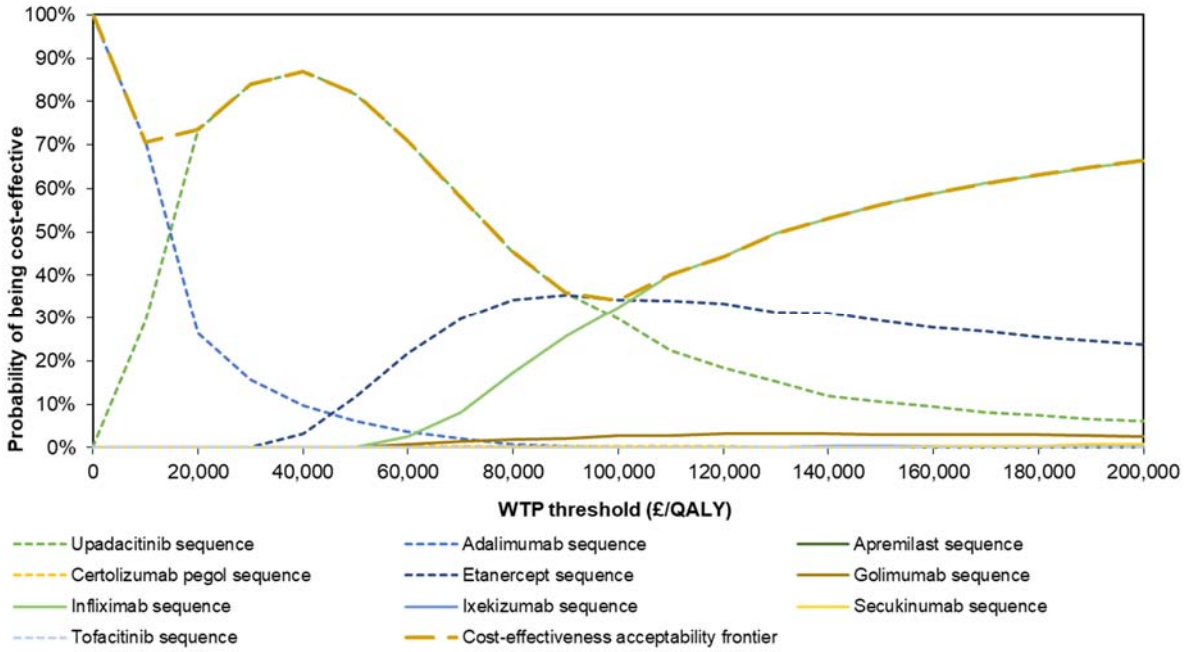
Key: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 22: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-naïve population with mild-to-moderate psoriasis



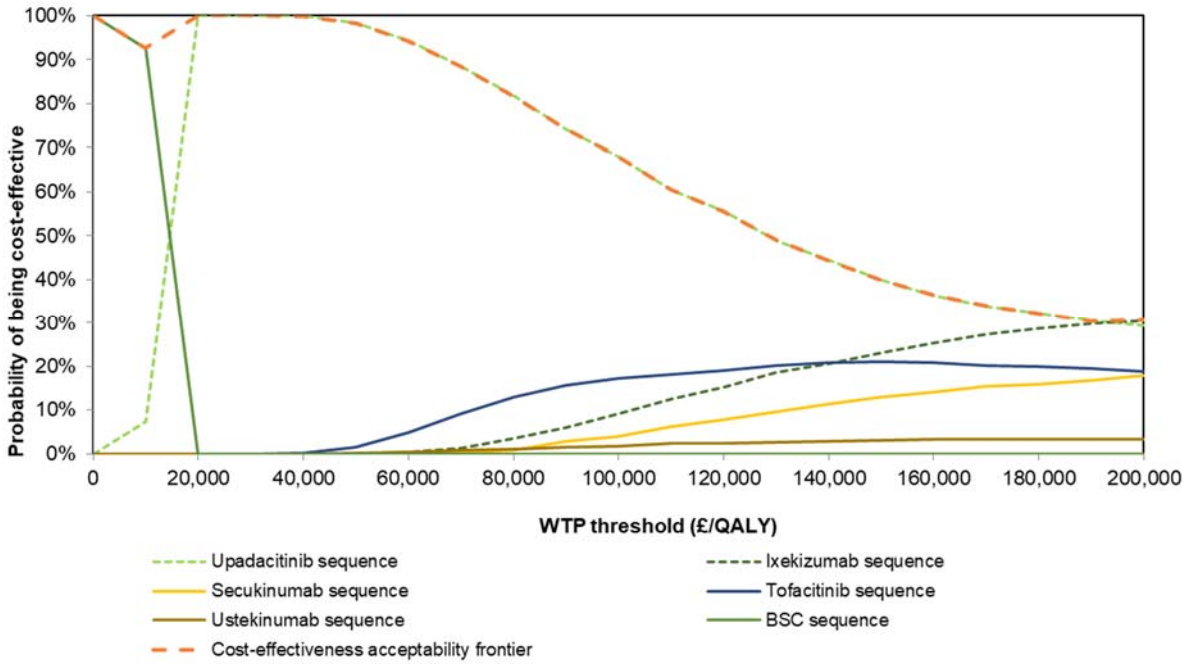
Key: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 23: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-naïve population with moderate-to-severe psoriasis



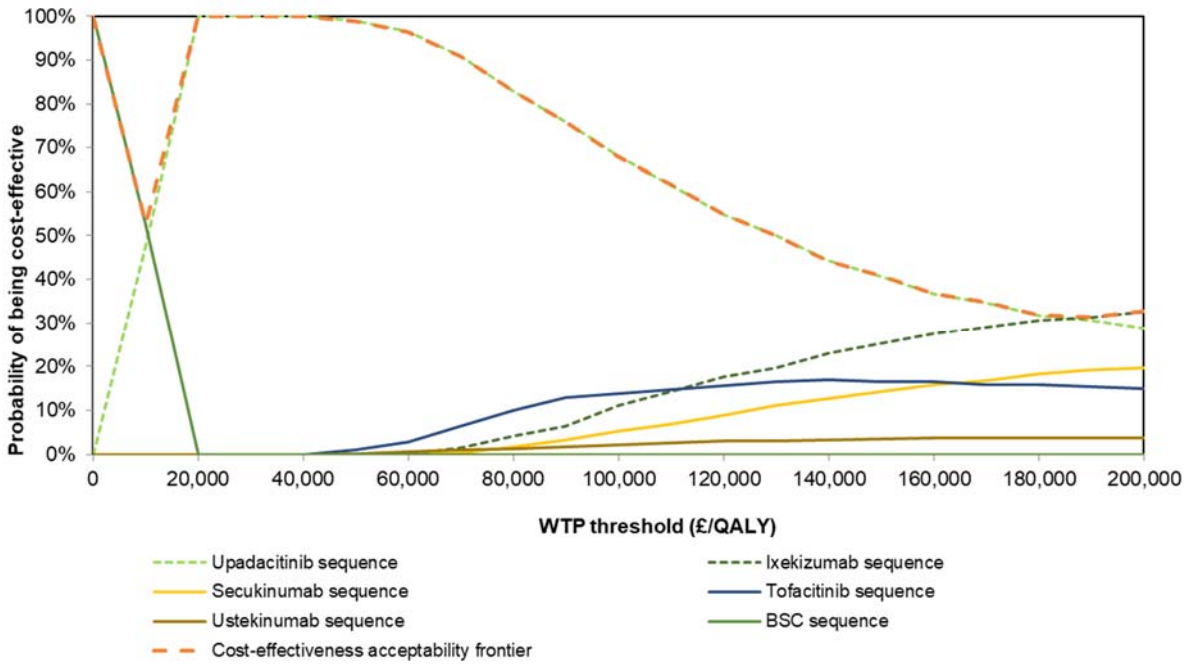
Key: QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 24: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-experienced population with no psoriasis



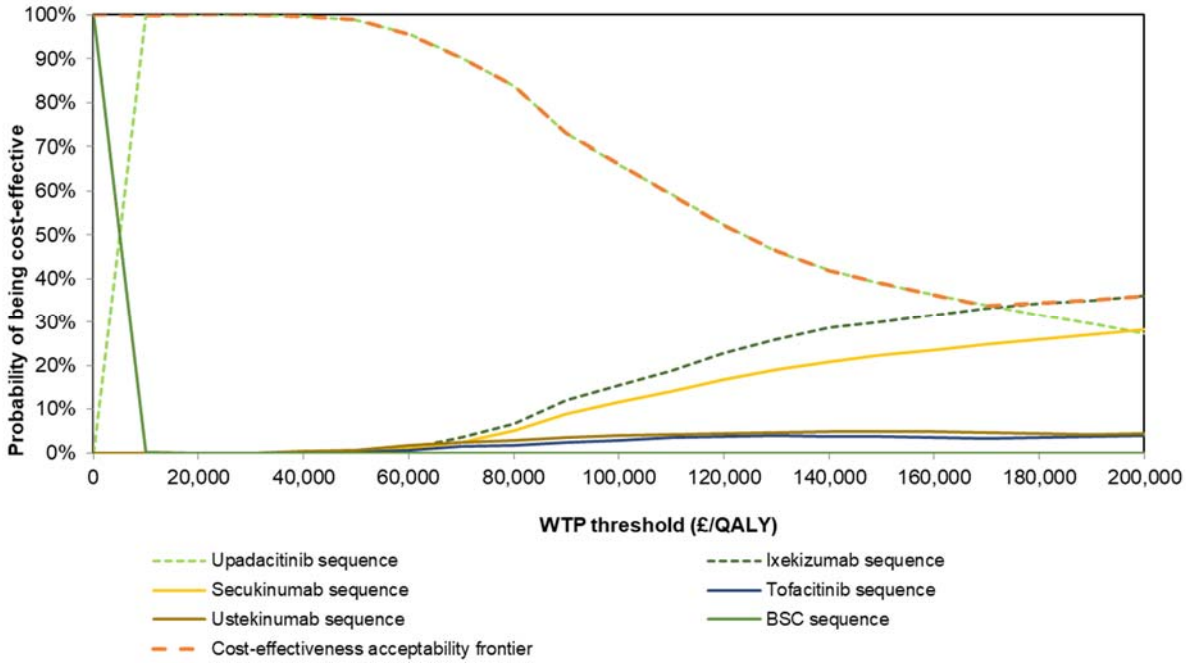
Key: BSC, best supportive care; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 25: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-experienced population with mild-to-moderate psoriasis



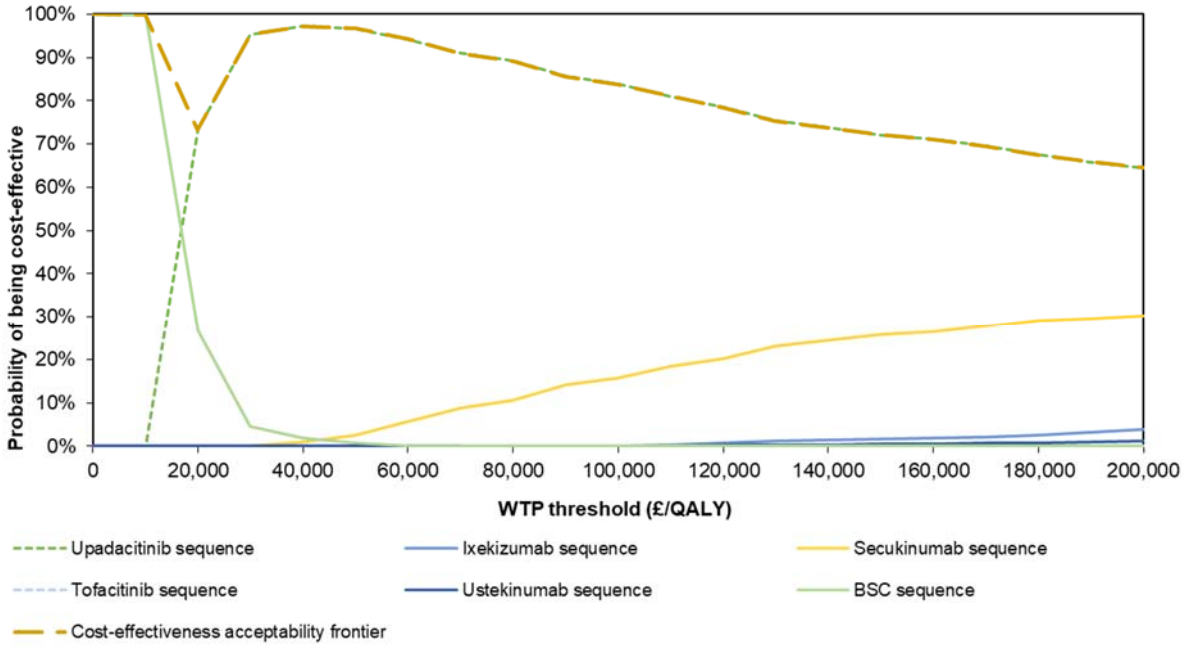
Key: BSC, best supportive care; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 26: Combined cost-effectiveness acceptability curve: all treatment sequences – biologic-experienced population with moderate-to-severe psoriasis



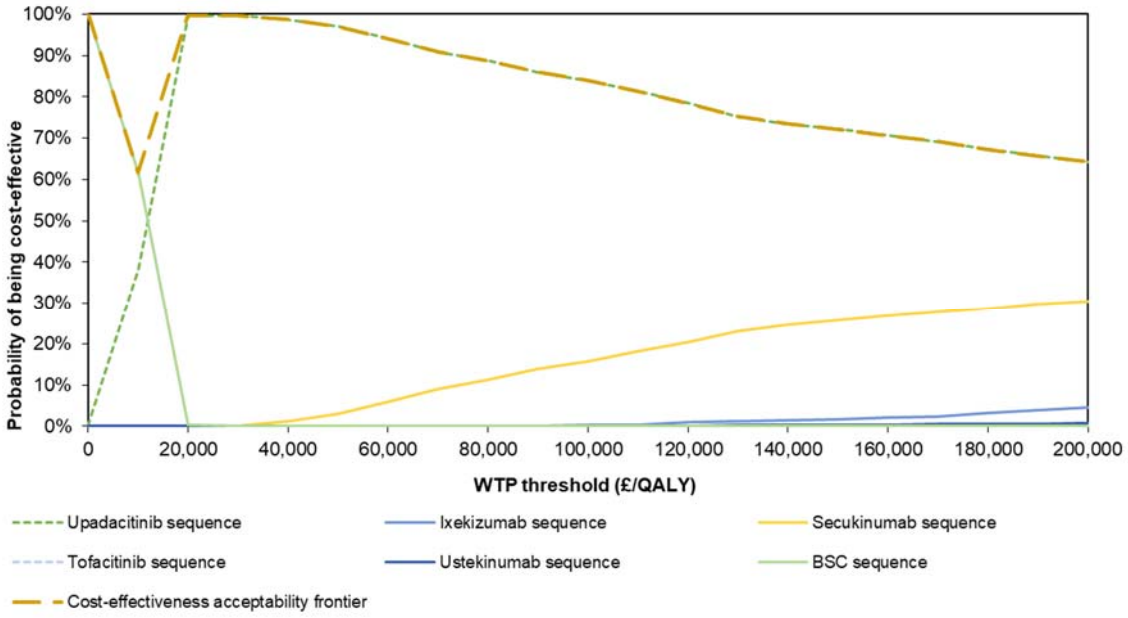
Key: BSC, best supportive care; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 27: Combined cost-effectiveness acceptability curve: all treatment sequences – TNFα inhibitor-contraindicated population with no psoriasis



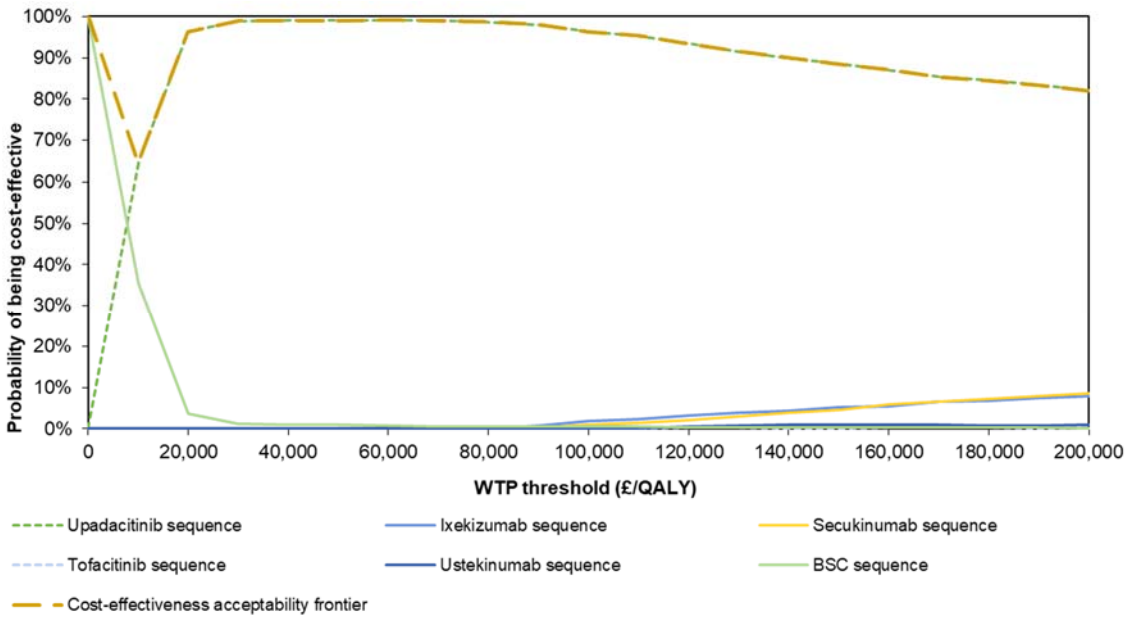
Key: BSC, best supportive care; QALY, quality-adjusted life year; TNFα, tumour necrosis factor alpha; WTP, willingness to pay.

Figure 28: Combined cost-effectiveness acceptability curve: all treatment sequences – TNFα inhibitor-contraindicated population with mild-to-moderate psoriasis



Key: BSC, best supportive care; QALY, quality-adjusted life year; TNFα, tumour necrosis factor alpha; WTP, willingness to pay.

Figure 29: Combined cost-effectiveness acceptability curve: all treatment sequences – TNFα inhibitor-contraindicated population with moderate-to-severe psoriasis



Key: BSC, best supportive care; QALY, quality-adjusted life year; TNFα, tumour necrosis factor alpha; WTP, willingness to pay.

B.3.8.2 Deterministic sensitivity analysis

To assess the robustness of the model results, one-way sensitivity analyses (OWSA) were conducted in which one model input or assumption was varied at a time. Values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the CIs reported in Appendix N.

Tornado diagrams illustrate the impact on base case model results for pairwise comparisons of the upadacitinib sequence against comparator sequences. To account for the analyses that resulted in negative ICERs, the tornado diagrams were instead presented using net monetary benefit (NMB), at a WTP threshold of £30,000.

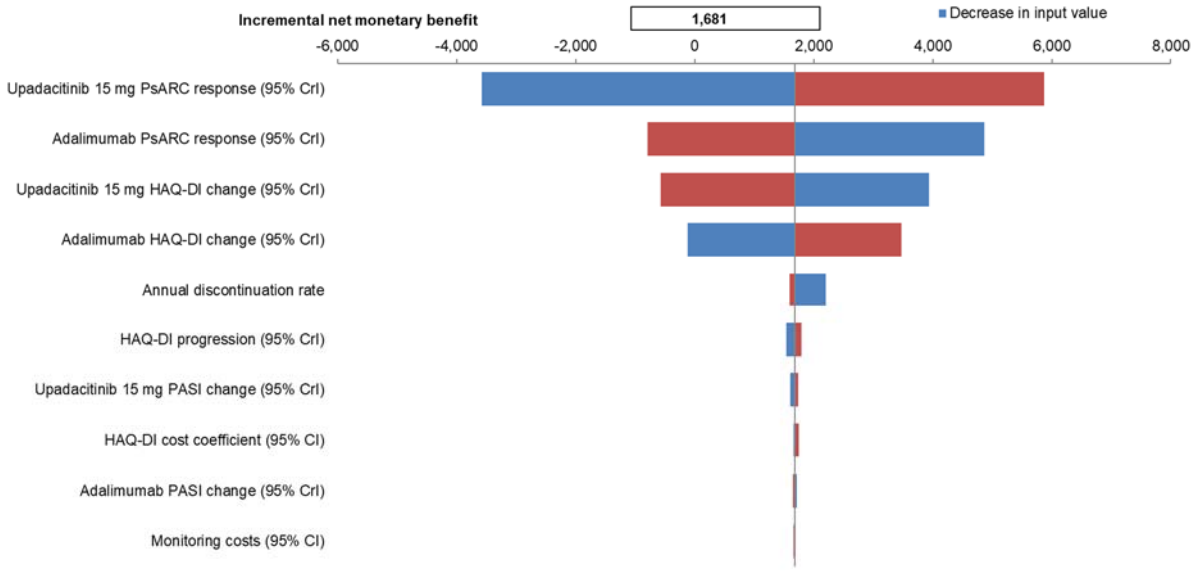
Figure 30 to Figure 32 present the OWSA results of the upadacitinib sequence against the adalimumab sequence in the biologic-naïve population. The tornado diagrams demonstrate that the NMB versus adalimumab is most sensitive to parameter uncertainty around the upadacitinib and adalimumab PsARC response and HAQ-DI change estimates from the NMA (described in Sections B.3.3.1 and B.3.3.2). Interestingly, PASI change for upadacitinib becomes a model driver for the severe psoriasis population.

Figure 33 to Figure 35 present the one-way sensitivity results of the upadacitinib sequence against the BSC sequence in the biologic-experienced population. These show that the HAQ-DI change and PsARC response for upadacitinib and the annual discontinuation rate applied (described in Sections B.3.3.2 and B.3.3.4.2, respectively) have the largest impact on the resulting NMB.

Figure 36 to Figure 38 present the one-way sensitivity results of the upadacitinib sequence against the BSC sequence in the TNFα inhibitor-contraindicated population. The results show that the NMB is most sensitive to the annual discontinuation rates and upadacitinib PsARC response from the NMA (described in Sections B.3.3.4.2 and B.3.3.1, respectively).

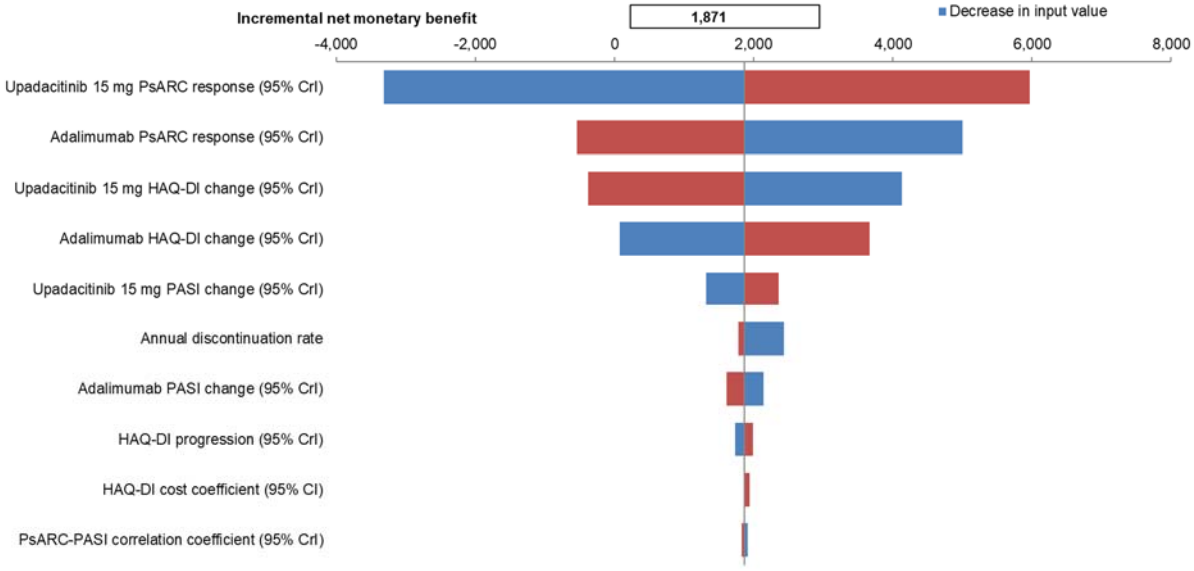
Pairwise comparisons with all other comparators are provided in the economic model.

Figure 30: Tornado diagrams: upadacitinib sequence versus adalimumab sequence – biologic-naïve population with no psoriasis



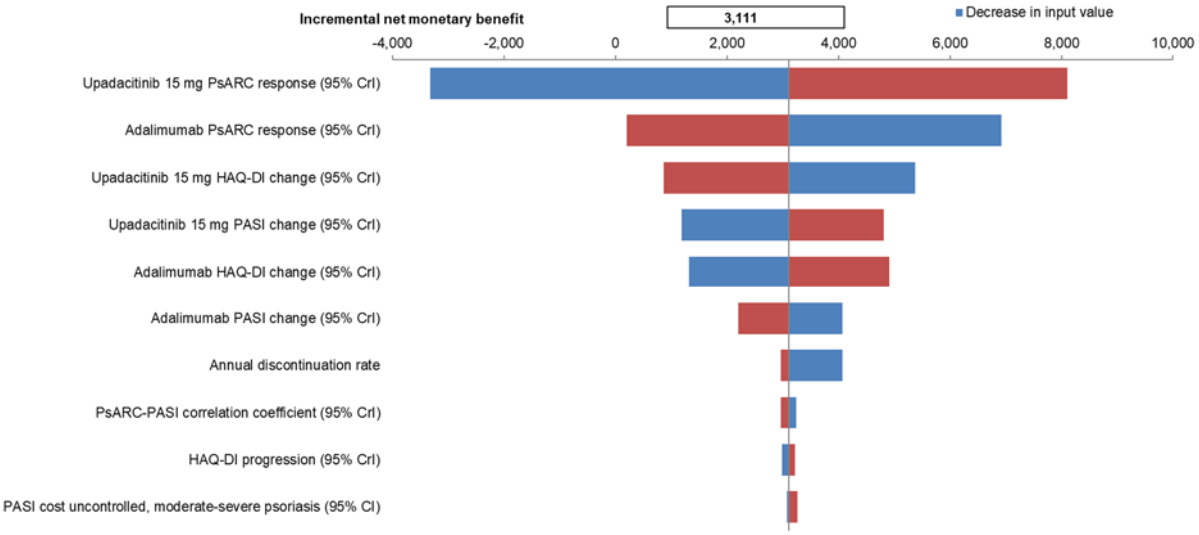
Key: CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 31: Tornado diagrams: upadacitinib sequence versus adalimumab sequence – biologic-naïve population with mild-to-moderate psoriasis



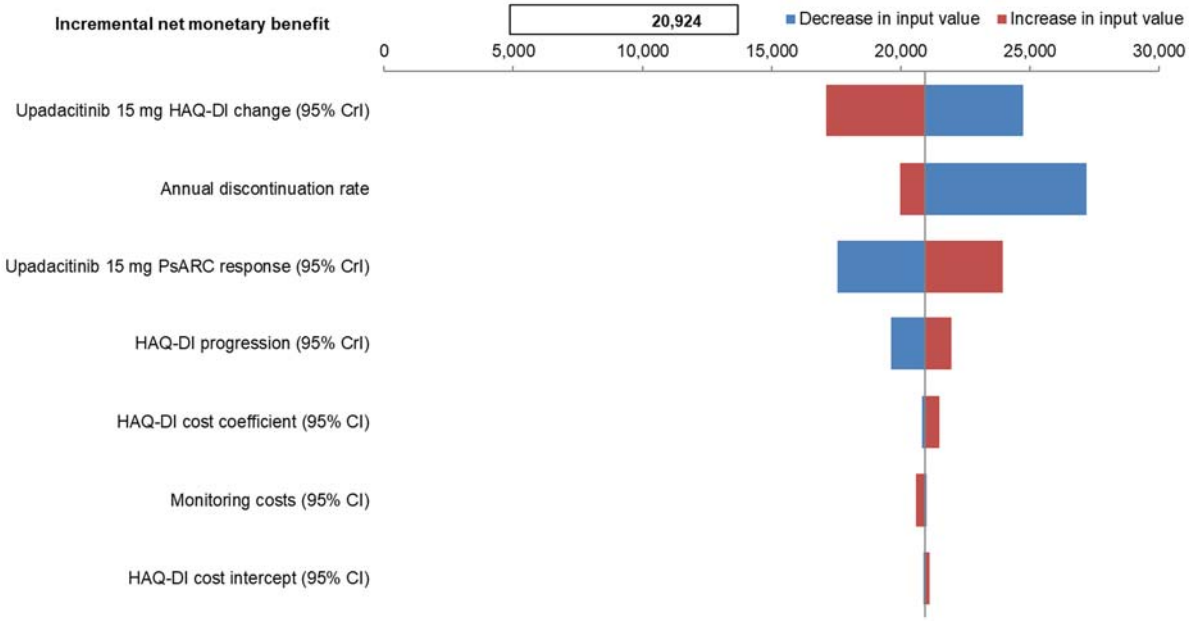
Key: CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 32: Tornado diagrams: upadacitinib sequence versus adalimumab sequence – biologic-naïve population with moderate-to-severe psoriasis



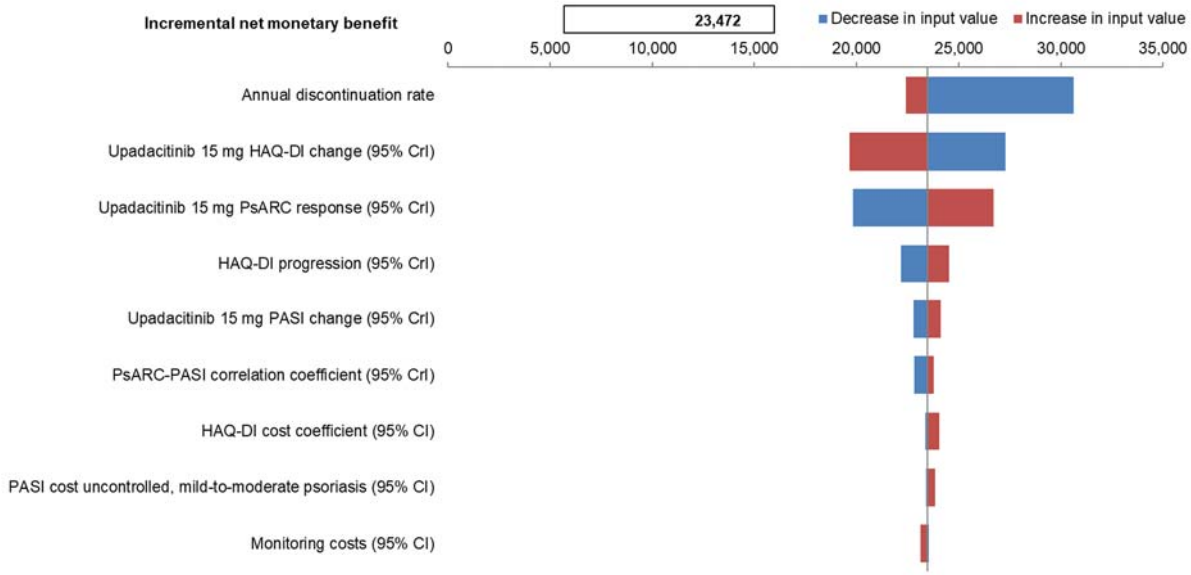
Key: CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 33: Tornado diagrams: upadacitinib sequence versus BSC sequence – biologic-experienced population with no psoriasis



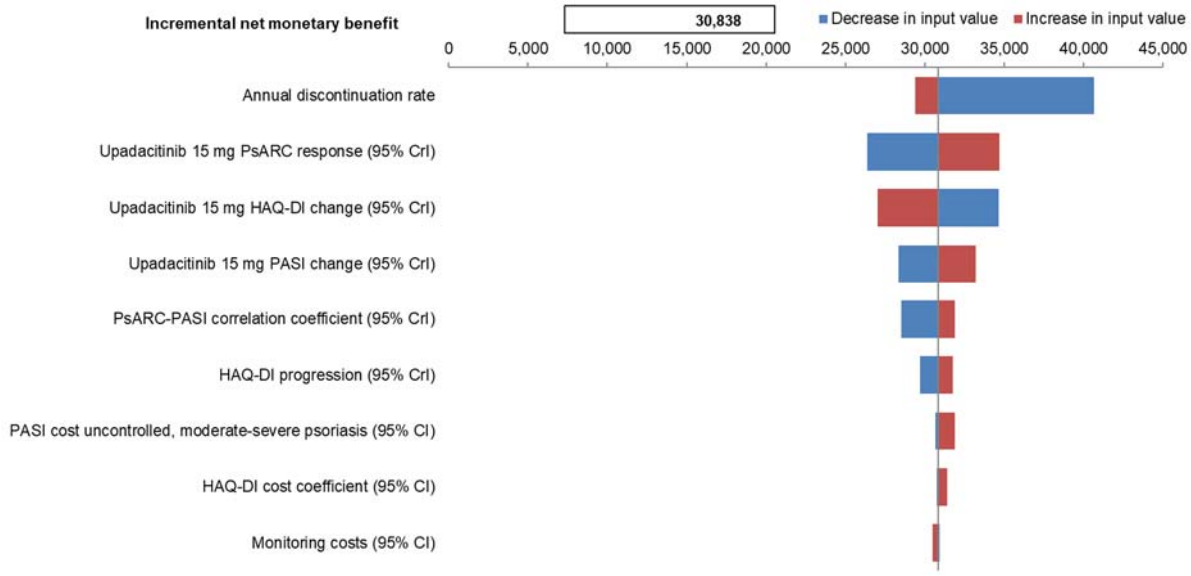
Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 34: Tornado diagrams: upadacitinib sequence versus BSC sequence – biologic-experienced population with mild-to-moderate psoriasis



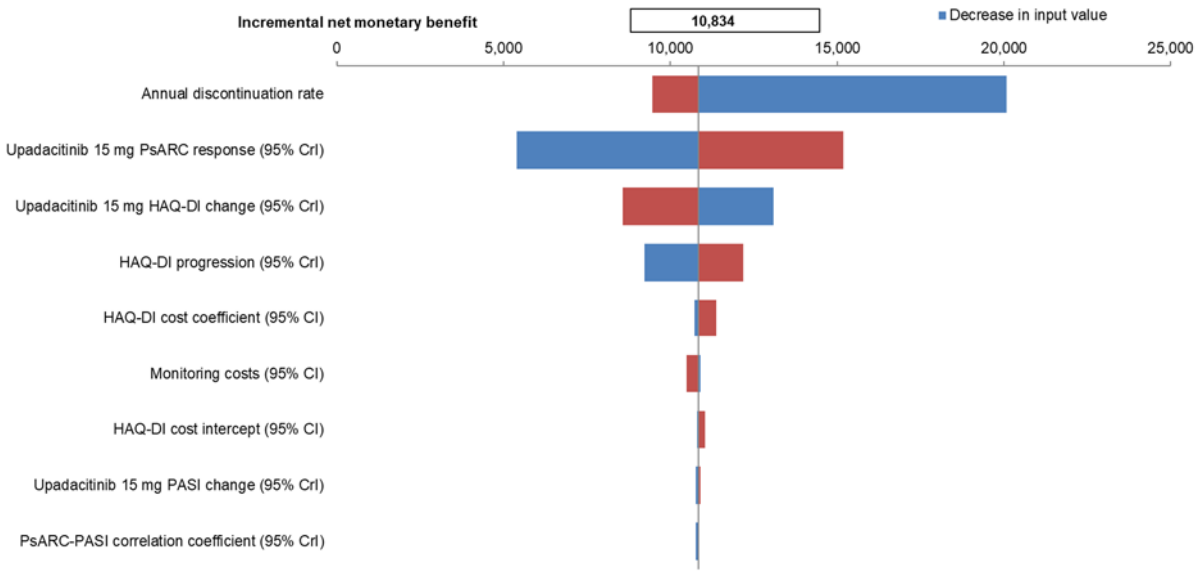
Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 35: Tornado diagrams: upadacitinib sequence versus BSC sequence – biologic-experienced population with moderate-to-severe psoriasis



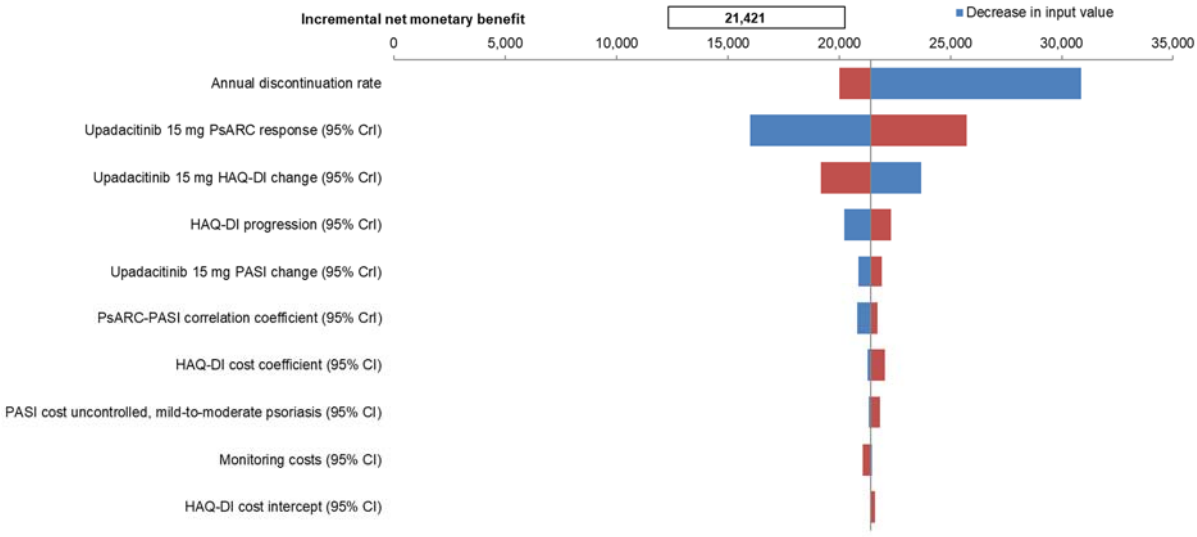
Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Figure 36: Tornado diagrams: upadacitinib sequence versus BSC sequence – TNFα inhibitor-contraindicated population with no psoriasis



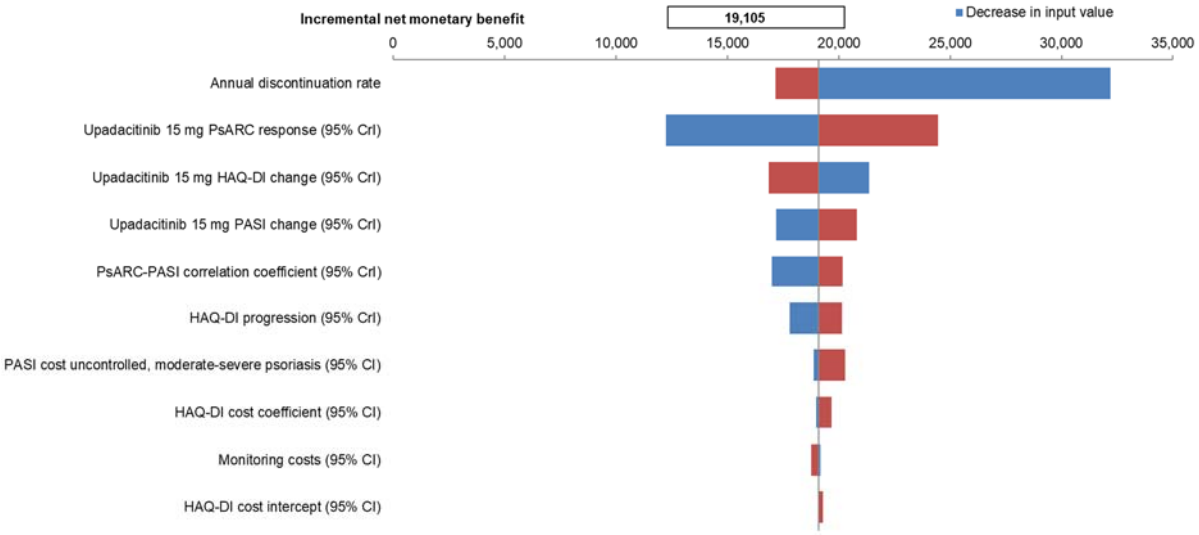
Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria; TNFα, tumour necrosis factor alpha.

Figure 37: Tornado diagrams: upadacitinib sequence versus BSC sequence – TNFα inhibitor-contraindicated population with mild-to-moderate psoriasis



Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria; TNFα, tumour necrosis factor alpha..

Figure 38: Tornado diagrams: upadacitinib sequence versus BSC sequence – TNFα inhibitor-contraindicated population with moderate-to-severe psoriasis



Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria; TNFα, tumour necrosis factor alpha.

B.3.8.3 Scenario analysis

Scenario analyses were conducted to test the sensitivity of cost-effectiveness results to methodological, parameter and structural uncertainties in the cost-effectiveness analysis, and form an important element of this submission. Table 83 describes the different scenarios tested and the rationale behind each.

Table 84, Table 85 and Table 86 document the ICER associated with each scenario in turn for the biologic-naïve, biologic-experienced and TNFα inhibitor-contraindicated populations, respectively. Summary results are generally robust to changes tested across the broad range of scenarios. The most impactful scenarios are those associated with time horizon and PsARC assessment time point assumptions.

Table 83: Summary of scenario analyses explored

Base case equivalent	Scenario detail	Brief rationale
Time horizon: 48.5 years (lifetime)	Time horizon: 5 years	Alternative time horizons
	Time horizon: 15 years	
Discount rate: 3.5%	Annual discount rate for costs 0%; QALYs 0%	Alternative time discounting assumptions
	Annual discount rate for costs 6.0%; QALYs 6.0%	
PsARC assessment time point: 12 weeks	PsARC assessment time point: 24 weeks	Alternative response assessment assumptions
Excess mortality: SMR = 1.05	Excess mortality: SMR = 1.36	Alternative survival assumptions
No expectation effect adjustment applied	Expectation effect adjustment applied	Alternative treatment effect assumptions
Same treatment discontinuation rate applied across different lines of therapy	Different treatment discontinuation rates applied for different lines of therapy	
	Different source to estimate annual discontinuation	
Assume linear improvement of utility and disease management costs during the trial period	Assume immediate improvement of utility and disease management costs during the trial period	
	Assume no improvement of utility and disease management costs during the trial period	
Utility regression source: SELECT-PsA 1 (biologic-naïve and TNFα inhibitor-contraindicated) and SELECT-PsA 2 (biologic-experienced) data	Utility regression source: pooled SELECT-PsA 1 and 2	Alternative utility assumptions
	Utility regression source: coefficients obtained from TA445	
Excess mortality: SMR = 1.05	Excess mortality: SMR = 1.36	Alternative survival assumptions
Proportion of patients receiving concomitant methotrexate: based on clinical opinion per 22 May 2020 advisory board	Proportion of patients receiving concomitant methotrexate: 58%	Alternative cost and resource use assumptions
	Proportion of patients receiving concomitant methotrexate: 0%	
No vial sharing for infliximab	Allow vial sharing	
Resource use (treatment monitoring) estimates based on	Include dermatologist visit costs for moderate to severe psoriasis patients	

combination of TA445 and clinical opinion	Resource use frequencies based on TA445 only	
Key: PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio; TNFα, tumour necrosis factor alpha.		

Table 84: Scenario analysis summary: biologic-naïve population

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	**% change from base case**	**ICER vs adalimumab**	**% change from base case**	**ICER vs adalimumab**	**% change from base case**
Base case	£19,322	-	£17,980	-	£12,701	-
Time horizon						
Time horizon: 5 years	£27,001	39.7%	£25,615	42.5%	£16,808	32.3%
Time horizon: 15 years	£24,664	27.6%	£23,156	28.8%	£15,703	23.6%
Annual discount rate						
Annual discount rate for costs 0%; QALYs 0%	£16,330	-15.5%	£15,099	-16.0%	£10,986	-13.5%
Annual discount rate for costs 6.0%; QALYs 6.0%	£20,994	8.7%	£19,602	9.0%	£13,626	7.3%
Model assumptions						
PsARC assessment time point: 24 weeks	£12,165	-37.0%	£11,484	-36.1%	£8,591	-32.4%
Excess mortality: SMR = 1.36	£19,598	1.4%	£18,249	1.5%	£12,851	1.2%
Adjust for perceived expectation effect	£20,226	4.7%	£18,838	4.8%	£13,245	4.3%
Treatment discontinuation						
Annual discontinuation based on Fagerli 2018	£19,281	-0.2%	£17,956	-0.1%	£12,664	-0.3%
Different treatment discontinuation rates applied for different lines of therapy	£19,369	0.2%	£18,013	0.2%	£12,726	0.2%
Trial period response assumptions						
Assume no improvement of utility and disease management costs during the trial period	£19,639	1.6%	£18,322	1.9%	£13,006	2.4%

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	**% change from base case**	**ICER vs adalimumab**	**% change from base case**	**ICER vs adalimumab**	**% change from base case**
Assume immediate improvement of utility and disease management costs during the trial period	£19,013	-1.6%	£17,649	-1.8%	£12,404	-2.3%
Utility source						
Utility regression source: pooled SELECT-PsA 1 and 2	£19,701	2.0%	£18,370	2.2%	£13,059	2.8%
Utility regression source: coefficients obtained from TA445	£15,591	-19.3%	£14,698	-18.3%	£11,168	-12.1%
Cost assumptions						
Proportion of patients receiving concomitant methotrexate: 58%	£19,311	-0.1%	£17,970	-0.1%	£12,691	-0.1%
Treatment monitoring frequency source: TA445	£18,836	-2.5%	£17,489	-2.7%	£12,275	-3.3%
Proportion of patients receiving concomitant methotrexate: 0%	£19,304	-0.1%	£17,963	-0.1%	£12,685	-0.1%
Allow vial sharing for infliximab	£19,322	0.0%	£17,980	0.0%	£12,701	0.0%
Include cost of dermatologist visit for moderate-to-severe psoriasis patients	£19,322	0.0%	£17,980	0.0%	£13,046	2.7%

Key: ICER, incremental cost effectiveness ratio; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio

Table 85: Scenario analysis summary: biologic-experienced population

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case
Base case	£11,513	-	£9,775	-	£6,165	-
Time horizon						
Time horizon: 5 years	£34,843	202.6%	£29,342	200.2%	£16,393	165.9%
Time horizon: 15 years	£17,562	52.5%	£14,956	53.0%	£8,998	46.0%
Annual discount rate						
Annual discount rate for costs 0%; QALYs 0%	£8,291	-28.0%	£6,970	-28.7%	£4,441	-28.0%
Annual discount rate for costs 6.0%; QALYs 6.0%	£13,894	20.7%	£11,835	21.1%	£7,387	19.8%
Model assumptions						
PsARC assessment time point: 24 weeks	£10,995	-4.5%	£9,276	-5.1%	£5,738	-6.9%
Excess mortality: SMR = 1.36	£11,756	2.1%	£9,986	2.2%	£6,284	1.9%
Adjust for perceived expectation effect	£12,420	7.9%	£10,544	7.9%	£6,641	7.7%
Treatment discontinuation						
Annual discontinuation based on Fagerli 2018	£11,572	0.5%	£9,808	0.3%	£6,147	-0.3%
Different treatment discontinuation rates applied for different lines of therapy	£11,468	-0.4%	£9,760	-0.1%	£6,209	0.7%
Trial period response assumptions						
Assume no improvement of utility and disease management costs during the trial period	£11,601	0.8%	£9,893	1.2%	£6,339	2.8%

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case
Assume immediate improvement of utility and disease management costs during the trial period	£11,426	-0.8%	£9,658	-1.2%	£5,994	-2.8%
Utility source						
Utility regression source: pooled SELECT-PsA 1 and 2	£11,737	1.9%	£9,976	2.1%	£6,329	2.7%
Utility regression source: coefficients obtained from TA445	£9,307	-19.2%	£8,031	-17.8%	£5,635	-8.6%
Cost assumptions						
Proportion of patients receiving concomitant methotrexate: 58%	£11,517	0.0%	£9,779	0.0%	£6,168	0.1%
Treatment monitoring frequency source: TA445	£10,388	-9.8%	£8,677	-11.2%	£5,180	-16.0%
Proportion of patients receiving concomitant methotrexate: 0%	£11,505	-0.1%	£9,767	-0.1%	£6,158	-0.1%
Allow vial sharing for infliximab	£11,513	0.0%	£9,775	0.0%	£6,165	0.0%
Include cost of dermatologist visit for moderate-to-severe psoriasis patients	£11,513	0.0%	£9,775	0.0%	£6,951	12.7%

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio

Table 86: Scenario analysis summary: TNFα inhibitor-contraindicated population

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case	ICER vs BSC	% change from base case
Base case	£16,931	-	£10,492	-	£8,809	-
Time horizon						
Time horizon: 5 years	£33,509	97.9%	£24,278	131.4%	£15,660	77.8%
Time horizon: 15 years	£21,610	27.6%	£14,322	36.5%	£10,532	19.6%
Annual discount rate						
Annual discount rate for costs 0%; QALYs 0%	£14,037	-17.1%	£8,150	-22.3%	£7,671	-12.9%
Annual discount rate for costs 6.0%; QALYs 6.0%	£19,015	12.3%	£12,156	15.9%	£9,701	10.1%
Model assumptions						
PsARC assessment time point: 24 weeks	£14,221	-16.0%	£9,311	-11.3%	£6,938	-21.2%
Excess mortality: SMR = 1.36	£17,036	0.6%	£10,611	1.1%	£8,803	-0.1%
Adjust for perceived expectation effect	£19,047	12.5%	£11,521	9.8%	£9,914	12.5%
Treatment discontinuation						
Annual discontinuation based on Fagerli 2018	£15,595	-7.9%	£10,200	-2.8%	£7,995	-9.2%
Different treatment discontinuation rates applied for different lines of therapy	£16,931	0.0%	£10,492	0.0%	£8,809	0.0%
Trial period response assumptions						
Assume no improvement of utility and disease management costs during the trial period	£17,189	1.5%	£10,674	1.7%	£9,164	4.0%

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs BSC	**% change from base case**	**ICER vs BSC**	**% change from base case**	**ICER vs BSC**	**% change from base case**
Assume immediate improvement of utility and disease management costs during the trial period	£16,680	-1.5%	£10,314	-1.7%	£8,466	-3.9%
Utility source						
Utility regression source: pooled SELECT-PsA 1 and 2	£13,322	-21.3%	£8,554	-18.5%	£6,155	-30.1%
Utility regression source: coefficients obtained from TA445	£10,496	-38.0%	£6,921	-34.0%	£5,321	-39.6%
Cost assumptions						
Proportion of patients receiving concomitant methotrexate: 58%	£16,927	0.0%	£10,489	0.0%	£8,806	0.0%
Treatment monitoring frequency source: TA445	£15,327	-9.5%	£9,281	-11.5%	£7,334	-16.7%
Proportion of patients receiving concomitant methotrexate: 0%	£16,910	-0.1%	£10,476	-0.2%	£8,790	-0.2%
Allow vial sharing for infliximab	£16,931	0.0%	£10,492	0.0%	£8,809	0.0%
Include cost of dermatologist visit for moderate-to-severe psoriasis patients	£16,931	0.0%	£10,492	0.0%	£9,987	13.4%

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio

B.3.8.4 Summary of sensitivity analyses results

The results were robust to changes in the parameters and the key model assumptions. The one-way sensitivity analyses highlight that changes to the annual discontinuation rate, and PsARC response and HAQ-DI change estimates from the NMA has the biggest impact on the NMB in each population. In the biologic-experienced and TNFα inhibitor-contraindicated populations, the results of the pairwise comparison with BSC highlight that upadacitinib provides a positive NMB even with variations in each parameter. The scenario analyses demonstrate that the model is also robust to changes in key modelling assumptions and that upadacitinib remains cost-effective across the vast majority of analyses.

B.3.9. Subgroup analysis

No further subgroup analyses were conducted as part of this economic evaluation.

B.3.10. Validation

B.3.10.1 Validation of cost-effectiveness analysis

The economic model used in this analysis closely follows the precedent set by the second revision of the York Model used in TA445[5], developed by the Centre for Reviews and Dissemination and Centre for Health Economics at the University of York. This model also formed the basis of the two most recent PsA submissions (NICE TA543 and NICE TA537)[1, 82] in terms of patient population, the structure, inputs and assumptions used throughout.

The structure, inputs and assumptions of the cost-effectiveness analysis were reviewed during an advisory board of health economic and clinical experts, held on the 22 May 2020.[4] Expert opinion obtained during this meeting has been collated, considered and referenced throughout this document. The meeting report is enclosed as a documented reference to this submission.

Prior to submission, the cost-effectiveness model itself underwent quality control checks. In these processes, an economist not involved in the model build reviewed the model for coding errors, inconsistencies and the plausibility of inputs; this was done as a thorough sheet-by-sheet check. The model was also subject to review

against a checklist of known modelling errors and questioning of assumptions. The checklist followed was based on publicly available and peer-reviewed checklists.[142-144] Examples of some basic validity checks include the following:

- Extreme value testing
- Logical relationship testing (e.g. if intervention drug acquisition costs increase, do total intervention costs increase accordingly? Does the ICER increase accordingly?)
- Consistency checks (e.g. is an input parameter value cost in one cell consistently reflected elsewhere?)

Cross validity checks were also performed against the results presented in previous submissions. In the most recent NICE appraisal in PsA, TA543 (tofacitinib), all results were redacted, preventing a comparison being made. A comparison with the results of TA537 for ixekizumab was therefore explored. For the biologic-naïve population, the results presented for the base case analysis and those presented in TA537 are generally comparable, showing that for all psoriasis severity subgroups, only the etanercept and infliximab sequences lie on the cost-effectiveness frontier and are not dominated or extendedly dominated. Two differences with the results presented in this appraisal are that adalimumab is the cheapest option and also lies on the frontier, based on the adalimumab price deemed appropriate by NICE during the appraisal of upadacitinib in RA. For the biologic-experienced population, ixekizumab was only compared against BSC and ustekinumab in TA537, limiting the comparability with this appraisal.

In general, the total costs for each treatment sequence across the two appraisals appear comparable, though the total QALYs in this appraisal are generally lower than in TA537. The comparatively high total QALYs reported in TA537, when compared with those reported in TA445, was noted by the ERG as a potential face validity issue. However, given the NMA outcomes for PsARC response, HAQ-DI change and PASI response are redacted in TA537, it is difficult to ascertain why these differences were found. A possible explanation could be due to the observed lower baseline PASI scores from the SPIRIT-P1 and SPIRIT-P2 trials compared with the scores from SELECT-PsA 1 and SELECT-PsA 2, particularly for the no psoriasis

subgroup. Additionally, in TA537, the base case analysis assumes immediate improvement of utility during the trial period rather than assuming a linear improvement, which will result in higher total QALYs.

Long-term observational studies have not been carried out for upadacitinib; therefore, external validity of real-world clinical effectiveness is difficult to assess.

B.3.11. Interpretation and conclusions of economic evidence

Owing to the chronic and progressive nature of disease, most patients with PsA are expected to become non-responsive or intolerant to treatment over time.[16] As such, there is a need for treatment options to add the clinician's armamentarium to manage PsA over patients' lifetimes. Upadacitinib offers a well-characterised, tolerable, and oral treatment option, that may be given as monotherapy or in combination with methotrexate, to inhibit structural damage and minimise disease activity in PsA.

The cost-effectiveness analysis compared upadacitinib 15 mg with current treatments recommended by NICE and used in clinical practice across the three populations of interest, each further split by psoriasis severity. All analyses demonstrate that upadacitinib is a cost-effective option; fully incremental analyses performed for all populations show that upadacitinib is associated with ICERs of well below the £30,000 willingness to pay threshold in all comparisons, and below a £20,000 threshold for all pairwise comparisons. The ICER was largely insensitive to the majority of parameters and assumptions tested in one-way sensitivity analyses and scenario analyses; the parameters that had the biggest impact were the upadacitinib PsARC response and HAQ-DI change estimates from the NMA.

The de novo model follows the precedent of the York PsA models and subsequent PsA NICE appraisals, while also taking into account ERG and Committee feedback from these. The key strength of the economic evaluation is the transparent and flexible framework within which it harnesses data from the SELECT-PsA 1 and SELECT-PsA 2, which represent the largest clinical trial programme in PsA to date, as well as published sources for the comparator data, allowing robust NMAs to be conducted. The analysis provided is consistent with the NICE reference case and the decision problem at hand.

The model was designed to reflect the treatment pathway and captures the sequenced nature of treatments used in the NHS in England. The response assessment criteria used in the model – the achievement of PsARC at 12 weeks – align with the treatment continuation rule used in clinical practice; both the criteria and the rule were validated with clinical experts attending an advisory board.[4] SELECT-PsA 1 and SELECT-PsA 2 were also deemed representative of trial designs and patient populations commonly used in PsA and in the clinical practice. Furthermore, the exploration of key scenario analyses and sensitivity analyses demonstrate that the results presented herein are robust and offer low uncertainty.

We acknowledge limitations in the analysis, such as the inability to include certolizumab pegol as a comparator in the biologic-naïve network, due to the lack of publicly available sources/data. Additionally, for a small number of the biologic-experienced networks relevant comparators could not be included due to data pooling issues as well as a lack of publicly available information. Some assumptions also rely on older observational data. Finally, the presence of confidential PAS discounts approved for the comparator treatment options are not accounted for in the model, given that these are not publicly available. Nonetheless, we have worked to use previously accepted data sources and methods, and explored scenario analyses with alternative approaches where possible.

In summary, this robust analysis demonstrates that upadacitinib presents a cost-effective treatment option for use in the NHS in England. Access to upadacitinib would provide an additional option to manage this lifelong, relapsing and remitting disease.

B.4. References

1. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA543]. Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID1220]. Committee Papers. 2018. Available at: https://www.nice.org.uk/guidance/ta543/documents/committee-papers. Accessed: 27 April 2020.
2. National Institute for Health and Care Excellence. Ustekinumab for treating active psoriatic arthritis [TA340]. 2017. Available at: https://www.nice.org.uk/guidance/ta340. Accessed: 29 April 2020.

3. National Institute for Health and Care Excellence. Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs [TA537]. 2018. Available at: https://www.nice.org.uk/guidance/ta537. Accessed: 18 Nov 2020.
4. AbbVie. Upadacitinib in psoriatic arthritis HTA advisory board. May 2020 2020. Data on File.
5. National Institute for Health and Care Excellence (NICE). Multiple Technology Appraisal [TA445]. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]. Committee papers. 2016. Available at: https://www.nice.org.uk/guidance/ta445/documents/committee-papers. Accessed: 27 April 2020.
6. AbbVie. Upadacitinib (RINVOQ) 15 mg prolonged-release tablets. 2020.
7. (EMA) EMA. Summary of Product Characteristics - Nivestim. 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/nivestim-epar-product-information_en.pdf. Accessed: 20 January 2020.
8. Veale DJ. Psoriatic arthritis: recent progress in pathophysiology and drug development. *Arthritis Research & Therapy*. 2013; 15(6):224.
9. National Breast Cancer Foundation Inc. BRCA: The Breast Cancer Gene. 2020. Available at: https://www.nationalbreastcancer.org/what-is-brca. Accessed: 11 February 2020.
10. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005; 64 Suppl 2(suppl 2):ii14-7.
11. Gudu T and Gossec L. Quality of life in psoriatic arthritis. *Expert Rev Clin Immunol*. 2018; 14(5):405-17.
12. Warren R and Menter A. *Handbook of Psoriasis and Psoriatic Arthritis*. Springer, 2016.
13. Gossec L, McGonagle D, Korotaeva T, et al. Minimal disease activity as a treatment target in psoriatic arthritis: a review of the literature. *The Journal of Rheumatology*. 2018; 45(1):6-13.
14. Geijer M, Lindqvist U, Husmark T, et al. The Swedish early psoriatic arthritis registry 5-year followup: substantial radiographic progression mainly in men with high disease activity and development of dactylitis. *The Journal of Rheumatology*. 2015; 42(11):2110-7.
15. Coates LC and Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res (Hoboken)*. 2010; 62(7):965-9.
16. Mease PJ and Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs*. 2014; 74(4):423-41.
17. Ritchlin CT, Colbert RA and Gladman DD. Psoriatic Arthritis. *N Engl J Med*. 2017; 376(10):957-70.
18. Kerschbaumer A, Fenzl KH, Erlacher L and Aletaha D. An overview of psoriatic arthritis–epidemiology, clinical features, pathophysiology and novel treatment targets. *Wiener klinische Wochenschrift*. 2016; 128(21-22):791-5.
19. Raychaudhuri SK and Raychaudhuri SP. Janus kinase/signal transducer and activator of transcription pathways in spondyloarthritis. *Current opinion in rheumatology*. 2017; 29(4):311-6.

20. Grinnell-Merrick LL, Lydon EJ, Mixon AM and Saalfeld W. Evaluating Inflammatory Versus Mechanical Back Pain in Individuals with Psoriatic Arthritis: A Review of the Literature. *Rheumatology and therapy*. 2020:1-18.
21. America SAo. In Psoriatic Arthritis, Axial Involvement is Associated with More Severe Psoriasis. 2018. Available at: https://spondylitis.org/research-new/in-psoriatic-arthritis-axial-involvement-is-associated-with-more-severe-psoriasis/#:~:text=40%25%20of%20PsA%20patients%20will,to%20fusion%20within%20the%20vertebrate. Accessed: 26 October 2020.
22. Kavanaugh A, Helliwell P and 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(1):91-102.
23. Bagel J and Schwartzman S. Enthesitis and dactylitis in psoriatic disease: a guide for dermatologists. *Am J Clin Dermatol*. 2018; 19(6):839-52.
24. Zenke Y, Ohara Y, Kobayashi D, et al. Nail findings in patients with psoriatic arthritis: A cross-sectional study with special reference to transverse grooves. *J Am Acad Dermatol*. 2017; 77(5):863-7.
25. Rudwaleit M and Taylor WJ. Classification criteria for psoriatic arthritis and ankylosing spondylitis/axial spondyloarthritis. *Best Practice & Research Clinical Rheumatology*. 2010; 24(5):589-604.
26. Tillett W, Costa L, Jadon D, et al. The ClASsification for Psoriatic ARthritis (CASPAR) criteria–a retrospective feasibility, sensitivity, and specificity study. *The Journal of Rheumatology*. 2012; 39(1):154-6.
27. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology*. 2013; 52(3):568-75.
28. AbbVie. PsA Market Data. 2019.
29. Ogdie A, Haynes K, Troxel AB, et al. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. *Annals of the Rheumatic Diseases*. 2014; 73(1):149-53.
30. Ali Y, Tom BD, Schentag CT, et al. Improved survival in psoriatic arthritis with calendar time. *Arthritis & Rheumatism*. 2007; 56(8):2708-14.
31. Wong K, Gladman DD, Husted J, et al. Mortality studies in psoriatic arthritis. Results from a single outpatient clinic. I. Causes and risk of death. *Arthritis & Rheumatism*. 1997; 40(10):1868-72.
32. Duarte GV, Faillace C and de Carvalho JF. Psoriatic arthritis. *Best Practice & Research Clinical Rheumatology*. 2012; 26(1):147-56.
33. Gladman DD and Chandran V. Observational cohort studies: lessons learnt from the University of Toronto Psoriatic Arthritis Program. *Rheumatology*. 2011; 50(1):25-31.
34. Busquets-Pérez N, Rodriguez-Moreno J, Gómez-Vaquero C and Nolla-Solé JM. Relationship between psoriatic arthritis and moderate–severe psoriasis: analysis of a series of 166 psoriatic arthritis patients selected from a hospital population. *Clinical rheumatology*. 2012; 31(1):139-43.
35. Reich K, Krüger K, Mössner R and Augustin M. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. *British Journal of Dermatology*. 2009; 160(5):1040-7.

36. Egeberg A, Khalid U, Gislason GH, et al. Association of psoriatic disease with uveitis: a Danish nationwide cohort study. *JAMA dermatology*. 2015; 151(11):1200-5.
37. Magrey MN, Antonelli M, James N and Khan MA. High frequency of fibromyalgia in patients with psoriatic arthritis: a pilot study. *Arthritis*. 2013; 2013.
38. Husni ME. Comorbidities in psoriatic arthritis. *Rheumatic Disease Clinics*. 2015; 41(4):677-98.
39. Cantini F, Niccoli L, Nannini C, et al. Psoriatic arthritis: a systematic review. *International journal of rheumatic diseases*. 2010; 13(4):300-17.
40. Coates LC. Impact of Psoriatic Arthritis from the Patient's Perspective in the Context of the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire: An Online Global Survey. *2018 ACR/ARHP Annual Meeting*. ACR, 2018.
41. Lee S, Mendelsohn A and Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. *Pharmacy and Therapeutics*. 2010; 35(12):680.
42. Gudu T, Etcheto A, de Wit M, et al. Fatigue in psoriatic arthritis–a cross-sectional study of 246 patients from 13 countries. *Joint Bone Spine*. 2016; 83(4):439-43.
43. McDonough E, Ayearst R, Eder L, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. *The Journal of Rheumatology*. 2014; 41(5):887-96.
44. Feldman S, Malakouti M and Koo J. Social impact of the burden of psoriasis: Effects on patients and practice. *Dermatology online journal*. 2014; 20.
45. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. *Annals of the Rheumatic Diseases*. 2006; 65(9):1175-83.
46. McHugh N, Maguire Á, Handel I, et al. Evaluation of the economic burden of psoriatic arthritis and the relationship between functional status and healthcare costs. *J Rheumatol*. 2020; 47(5):701-7.
47. Ritchlin CT, Colbert RA and Gladman DD. Psoriatic arthritis. *New England Journal of Medicine*. 2017; 376(10):957-70.
48. AbbVie. RINVOQ in PsA Integrated Access Strategy. 29 May 2020 2020. Data on file.
49. Abbvie. Clinical Study Protocol M15-572. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1. 22 March 2018. Data on file.
50. Abbvie. Clinical Study Protocol M15-554. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. 14 January 2019. Data on file.
51. Elyoussfi S, Thomas BJ and Ciurtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. *Rheumatol Int*. 2016; 36(5):603-12.
52. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Annals of the Rheumatic Diseases*. 2020; 79(6):700-12.

53. 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(10):1754-7.
54. Noureldin B and Barkham N. The current standard of care and the unmet needs for axial spondyloarthritis. *Rheumatology*. 2018; 57(suppl_6):vi10-vi7.
55. National Institute for Health and Care Excellence (NICE). NICE Pathways: Managing peripheral spondyloarthritis in adults. 2019. Available at: https://pathways.nice.org.uk/pathways/spondyloarthritis/managing-peripheral-spondyloarthritis-in-adults#content=view-index&path=view%3A/pathways/spondyloarthritis/managing-peripheral-spondyloarthritis-in-adults.xml. Accessed: 27 April 2020.
56. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management [NG65]. 2017. Available at: https://www.nice.org.uk/guidance/ng65. Accessed: 29 April 2020.
57. Perrotta FM, Marchesoni A and Lubrano E. Minimal disease activity and remission in psoriatic arthritis patients treated with anti-TNF-α drugs. *The Journal of Rheumatology*. 2016; 43(2):350-5.
58. Nystad TW, Husum YS, Furnes ON and Fevang B-TS. Incidence and predictive factors for orthopedic surgery in patients with psoriatic arthritis. *The Journal of Rheumatology*. 2018; 45(11):1532-40.
59. Gossec L, Smolen J, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Annals of the Rheumatic Diseases*. 2016; 75(3):499-510.
60. Alamanos Y, Papadopoulos NG, Voulgari PV, et al. Epidemiology of psoriatic arthritis in northwest Greece, 1982-2001. *The Journal of Rheumatology*. 2003; 30(12):2641-4.
61. Savolainen E, Kaipiainen-Seppänen O, Kröger L and Luosujärvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. *The Journal of Rheumatology*. 2003; 30(11):2460-8.
62. Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. *Digestive diseases*. 2010; 28(3):536-42.
63. European Medicines Agency. Cosentyx: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf. Accessed: 15 August 2019.
64. European Medicines Agency. Stelara: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed: 15 August 2019.
65. European Medicines Agency. Enbrel: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/enbrel-epar-product-information_en.pdf. Accessed: 15 August 2019.
66. European Medicines Agency. Remicade: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf. Accessed: 15 August 2019.
67. 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. *J Am Acad Dermatol*. 2014; 70(5):871-81.e1-30.

68. van den Bemt BJ, Gettings L, Domańska B, et al. A portfolio of biologic self-injection devices in rheumatology: how patient involvement in device design can improve treatment experience. *Drug delivery*. 2019; 26(1):384-92.
69. Xu Y, Sudharshan L, Hsu M-A, et al. Patient preferences associated with therapies for psoriatic arthritis: a conjoint analysis. *American health & drug benefits*. 2018; 11(8):408.
70. Aletaha D, Husni ME, Merola JF, et al. Treatment Mode Preferences in Psoriatic Arthritis: A Qualitative Multi-Country Study. *Patient Preference and Adherence*. 2020; 14:949-61.
71. Bonafede M, Fox KM, Watson C, et al. Treatment patterns in the first year after initiating tumor necrosis factor blockers in real-world settings. *Advances in therapy*. 2012; 29(8):664-74.
72. Chastek B, Fox KM, Watson C and Gandra SR. Etanercept and adalimumab treatment patterns in psoriatic arthritis patients enrolled in a commercial health plan. *Advances in therapy*. 2012; 29(8):691-7.
73. Glintborg B, Østergaard M, Dreyer L, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti–tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. *Arthritis & Rheumatism*. 2011; 63(2):382-90.
74. Zhang HF, Gauthier G, Hiscock R and Curtis JR. Treatment patterns in psoriatic arthritis patients newly initiated on oral nonbiologic or biologic disease-modifying antirheumatic drugs. *Arthritis Research & Therapy*. 2014; 16(4):420.
75. Rheumatology BSf. COVID-19 guidance. 2020. (Updated: 29 July 2020) Available at: https://www.rheumatology.org.uk/practice-quality/covid-19-guidance. Accessed: 06 August 2020.
76. Mahmood F, Coates LC and Helliwell PS. Current concepts and unmet needs in psoriatic arthritis. *Clinical rheumatology*. 2018; 37(2):297-305.
77. European Medicines Agency. Xeljanz: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed: 15 August 2019.
78. AbbVie. Clinical Study Report M15-572. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 2020.
79. AbbVie. Clinical Study Report M15-554. A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease-Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. 2020.
80. Felson DT and LaValley MP. The ACR20 and defining a threshold for response in rheumatic diseases: too much of a good thing. *Arthritis Research & Therapy*. 2014; 16(1):101.
81. Use CfMPfH. Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis. *London: European Medicines Agency*. 2006.
82. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA537]. Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]. Committee Papers. 2018. Available at:

https://www.nice.org.uk/guidance/ta537/evidence/committee-papers-pdf-4913117821. Accessed: 27 April 2020.
83. Mease P, Lertratanakul A, Anderson J, et al. Upadacitinib for Psoriatic Arthritis Refractory to Biologics: SELECT-PsA 2. *Ann Rheum Dis*. 2020.
84. AbbVie. Statistical Analysis Plan, Study M15-554: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2 02 Oct 2019 2019.
85. AbbVie. Statistical Analysis Plan, Study M15-572: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 12 Dec 2019 2019.
86. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis. 2006. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-psoriatic-arthritis_en.pdf. Accessed: 25 May 2020.
87. AbbVie. SELECT-PsA 1 topline data. 2020.
88. Mease P, Strand V and Gladman D. Functional impairment measurement in psoriatic arthritis: Importance and challenges. *Semin Arthritis Rheum*. 2018; 48(3):436-48.
89. Kwok T and Pope JE. Minimally important difference for patient-reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue, and global visual analog scales. *The Journal of Rheumatology*. 2010; 37(5):1024-8.
90. Rodgers M, Epstein D, Bojke L, et al. Estimation of Psoriasis Area and Severity Index score for treatment responders in the decision model. NIHR Journals Library, 2011.
91. Coates LC, Strand V, Wilson H, et al. Measurement properties of the minimal disease activity criteria for psoriatic arthritis. *RMD open*. 2019; 5(2):e001002.
92. AbbVie. SELECT-PsA 2 topline data. 2020.
93. Mease P, Lertratanakul A, Strober B, et al. Efficacy of upadacitinib in patients with psoriatic arthritis stratified by number of prior biologic disease-modifying antirheumatic drugs. American College of Rheumatology's All-Virtual Annual Meeting. November 5–9 2020.
94. AbbVie. Network Meta-Analysis of Treatments for Moderately to Severely Active Psoriatic Arthritis; Feasibility Report. 2020.
95. Elsenbruch S and Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nature reviews Gastroenterology & hepatology*. 2015; 12(8):472.
96. Enck P, Klosterhalfen S, Weimer K, et al. The placebo response in clinical trials: more questions than answers. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2011; 366(1572):1889-95.
97. Khan A, Mar KF, Schilling J and Brown WA. Magnitude and Pattern of Placebo Response in Clinical Trials of Oral Antihyperglycemic Agents: Data From the US Food and Drug Administration, 1999–2015. *Diabetes Care*. 2018; 41(5):994-1000.

98. Dias S, Sutton AJ, Welton NJ and Ades A. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011.
99. National Institute for Health and Care Excellence. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs: Final appraisal determination. 2017. (Updated: 13 April 2017) Available at: https://www.nice.org.uk/guidance/ta445/documents/final-appraisal-determination-document. Accessed: 20 July 2020.
100. Burmester G, Winthrop K, Nash P, et al. Safety Profile of Upadacitinib In Psoriatic Arthritis: Integrated Analysis from Two Phase 3 Trials. American College of Rheumatology. Virtual. 5 to 9 November 2020.
101. Retuerto-Guerrero M, Trujillo E, Valero C, et al. Efficacy and safety of switching jakinibs in rheumatoid arthritis. BMJ Publishing Group Ltd, 2020.
102. Fieldhouse KA, Ukaibe S, Crowley EL, et al. Inflammatory bowel disease in patients with psoriasis treated with interleukin-17 inhibitors. *Drugs in Context*. 2020; 9.
103. van der Heijde D, Song I-H, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *The Lancet*. 2019; 394(10214):2108-17.
104. Walsh J, Ogdie A, Michaud K, et al. Enthesitis, Dactylitis, and Axial Disease in Psoriatic Arthritis (PsA): Impact on Patient Quality of Life and Work Productivity [abstract]. *Arthritis Rheumatol*. 2019; (71 (suppl 10)).
105. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA220]. Golimumab for Psoriatic Arthritis (manufacturer's submission). 2010. Available at: https://www.nice.org.uk/guidance/ta220. Accessed: 27 April 2020.
106. National Institute for Health and Care Excellence (NICE). Psoriatic arthritis (active) - ustekinumab (Rapid Rev TA313): Committee papers. 2014. Available at: https://www.nice.org.uk/guidance/ta340/documents/psoriatic-arthritis-active-ustekinumab-rapid-rev-ta313-committee-papers-. Accessed: 27 April 2020.
107. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013. (Updated: 4 April 2013) Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed: 20 July 2020.
108. National Institute for Health and Care Excellence. Apremilast for treating active psoriatic arthritis [TA433]. 2017. Available at: https://www.nice.org.uk/guidance/ta433. Accessed: 27 April 2020.
109. National Institute for Health and Care Excellence (NICE). Psoriatic arthritis - etanercept, infliximab and adalimumab: Final Assessment Report [TA199]. 2009. Available at: https://www.nice.org.uk/guidance/ta199/documents/psoriatic-arthritis-etanercept-infliximab-adalimumab-review-acd-assessment-report3. Accessed: 27 April 2020.
110. Mease P, Fleischmann R, Deodhar A, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Annals of the Rheumatic Diseases*. 2014; 73(1).
111. National Institute for Health and Care Excellence (NICE). Spondyloarthritis in over 16s: diagnosis and management. 2017. (Updated: 02 June 2017) Available at: https://www.nice.org.uk/guidance/ng65. Accessed: 11 May 2020.

112. 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 Technol Assess*. 2011; 15(10):i-xxi, 1-329.
113. Morgan C, Lunt M, Bunn D, et al. Five-year outcome of a primary-care-based inception cohort of patients with inflammatory polyarthritis plus psoriasis. *Rheumatology (Oxford)*. 2007; 46(12):1819-23.
114. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [ID1658]. Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs. 2020. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10561/documents.
115. Ruyssen-Witrand A, Perry R, Watkins C, et al. Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. *RMD open*. 2020; 6(1).
116. Mease P, FitzGerald O, Van der Heijdge D, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. *N Engl J Med*. 2017.
117. 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(10086):2317-27.
118. Gladman D, Rigby W, Azevedo V, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. *N Engl J Med*. 2017.
119. Mease P, Ory P, Sharp J, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis*. 2009; 68(5):702–9.
120. Gabay C, Riek M, Scherer A, et al. Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. *Rheumatology*. 2015; 54(9):1664-72.
121. Office for National Statistics. National life tables: England and Wales (2017-2019). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. Accessed: 29 October 2020.
122. Ali Y, Tom BD, Schentag CT, et al. Improved survival in psoriatic arthritis with calendar time. *Arthritis Rheum*. 2007; 56(8):2708-14.
123. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set. 2019. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf. Accessed: 27 April 2020.
124. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012; 15(5):708-15.
125. Curtis L and Burns A. Unit Costs of Health and Social Care 2019. 2018. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Accessed: 19 April 2020.
126. Monthly Index of Medical Specialities (MIMS). Available at: http://www.mims.co.uk/drugs. Accessed: 27 April 2020.
127. National Health Service. National schedule of NHS costs - Year 2018-19. 2020. (Updated: 19 February 2020) Available at:

https://improvement.nhs.uk/resources/national-cost-collection/. Accessed: 11 June 2020.
128. Office for National Statistics. Consumer Prices Index, Special Aggregate: 06 Health. Available at: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l528. Accessed: 20 April 2020.
129. European Medicines Agency. Humira: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf. Accessed: 15 August 2019.
130. European Medicines Agency. Cimzia: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/cimzia-epar-product-information_en.pdf. Accessed: 15 August 2019.
131. European Medicines Agency. Simponi: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf. Accessed: 15 August 2019.
132. European Medicines Agency. Taltz: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/taltz-epar-product-information_en.pdf. Accessed: 15 August 2019.
133. European Medicines Agency. Otezla: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/otezla-epar-product-information_en.pdf. Accessed: 15 August 2019.
134. European Medicines Agency. Jylamvo: EPAR - Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/jylamvo-epar-product-information_en.pdf. Accessed: 15 August 2019.
135. National Health Service. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed: 27 August 2019.
136. UK Department of Health National Health Services (NHS). NHS Reference Costs 2017-2018. National Schedule of Reference Costs: The Main Schedule. Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed: 27 April 2020.
137. Corbett M, Chehadah F, Biswas M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to diseasemodifying antirheumatic drugs: a systematic review and economic evaluation. *Health Technol Assess Rep*. 2017; 21(56).
138. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA574]. Certolizumab pegol for treating moderate to severe plaque psoriasis [ID1232]. Committee Papers. . 2019. Available at: https://www.nice.org.uk/guidance/ta574/documents/committee-papers. Accessed: 24 November 2020.
139. Bansback N, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. *Rheumatology*. 2006; 45(8):1029-38.
140. Kobelt G, Jonsson L, Lindgren P, et al. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum*. 2002; 46(9):2310-9.

141. Hartman M, Prins M, Swinkels OQ, et al. Cost-effectiveness analysis of a psoriasis care instruction programme with dithranol compared with UVB phototherapy and inpatient dithranol treatment. *Br J Dermatol*. 2002; 147(3):538-44.
142. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL and Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. *Pharmacoeconomics*. 2019; 37(11):1391-408.
143. Drummond M, Sculpher M, Torrance G, et al. Methods for the economic evaluation of health care programmes–3rd edition: Oxford University Press. Oxford, 2005.
144. Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics*. 2006; 24(4):355-71.

B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Measures of disease activity in PsA

Appendix M: Expectation effect adjustment

Appendix N: Summary of base-case analysis inputs

Appendix O: Probabilistic sensitivity analysis scatter plots

Appendix P: Base case incremental cost-effectiveness analysis results: list price

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Clarification questions

January 2021

File name	Version	Contains confidential information	Date
ID2690 upadacitinib ERG clarification letter_[REDACTED]_29Jan21	V1	No	29/01/21

Section A: Clarification on effectiveness data

SELECT-PsA 1 and SELECT-PsA 2 trials

A1. Hierarchical testing strategy in the SELECT-PsA 1 and SELECT-PsA 2 trials:

i. Please clarify whether a formal statistical test was performed for the superiority testing of UPA versus ADA for the outcome of ACR20 (as part of the hierarchical testing strategy of the SELECT-PsA 1 trial) and, if so, provide the results of this test.

Company response:

Yes, a formal statistical test was performed for the superiority testing of upadacitinib (UPA) versus adalimumab (ADA) for the outcome of American College of Rheumatology 20 (ACR20) response at Week 12 using the Cochran-Mantel-Haenszel (CMH) test while adjusting for the main stratification factor of current disease-modifying anti-rheumatic drug (DMARD) use (yes/no). These results are detailed in CS Table 12, which includes the results of all primary and key secondary outcome measures in SELECT PsA-1 and SELECT-PsA-2, and in CS Table 13, which describes the ACR20 response rate at Week 12, specifically.

The results of the superiority testing for UPA versus ADA in SELECT-PsA 1 are summarized in Table 1 below.

Table 1: ACR20 response rate at Week 12, superiority of UPA versus ADA (SELECT-PsA 1, FAS NRI)

	Within group point estimate (95% CI)[a]	Between group difference (UPA – control)		
		Point estimate (95% CI)[b]	Nominal p-value[c]	Multiplicity adjusted p value
UPA 15 mg (N = 429)	[redacted]	-	-	-
PBO (N = 423)	[redacted]	-	-	-
ADA 40 mg (N = 429)	[redacted]	[redacted]	[redacted]	[redacted]

Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.

Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation; [c], nominal p-value was constructed using the Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).

Source: SELECT-PsA 1 clinical study report.[1]

ii. Please clarify why the p-values provided in Table 13 and Table 26 of the CS are stated to be “nominal”. Statistical tests for the analyses presented in these tables should have been part of the hierarchical testing strategies of the SELECT-PsA 1 trial and SELECT-PsA 2 trial, respectively.

Company response:

The comparison UPA versus PBO for the outcome of ACR20 at Week 12 was the primary endpoint of SELECT-PsA 1 and SELECT-PsA 2 and was tested for superiority using the CMH test while adjusting for the main stratification factor of current DMARD use (yes/no).

The nominal p-values included in CS Tables 13 and 26 were the unadjusted p-values directly calculated from the statistical models. They reflect the observed significance based on a given model and preserve information from original data.

Multiplicity-adjusted p-value calculation was conducted using the algorithm in a paper by Bretz et al[2]; this was calculated as ‘the smallest significance level at which one can reject the hypothesis using the given multiple test procedure’. The paper

also provides an SAS macro to compute the adjusted p-value for each hypothesis included in the graph. Multiplicity adjusted p-values incorporated the prespecified graphical testing procedures so the test could be performed at the significance level α for the decision. Statistical significance was achieved for an endpoint when the adjusted p-value was ≤ 0.05.

Multiplicity-adjusted p-values have been added (as an adaptation to CS Table 13 and Table 26) in Table 2 and Table 3 below.

Table 2: ACR20 response rate at Week 12 (SELECT-PsA 1, FAS NRI)

	Within group point estimate (95% CI)[a]	**Between group difference (UPA – control)**		
		Point estimate (95% CI)[b]	**Nominal p-value[c]**	**Multiplicity adjusted p-value**
UPA 15 mg (N = 429)	[redacted]	-	-	-
PBO (N = 423)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 429)	[redacted]	-	-	-

Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.

Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation; [c], nominal p-value was constructed using the Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).

Source: SELECT-PsA 1 clinical study report.[1]

Table 3: ACR20 response rate at Week 12 (SELECT-PsA 2, FAS NRI)

	Within group point estimate (95% CI)[a]	Between group difference (UPA – PBO)		
		Point estimate (95% CI)[b]	Nominal p-value[c]	Multiplicity adjusted p-value
UPA 15 mg (N = 211)	56.9 [redacted]	-	-	-
PBO (N = 212)	24.1 [redacted]	32.8 (24.0, 41.6)	[redacted]	[redacted]

Key: ACR, American College of Rheumatology; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.

Notes: [a] 95% CIs for response rate were calculated based on normal approximation to the binominal distribution; [b], 95% CIs for response rate difference were calculated based on normal approximation; [c], nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for the main stratification factor of current DMARD use (yes/no).

Source: SELECT-PsA 2 clinical study report[3] and Mease et al. 2020[4]

iii. Please clarify why a "multiplicity adjusted p-value" is provided for the comparison of UPA versus ADA in Table 14 (HAQ-DI at Week 12) and Table 21 (assessment of pain) of the CS, and for the comparison of UPA versus PBO in Table 20 (dactylitis resolution) of the CS when no formal statistical testing should have been performed for these analyses according to the hierarchical testing strategy of the SELECT-PsA 1 trial.

These endpoints are prespecified multiplicity-controlled endpoints/hypothesis where formal statistical testing were planned. As per the Bretz et al. paper[2], multiplicity adjusted p-values can be produced regardless of whether the graphical testing procedure is stopped or not. If the multiplicity adjusted p-value was greater than α, it indicated that statistical significance was not reached for the hypothesis. The multiplicity adjusted p-values for all multiplicity-controlled endpoints are provided for completeness, regardless of whether they were deemed statistically significant. Accordingly, results for multiplicity-adjusted analyses (i.e. Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12 vs ADA, pain at Week 12 vs ADA, and dactylitis resolution vs placebo [PBO]) which fell after the break in the prespecified testing hierarchy were still provided in the tables of the clinical study report.

iv. Please clarify why both "nominal" and "multiplicity adjusted" p-values are provided for the comparison of UPA versus PBO in Tables 14 to 19 and

Tables 27 to 31 of the CS. Please explain how the calculations for these p-values differ.

A multiplicity adjusted p-value calculation was conducted referring to the algorithm in the Bretz et al paper (see clarification A1.ii).[2]

Nominal p-values were unadjusted p-values directly produced from the pre-specified statistical models which adjusted for current DMARD use (yes/no), a main stratification factor. The nominal p-values did not incorporate the multiple testing procedures and cannot be directly used for the comparisons. These nominal (unadjusted) p-values were included for all pre-specified endpoints in the statistical analysis plan because they preserve information from the original data. The multiplicity adjusted p-values are instruments for judgment of the comparisons under multiple testing procedures.

v. Please clarify why no point estimates and nominal p-values are provided in Table 19 and Table 23 of the CS for the comparison of UPA versus ADA (FACIT-F at Week 12, SHS at Week 24, JSN, joint erosion score), or in Table 21 of the CS for the comparison of UPA versus PBO (pain assessment at Week 12).

A statistical comparison between UPA and ADA on FACIT-F was not planned as part of the testing hierarchy. Further details have been added (as an adaptation to CS Table 19) in Table 4 below.

Table 4: Change from baseline in FACIT-F at Week 12 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean	95% CI	Between group LS mean difference (UPA – control)		
			Point estimate (95% CI)	Nominal p-value	Multiplicity adjusted p-value
UPA 15 mg (N = 404)	[redacted]	[redacted]	–	–	–
PBO (N = 394)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 410)[a]	[redacted]	[redacted]	[redacted]	[redacted]	–

Key: ADA, ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; LS, least square; MMRM, mixed-effect model repeated measurement; PBO, placebo; UPA, upadacitinib.

Note: Within group LS mean and 95% CI, between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis used observed longitudinal data up to Week 12 prior to study drug premature discontinuation.

Source: SELECT-PsA 1 clinical study report.[1]

A statistical comparison between UPA versus ADA on either Sharp van der Heijde Score (SHS) or JSN was not planned as part of either the testing hierarchy or the statistical analysis plan. ADA may only be used as a reference arm and no formal comparison or claim can be made with UPA. These endpoints are not intended to be used as comparison versus ADA, but rather to show that UPA demonstrated inhibition of radiographic disease progression (as measured by SHS and JSN) versus placebo – signalling that UPA is a treatment that successfully inhibits the progression of structural damage for PsA patients.

A statistical comparison between UPA and PBO on pain was not planned as part of the testing hierarchy and was not listed as a key secondary endpoint in the statistical analysis plan. Further details have been added (as an adaptation to CS Table 21) in Table 5 below.

Table 5: Change from baseline in patient's assessment of pain at Week 12, superiority of UPA vs ADA (SELECT-PsA 1, FAS MMRM)

	Within group LS mean	95% CI	Between group LS mean difference (UPA – control)		
			Point estimate (95% CI)	Nominal p-value	Multiplicity adjusted p-value
UPA 15 mg (N = 404)	[redacted]	[redacted]	–	–	–
PBO (N = 392)	[redacted]	[redacted]	[redacted]	[redacted]	–
ADA 40 mg (N = 406)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADA, adalimumab; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measurement; PBO, placebo; UPA, upadacitinib.

Note: Within-group LS mean and 95% CI, and between-group LS mean difference and 95% CI, and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis used observed longitudinal data up to Week 12 prior to study drug premature discontinuation.

Source: SELECT-PsA 1 clinical study report.[1]

vi. Please clarify why a nominal p-value has been given for the comparison of UPA versus PBO for the outcome of SHS at Week 24 (CS, Table 23), rather than the p-value from the formal statistical test that forms part of the hierarchical testing strategy of the SELECT-PsA 1 trial (as presented in Table 12 of the CS).

The change from baseline in Modified PsA SHS at Week 24 was a key secondary endpoint in SELECT-PsA-1 and part of the formal hierarchy testing strategy of the SELECT-PsA-1 trial. As indicated above, multiplicity-adjusted analyses as well as nominal p-value comparisons were included for all key secondary endpoints in SELECT-PsA-1 and provided in the clinical study report. The nominal p-value was correctly included in CS Table 23, but the multiplicity-adjusted p-value was inadvertently excluded in CS Table 23 (and correctly included in CS Table 12).

Further details have been added (as an adaptation to CS Table 23) in Table 6 below.

Table 6 Summary of change from baseline in SHS at Week 24 (SELECT-PsA 1, FAS linear extrapolation)

	Within group LS mean (95% CI)	Between group difference (UPA – PBO)		
		Point estimate (95% CI)	Nominal p value	Multiplicity adjusted p-value
Linear extrapolation for missing data				
UPA 15 mg (N = 391)	[redacted]	-	-	-
PBO (N = 372)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 384)	[redacted]	-	-	-
As observed data				
UPA 15 mg (N = 391)	[redacted]	-	-	-
PBO (N = 365)	[redacted]	[redacted]	[redacted]	-
ADA 40 mg (N = 391)	[redacted]	-	-	-

Key: ANCOVA, analysis of covariance; AO, as observed; ADA, adalimumab; CI, confidence interval; diff, difference; DMARD, disease-modifying anti-rheumatic drug; FAS, full analysis set; LS, least square; PBO, placebo; SHS, Sharp van der Heijde Score; UPA, upadacitinib.

Note: Within-group LS mean and 95% CI, and between group LS mean difference and 95% CI, and nominal p-value are based on ANCOVA model including treatment and the stratification factor current DMARD use (yes/no) as fixed factors and baseline value as covariate.

Source: SELECT-PsA 1 clinical study report.[1]

A2. Please provide full results for SF-36 at 12 weeks and SAPS at 16 weeks in the SELECT-PsA 1 trial, including effect estimates for UPA 15mg versus ADA, and UPA 15mg versus PBO and the corresponding p-values (multiplicity-adjusted p-values where the tests form part of the hierarchical testing strategy and nominal p-values otherwise).

Company response:

SF-36 Physical Component Summary (PCS) at Week 12 was a secondary endpoint in SELECT-PsA-1 and part of the formal hierarchy testing strategy of the trial. Patients treated with UPA 15 mg had a significantly better change from baseline in SF-36 PCS at Week 12 than those treated with placebo (between-group difference [redacted]).[1] While not powered for superiority, there were

numerically better changes from baseline in SF-36 PCS scores observed for UPA compared with ADA ([redacted]), as shown in Table 7.[1]

Table 7: Change from baseline in SF-36 at Week 12 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean point estimate (95% CI)	Between group LS mean difference (UPA – control)		
		Point estimate (95% CI)	Nominal p-value	Multiplicity adjusted p-value
Physical component summary				
UPA 15 mg (N = 405)	[redacted]	–	–	–
PBO (N = 394)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 410)	[redacted]	–	–	–

Key: ADA, adalimumab; CI, confidence interval; FAS, full analysis set; HAQ-DI, LS, least square; MMRM, mixed-effect model repeated measurement; PBO, placebo; SF-36 PCS, Short Form 36 Physical Component Summary; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis used observed longitudinal data up to Week 12 prior to study drug premature discontinuation.
Source: SELECT-PsA 1 clinical study report.[1]

Similarly, SAPS at Week 16 was a secondary endpoint in SELECT-PsA-1 and part of the formal hierarchy testing strategy of the trial. In SELECT-PsA 1, patients treated with UPA 15 mg had a numerically better change from baseline in SAPS at Week 16 than those treated with placebo (between group difference [redacted]).[1] While not powered for superiority, there were numerically better changes from baseline in SAPS scores observed for UPA compared with ADA [redacted]), as shown in Table 8.[1]

Table 8: Change from baseline in SAPS at Week 16 (SELECT-PsA 1, FAS MMRM)

	Within group LS mean point estimate (95% CI)	Between group LS mean difference (UPA – PBO)		
		Point estimate (95% CI)	Nominal p-value	Multiplicity adjusted p-value
UPA 15 mg (N = 396)	[redacted]	–	–	–
PBO (N = 388)	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg (N = 407)	[redacted]	–	–	–

Key: ADA, adalimumab; CI, confidence interval; FAS, full analysis set; HAQ-DI, LS, least square; MMRM, mixed-effect model repeated measurement; PBO, placebo; SAPS, self-assessment of psoriasis symptoms; UPA, upadacitinib.
Notes: Within group LS mean and 95% CI, and between group LS mean difference and 95% CI and nominal p-value are based on MMRM analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement. MMRM analysis uses observed longitudinal data up to Week 12 prior to study drug premature discontinuation.
Source: SELECT-PsA 1 clinical study report.[1]

A3. Priority question. Please provide justification for the choice of non-inferiority margin (50% of the placebo-adjusted effectiveness of adalimumab) used for the comparison of UPA versus ADA using data from the SELECT-PsA1 trial.

Company response:

In SELECT-PsA 1, the prespecified approach to testing non-inferiority (NI) of each UPA dose versus ADA for ACR20 response rate at Week 12 was based on the placebo-subtracted treatment difference using Koch's 3-arm test statistic.[5] Details of the statistical methodology are as follows.

Let parameters *T*, *R*, and *P* represent the ACR20 response rates for an UPA dose group, the ADA group, and the combined placebo group, respectively. The null and alternative hypotheses of non-inferiority testing have the form:

$$H_0: T - R \leq -(1-\phi)(R-P) \quad vs. \quad H_1: T - R > -(1-\phi)(R-P).$$

ϕ is a prespecified fraction of reference drug effect to be retained by the test drug, and it is set to be 50% in this NI comparison.

For the conventional two-arm NI method, the NI margin (1- ϕ) (*R-P*) is usually specified to be 50% of the placebo-subtracted reference drug effect (*R-P*), and (*R-P*) is estimated based on the literature and is subject to the limitation of between trial difference and assay sensitivity. Use of 50% as the prespecified fraction of reference drug effect to be retained by test drug (ϕ) is a commonly accepted practice, as detailed in a 2017 publication in the British Journal of Clinical Pharmacology.[6] This is further corroborated in the FDA's '*Final Guidance on Non-Inferiority Clinical Trials to Establish Effectiveness',* whereby a typical value for (the pre-specified fraction of reference drug effect to be retained by test drug [ϕ]) is often 50% at least partly because the sample sizes needed to retain a larger amount, e.g., 60% or more, of the active control effect become impractically large.[7] Using the three-arm approach, (*R-P*) can be directly estimated from the current clinical trial and offers a direct contrast between test drug and reference drug, without the aforementioned limitation of the conventional approach.

The study design of SELECT-PSA 1 allowed direct estimation of the ADA treatment effect versus PBO. In addition, the sample size for this study (N = 410 per group; actual enrolment N = 429 ADA, N = 423 PBO) is comparable to the collective sample sizes of ADA and PBO arms in historical trials (N = 409 for ADA, N = 422 for PBO), see Table 9. With this large sample size, Koch's 3-arm comparison provides a robust NI assessment.

AbbVie also evaluated a NI margin using a conventional 2twoarm NI approach. AbbVie had performed a literature review of ADA trials and identified four placebo-controlled psoriatic arthritis (PsA) trials that included an ADA arm. Of note, these studies were heterogenous and none had identical enrolment criteria to SELECT-PSA 1, so resultant differences in patient populations were expected. Additionally, since 2003 when the first study with an ADA arm was initiated, there has been a shift in the characteristics of PsA patients enrolled in clinical trials. While mean age and gender have remained relatively stable, clinically important differences in disease duration, baseline radiographic damage (modified total Sharp/van der Heijde score), baseline methotrexate use, joint counts, enthesitis, and dactylitis have been observed in these studies, as shown in Table 9.

Table 9: Baseline characteristics of SELECT-PsA 1 and historical PsA clinical studies inclusive of an ADA arm

	SELECT-PsA 1	ADEPT	M02-570	SPIRIT-P1	OPAL BROADEN
Number of subjects in ADA arm	[redacted]	151	51	101	106
Year first subject enrolled	[redacted]	2003	2003	2012	2014
Age, years	[redacted]	48.6	50.4	48.6	47.4
Female, %	[redacted]	43.7	43.1	49.5	47.2
Weight, kg	[redacted]	86.0	91.5	91.6	NA
BMI (kg/m^2), mean	[redacted]	NA	NA	32.1	28.8
Duration of psoriatic arthritis (years), mean	[redacted]	9.8	7.5	6.9	5.3
Use of conventional DMARDs prior to baseline; %	[redacted]	84.8	100	86.1	100
Baseline use of methotrexate, %	[redacted]	51	47.1	56	74.5
Modified Total Sharp Score, mean/median[a]	[redacted]	22.7	NA	15.9	4.0
Presence of enthesitis, %[b]	[redacted]	37.7	NA	55.4	71.7
Presence of dactylitis, %	[redacted]	37.4	NA	22.8	54.7
Tender joint count, mean[c]	[redacted]	23.9	25.3	19.3	17.1
Swollen joint count, mean[c]	[redacted]	14.3	18.2	9.9	9.8

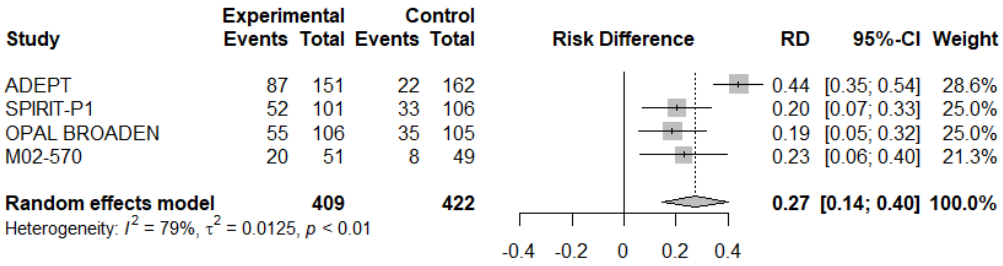
Key: ADA, adalimumab; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drug; PsA, psoriatic arthritis.

Notes: [a], Opal-Broaden reported median; [b], studies evaluated variable sites for enthesitis assessment; [c], 76 swollen and 78 tender joint counts were used for ADEPT and M02-570; 66 swollen and 68 tender joint counts were used for M15-572, SPIRIT-P1 and OPAL BROADEN.

Sources: Mease et al. 2005[8], Genovese et al. 2007[9], Mease et al. 2017a[10], Mease et al. 2017b[11]

To determine placebo-subtracted ADA treatment effect, a meta-analysis of these four pre-existing Phase III trials inclusive of ADA data using a traditional NI margin based on 50% of the lower bound (conservative estimate) of the ADA effect was performed, as shown in Figure 1. This meta-analysis established an NI margin of 7%. Of note, the meta-analysis demonstrated a significant between-trial difference of ADA treatment effect with a $p < 0.01$. This large between-trial variability leads to large confidence intervals in the treatment effect of ADA, with a resulting small NI margin which would have required a very large sample size to have adequate power.

Figure 1: Meta-analysis of ACR20 placebo subtracted treatment effect of ADA at Week 12



Key: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval.
Sources: Mease et al. 2005[8], Genovese et al. 2007[9], Mease et al. 2017a[10], Mease et al. 2017b[11]

In the full analysis set (FAS) population of SELECT-PSA 1, ACR20 response rates at Week 12 were [redacted]% in the UPA 15 mg arm and [redacted]% in the ADA arm. The placebo adjusted effect of UPA 15 mg was [redacted]% (95% CI: [redacted]) and the placebo-adjusted effect of ADA was [redacted]% (95% CI: [redacted]).[1] These results established assay sensitivity of the study to show treatment effect for both test drug and reference drug. Using the three-arm NI approach, UPA 15 mg preserved [redacted]% (95% CI: [redacted]) of ADA effect, with a point estimate of [redacted]% exceeding ADA effect (100% means equal), and a lower bound ([redacted]%) well above the pre specified 50%.

To offer more direct interpretation of the observed UPA 15 mg and ADA effect in the context of the conventional two-arm NI approach, one may look at the response rate difference in ACR20: [redacted]% (95% CI: [redacted]). This translates to loss of ADA effect of at most [redacted]%; this magnitude is considered not clinically relevant. Putting the result in the framework of a two-arm NI test, we compare the lower bound of the 95% CI against the negative NI margin. Note that meta-analysis established a 7% NI margin based on ADA trials. The lower bound of UPA 15 mg versus ADA treatment difference is [redacted]%, well above the negative NI margin of -7%, demonstrating robustness of the observed UPA 15 mg effect over ADA on non-inferiority. Furthermore, a 7% NI margin is conservative based on previous trials. For example, it is significantly smaller than the equivalence margin of 15%, European Medicines

Agency (EMA) considered clinically relevant in the infliximab biosimilar pivotal study.[12]

The results for the comparison between UPA 15 mg and ADA based on the pre-specified three-arm NI test are relevant to clinical practice. While statistical superiority was not achieved for the UPA 15 mg group versus the ADA group for ACR20 response rate at Week 12, the UPA 15 mg group ([redacted]%) demonstrated a numerically higher response than the ADA group ([redacted]%), as shown in Figure 2.

The numerically superior result for ACR20 response in the UPA 15 mg group compared with the ADA group validates the clinical relevance of the prespecified three-arm NI result, which was statistically robust under the conventional two-arm approach. Furthermore, in SELECT-PsA 1, ADA performed within the range of results observed in prior PsA trials with a placebo-adjusted treatment effect of [redacted]%, compared with prior studies which ranged from 19% to 44%, as shown in Figure 1.

As the reference product, ADA, is licensed for the treatment of PsA and known to consistently result in a clinically relevant placebo-adjusted treatment effect, the difference between the ADA and placebo groups observed in this trial supports the assay sensitivity and clinical relevance of the observed NI result.

Figure 2: Benefit forest plot of UPA 15 mg QD compared with ADA in non-biological DMARD-IR patients through Week 24 (SELECT-PsA 1)

Key: ADA, adalimumab; DMARD-IR, disease-modifying anti-rheumatic drug inadequate response; QD, once daily; UPA, upadacitinib.

In conclusion, based on the Koch's three-arm NI test and assessment of the clinical relevance under the conventional two-arm NI framework, the observed treatment effects of UPA 15 mg and ADA are robust to determine NI between UPA and ADA.

Network meta-analyses

A4. The baseline demographic information and disease characteristics of the patients in the studies included in the NMAs presented in Tables 7 and 8 of the NMA technical report:

i. The CHOICE and Mease (2018) studies are missing from Tables 7 and 8. Please provide baseline demographic information and disease characteristics for patients in these studies, or provide justification as to why these studies have not been included.

ii. Please explain why the EXCEED study has been included in Tables 7 and 8.

Company response:

i. The baseline demographic information and disease characteristics for CHOICE and Mease (2018) are extracted and provided in Table 10 and Table 11. These studies were missed from our submitted document however these are included in our NMAs and also in the NMA technical report submitted (section 1.2 Evidence networks).

ii. As the EXCEED trial is included in the NMAs for PASI 50/75/90 and ACR 20/50/70, the baseline demographic information and disease characteristics for the EXCEED trial have been summarised in Tables 7 and 8 of the company submission.

Table 10. Patient demographics and baseline characteristics of CHOICE and Mease (2018)

Trial name (reference)	Treatment name	ITT N	Age mean (SD)	Females (%)	Whites (%)	Asian (%)	Duration of PsA years, mean (SD)	Duration of psoriasis years, mean (SD)	Prior therapies			
									DMARDs, n (%)	MTX, n (%)	Biologics, n (%)	Biologic failure, n (%)
CHOICE	SEC 300 mg	103	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SEC 150 mg	103	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	52	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mease 2018	ABT-122 120 mg QW	71	51.0 (12.4)	37 (52.1)	70 (98.6)	NR	5.9 (7.1)	NR	71 (100)	71 (100)	NR	NR
	ABT-122 240 mg QW	73	47.4 (13.8)	37 (50.7)	70 (95.9)	NR	7.5 (8.2)	NR	73 (100)	73 (100)	NR	NR
	ADA 40 mg EOW	72	50.5 (12.0)	33 (45.8)	70 (97.2)	NR	8.4 (9.2)	NR	72 (100)	72 (100)	NR	NR
	Placebo QW	24	47.7 (13.7)	12 (50.0)	24 (100)	NR	7.6 (7.2)	NR	24 (100)	24 (100)	NR	NR

Table 11. Disease characteristics of CHOICE and Mease (2018)

Trial name (reference)	Treatment name	ITT N	Severity of disease					
			Patients with psoriasis involvement ≥3% BSA, n (%)	Tender joint count, mean (SD)	Swollen joint count, mean (SD)	CRP mg/dL, mean (SD)	RF, n (%) negative	DAS28-CRP, mean (S.D.)
CHOICE	SEC 300 mg	103	NR	NR	NR	NR	NR	NR
	SEC 150 mg	103	NR	NR	NR	NR	NR	NR
	Placebo	52	NR	NR	NR	NR	NR	NR
Mease 2018	ABT-122 120 mg QW	71	43 (60.6)	21.7 (14.6)	12.7 (10.4)	NR	NR	5.0 (1.2)
	ABT-122 240 mg QW	73	49 (67.1)	23.6 (14.3)	14.8 (11.8)	NR	NR	4.8 (1.3)
	ADA 40 mg EOW	72	33 (45.8)	23.4 (17.0)	14.0 (10.6)	NR	NR	5.1 (1.1)
	Placebo QW	24	11 (45.8)	19.0 (14.7)	13.4 (11.4)	NR	NR	4.6 (1.1)

A5. Please provide detailed justification for using only fixed effects models with no placebo adjustment in the biologic-experienced population NMAs (including plots demonstrating PBO response rates and model comparison statistics for all outcomes investigated).

Company response:

Fixed-effects models with no placebo adjustment were used for the biologic-experienced NMAs, due to the sparsity of the biologic-experienced networks.

The evidence networks for the biologic-experienced NMAs are sparse (Figure 5 through 8 in the NMA technical report). Specifically, there are 4 trials connecting 7 treatments in the PsARC network, 5 trials connecting 8 treatments in the PASI 50/75/90 network, 2 trials connecting 4 treatments in the HAQ-DI change conditional on PsARC response network, and 7 trials connecting 8 treatments in the ACR 20/50/70 network. For the PsARC, PASI, and HAQ-DI change conditional on PsARC networks, all the connections between treatments are based on only 1 trial. For the ACR network, all the connections (except for secukinumab vs. placebo) are based on only 1 trial.

Having only 1 trial connect all or most of the treatments has made it difficult to accurately estimate the cross-trial heterogeneity parameter in the random-effects model or accurately estimate the extent to which placebo response rates modify the treatment contrasts in the placebo-response adjusted model (e.g., Using a random-effects model or a placebo-response adjusted model, we would be estimating more parameters than the number of data points available for PsARC and HAQ-DI change conditional on PsARC response), which could result in a high level of uncertainty in the estimation. For example, as presented in the response to question A7, the heterogeneity parameters $1/\tau$ for the random-effects models are associated with wide 95% CrIs and thus are highly uncertain due to the lack of data for such an estimation. As a result, the posterior distributions for the treatment-effect estimates and pairwise comparisons in the random-effects models are also subject to high uncertainty. Lastly, random-effects models are associated with similar or even slightly larger DICs, compared with fixed-effects models.

Relatedly, the numbers of trials included in the biologic-experienced NMAs are too small to conclude with certainty about the systematic cross-trial differences in placebo response rates (Figure 22 through 26 in the NMA technical report).

A6. Please clarify whether the model comparison statistics presented in Table 9 of the NMA report for (i) “PASI” relate to PASI 50, PASI 70 or PASI 90 and (ii) whether those for “ACR” relate to ACR 20, ACR 50 or ACR 70.

Company response:

As ordinal NMAs were implemented to jointly model PASI 50, 75, and 90 and to jointly model ACR 20, 50, and 70, “PASI” and “ACR” presented in Table 9 are referred to PASI 50/75/90 and ACR 20/50/70.

A7. Please provide results of random effects models without placebo adjustment for the NMA of HAQ-DI score change (conditional on PsARC response) in the biologic-naïve population, and results of random effects models for the NMAs for all outcomes in the biologic-experienced population.

Company response:

The suggested NMAs using random-effects models are conducted for HAQ-DI change conditional on PsARC response in the biologic-naïve population and for all four outcomes (PsARC, PASI 50/75/90, HAQ-DI change conditional on PsARC response, and ACR 20/50/70) in the biologic-experienced population. Model diagnostic statistics (fixed-effects vs. random-effects), treatment-effect estimates (fixed-effects vs. random-effects), and pairwise comparisons estimated from the random-effects models are presented below.

HAQ-DI change conditional on PsARC response in the biologic-naïve population: The posterior distributions for the cross-trial heterogeneity (measured by $1/\tau$ in the random-effects models) for HAQ-DI change conditional on PsARC response in the biologic-naïve population have medians close to zero and tight 95% CrIs, suggesting limited cross-trial heterogeneity (Table 12). DICs for the fixed-effects model are lower than the random-effects model, indicating that a fixed-effects model is able to sufficiently model HAQ-DI change conditional on PsARC response for the biologic-naïve

population (Table 12). Additionally, the posterior medians for the treatment-effect estimates and pairwise comparisons from the random-effects model are similar to those from the fixed-effects model (Table 13; Table 14 vs. Table 21 from the NMA technical report; Table 15 vs. Table 22 from the NMA technical report).

PsARC, PASI 50/75/90, HAQ-DI change conditional on PsARC response, and ACR 20/50/70 in the biologic-experienced population: The posterior distributions of $1/\tau$ for the random-effects models for all outcomes in the biologic-experienced population are subject to high uncertainty (Table 12), due to the sparsity of the biologic-experienced networks (i.e., 4 trials connecting 7 treatments in the PsARC network; 5 trials connecting 8 treatments in the PASI 50/75/90 network, 2 trials connecting 4 treatments in the HAQ-DI change conditional on PsARC response network, and 7 trials connecting 8 treatments in the ACR 20/50/70 network). As a result, there lack sufficient data for the estimation of potential cross-trial heterogeneity, and the treatment-effect estimates and pairwise comparisons estimated from the random-effects models are all subject to high uncertainty, limiting their interpretability (Table 16through Table 28). Lastly, fixed-effects models also have similar or slightly smaller DICs compared with random-effects models (Table 12).

These results suggest that fixed-effects models are appropriate for HAQ-DI change conditional on PsARC response in the biologic-naïve population and for all four outcomes (PsARC, PASI 50/75/90, HAQ-DI change conditional on PsARC response, and ACR 20/50/70) in the biologic-experienced population.

Table 12. Statistics for model selection of NMAs at week 12 (random-effects model vs. fixed-effects model)

Outcome	Model	Data Points	1/τ Median (95% CrI)	Mean Residual Deviance	pD	DIC
Biologic-naïve population						
HAQ-DI among PsARC responder	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI among PsARC non-responder	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced population						
PsARC	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI among PsARC responder	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI among PsARC non-responder	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR	RE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FE without PBO-response adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Biologic-naïve NMAs at week 12

HAQ-DI change conditional on PsARC response

Table 13. Estimated HAQ-DI Change from Baseline among PsARC Responders and PsARC Non-Responders [Posterior Median (95% CrI)] from the Biologic-naïve NMAs at Week 12

Treatment	Posterior Median (95% CrI)			
	FE without PBO-response adjustment (CS base case)		RE without PBO-response adjustment	
	HAQ-DI Change among PsARC Responders	HAQ-DI Change among PsARC Non-Responders	HAQ-DI Change among PsARC Responders	HAQ-DI Change among PsARC Non-Responders
PBO	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]

Table 14. Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among PsARC Responders from the Biologic-naïve RE NMA at Week 12

PBO								
	APR							
		GOL						
			ADA					
				UST				
					UPA 15			
						UPA 30		
							ETN	
								INF

*denotes a significant difference in treatment effect.

Table 15. Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among PsARC Non-Responders from the Biologic-naïve RE NMA at Week 12

PBO								
	GOL							
		APR						
			UST					
				ADA				
					ETN			
						INF		
							UPA 15	
								UPA 30

*denotes a significant difference in treatment effect.

Biologic-experienced NMAs at week 12

PsARC response

Table 16. Estimated Probabilities of Achieving PsARC Response [Posterior Median (95% CrI)] from the Biologic-experienced NMA at Week 12

Treatment	Posterior Median (95% CrI)	
	FE without PBO-response adjustment Probability of Achieving PsARC Response	RE without PBO-response adjustment Probability of Achieving PsARC Response
PBO	[redacted]	[redacted]
UST	[redacted]	[redacted]
IXE 80 Q4W	[redacted]	[redacted]
IXE 80 Q2W	[redacted]	[redacted]
TOF	[redacted]	[redacted]
UPA 15	[redacted]	[redacted]
UPA 30	[redacted]	[redacted]

Table 17. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PsARC Response from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	IXE 80 Q4W	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	TOF	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q2W	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UPA 15	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UPA 30

PASI 50/75/90 response

Table 18. Estimated Probabilities of Achieving PASI Response [Posterior Median (95% CrI)] from the Biologic-experienced NMA at Week 12

Treatment	Posterior Median (95% CrI)					
	FE without PBO-response adjustment			RE without PBO-response adjustment		
	Probability of Achieving PASI 50 Response	Probability of Achieving PASI 75 Response	Probability of Achieving PASI 90 Response	Probability of Achieving PASI 50 Response	Probability of Achieving PASI 75 Response	Probability of Achieving PASI 90 Response
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 50 Response from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q4W	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q2W	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SEC 300	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UST

Table 20. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 75 Response from the Biologic-experienced RE NMA at Week 12

PBO							
	TOF						
		UPA 15					
			UPA 30				
				IXE 80 Q4W			
					IXE 80 Q2W		
						SEC 300	
							UST

Table 21. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving PASI 90 Response from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q4W	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q2W	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	SEC 300	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UST

HAQ-DI change conditional on PsARC response

Table 22. Estimated HAQ-DI Change from Baseline among PsARC Responders and PsARC Non-Responders [Posterior Median (95% CrI)] from the Biologic-experienced NMA at Week 12

Treatment	Posterior Median (95% CrI)			
	FE without PBO-response adjustment		RE without PBO-response adjustment	
	HAQ-DI Change among PsARC Responders	HAQ-DI Change among PsARC Non-Responders	HAQ-DI Change among PsARC Responders	HAQ-DI Change among PsARC Non-Responders
PBO	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]

Table 23. Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among PsARC Responders from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]
[redacted]	**UPA 15**	[redacted]	[redacted]
[redacted]	[redacted]	**UPA 30**	[redacted]
[redacted]	[redacted]	[redacted]	**UST**

Table 24. Estimated Differences [Posterior Median (95% CrI)] for Pairwise Comparisons of HAQ-DI Change from Baseline among PsARC Non-Responders from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]

[redacted]	**UST**	[redacted]	[redacted]
[redacted]	[redacted]	**UPA 15**	[redacted]
[redacted]	[redacted]	[redacted]	**UPA 30**

ACR 20/50/70 response

Table 25. Estimated Probabilities of Achieving ACR Response [Posterior Median (95% CrI)] from the Biologic-experienced NMA at Week 12

Treatment	Posterior Median (95% CrI)					
	FE without PBO-response adjustment			RE without PBO-response adjustment		
	Probability of Achieving ACR 20 Response	Probability of Achieving ACR 50 Response	Probability of Achieving ACR 70 Response	Probability of Achieving ACR 20 Response	Probability of Achieving ACR 50 Response	Probability of Achieving ACR 70 Response
PBO	[redacted]					
TOF						
UST						
SEC 300						
IXE 80 Q2W						
UPA 15						
IXE 80 Q4W						
UPA 30						

Table 26. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving ACR 20 Response from the Biologic-experienced RE NMA at Week 12

PBO							
	TOF						
		UST					
			SEC 300				
				IXE 80 Q2W			
					UPA 15		
						IXE 80 Q4W	
							UPA 30

Table 27. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving ACR 50 Response from the Biologic-experienced RE NMA at Week 12

PBO							
	TOF						
		UST					
			SEC 300				
				IXE 80 Q2W			
					UPA 15		
						IXE 80 Q4W	
							UPA 30

Table 28. Estimated Odds Ratios [Posterior Median (95% CrI)] for Pairwise Comparisons of Probabilities of Achieving ACR 70 Response from the Biologic-experienced RE NMA at Week 12

PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	SEC 300	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q2W	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UPA 15	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IXE 80 Q4W	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UPA 30

A8. Please clarify why an NMA for MDA response was performed for the biologic-experienced population (CS, Appendix v2, Section D.1.3.5) but not for the biologic-naïve population.

Company response:

The analysis was conducted as an exploratory expansion to the original NMA and performed in light of the increasing interest in the MD Anderson (MDA) criteria, given it is often explored in clinical trials. MDA criteria were initially created to target remission in rheumatoid arthritis and have since been adapted for PsA for the same purpose; however, implementation in clinical practice is not common for practical reasons. Similarly, MDA was not included as a required outcome in the National Institute for Health and Care Excellence (NICE) scope.

Additionally, the use of MDA as an outcome for economic modelling purposes was null – therefore, this NMA should only be considered as supplementary information. As a complementary analysis, MDA was seen only relevant for the most severe population as there is a perception that remission, as defined by MDA, is an unattainable treatment goal in more severe or established PsA. This population aligns mostly with the biologic-experience population in our submission; consequently, the NMA was conducted only for the biologic-experienced population.

A9. Please clarify why data from the FUTURE 2, FUTURE 3, FUTURE 5 and P SUMMIT 2 studies are included in both the biologic-naïve and biologic-experienced NMAs? Were subgroup data from each study used in the NMAs?

Company response:

The FUTURE 2, 3, 5 and PSUMMIT 2 trial included a mix of biologic-experienced and biologic-naïve patients. Subgroup data stratified by biologic-experience are available for some of the NMA endpoints and used in the NMAs. The details of the use of such data are provided in Table 29 (sourced from NMA technical report Table 1 for biologic-naïve networks at week 12) and Table 30 (sourced from NMA technical report Table 2 for biologic-experienced networks at week 12).

Table 29. Summary of the trials used to carry out the NMAs for the biologic-naïve patient population at week 12

Trial	Treatments	PsARC	PASI	HAQ-DI | PsARC	ACR
FUTURE 2	Secukinumab 300 mg Secukinumab 150 mg Placebo	Week 12 (pooled)	75/90 Week 16 (bio-naïve)		20 Week 12 (bio-naïve)
FUTURE 3	Secukinumab 300 mg Secukinumab 150 mg Placebo		75/90 Week 24 (pooled)		20/50 Week 12 (bio-naïve)
FUTURE 5	Secukinumab 300 mg Secukinumab 150 mg Placebo		75/90 Week 16 (pooled)		20/50/70 Week 12 (bio-naïve)
PSUMMIT 2	Ustekinumab 45 mg Placebo	Week 24 (bio-naïve)	75 Week 12 (bio-naïve)		20/50/70 Week 12 (bio-naïve)

Table 30. Summary of the trials used to carry out the NMAs for the biologic-experienced patient population at week 12

Trial	Treatments	PsARC	PASI	HAQ-DI | PsARC	ACR
FUTURE 2	Secukinumab 300 mg Placebo		75/90 Week 24 (bio-experienced)		20 Week 12 (bio-experienced)
FUTURE 3	Secukinumab 300 mg Placebo				20/50 Week 12 (bio-experienced)
FUTURE 5	Secukinumab 300 mg Placebo				20/50/70 Week 12 (bio-experienced)
PSUMMIT 2	Ustekinumab 45 mg Placebo	Week 12 (pooled)	75 Week 12 (bio-experienced)	Week 24 (bio-experienced)	20/50/70 Week 12 (bio-experienced)

Adverse events for comparator studies

A10. Please provide evidence to show how the safety of UPA in the SELECT-PsA 1 and SELECT-PsA 2 trials compares with the safety of the other comparators included in the NMAs.

Company response:

While safety analyses were not included as part of the indirect treatment comparison for UPA, the clinical systematic literature review captured sufficient publicly available evidence to inform a naïve comparison.

Safety evidence pertaining to mixed biologic-naive and experienced populations is summarized in Table 31, for biologic naïve populations in Table 32, and biologic-experienced populations in Table 33.

Overall, UPA 15 mg showed broadly equivalent safety findings compared to the current therapeutic options for treating PsA patients. Upadacitinib has a well-characterized, acceptable safety profile in the PsA population, with rates of adverse events (AEs), serious adverse events (SAEs), and AE-related discontinuations similar to those of other therapeutic options.

Table 31: Safety data in mixed populations

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE-related discontinuations	
				n	%	n	%	n	%
FUTURE 2 (NCT01752634)	SEC 300 mg QW then Q4W	Week 16	100	56	56	5	5	2	2
	SEC 150 mg QW then Q4W		100	57	57	1	1	0	0
	SEC 75 mg QW then Q4W		99	48	48	4	4	2	2
	PBO		98	57	58	2	2	3	3
	SEC 300 mg QW then Q4W	Week 24	145	113	***77.9***	10	***6.9***	3	***2.1***
	SEC 150 mg QW then Q4W		143	117	***81.8***	8	***5.6***	4	***2.8***
	SEC 75 mg QW then Q4W		99	77	***77.8***	12	***12.1***	4	***4***
	PBO		98	61	***62.2***	3	***3.1***	4	***4***
FUTURE 3	SEC 300 mg	Week 16	139	76	54.7	3	2.2	3	2.2
	SEC 150 mg		138	80	58.0	5	3.6	5	3.6
	PBO		137	77	56.2	9	6.6	5	3.6
	SEC 300 mg	Week 52	204	164	***80.4***	19	***9.3***	9	***4.4***
	SEC 150 mg		202	156	***77.2***	21	***10.4***	13	***6.4***
FUTURE 4	SEC 300 mg	Week 104	136	103	75.7	12	8.8	1	0.7
	SEC 150 mg		334	285	85.3	47	14.1	16	4.8

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE-related discontinuations	
				n	%	n	%	n	%
FUTURE 5	SEC 300 mg with loading dose	Week 24	222	140	63.1	7	3.2	3	1.4
	SEC 150 mg with loading dose		220	138	62.7	9	4.1	4	1.8
	SEC 150 mg without loading dose		222	136	61.3	6	2.7	3	1.4
	PBO		332	206	62	12	3.6	7	2.1
PALACE 1 (NCT01172938)	PBO	Week 24	168	81	48.2	7	4.2	8	4.8
	APR 20 mg BID		168	101	60.1	8	4.8	10	6
	APR 30 mg BID		168	103	61.3	9	5.4	12	7.1
	APR 20 mg BID	Week 52	245	164	66.9	14	5.7	16	6.5
	APR 30 mg BID		245	174	71	19	7.8	23	9.4
PALACE 2 (NCT01212757)	PBO	Week 24	159	72	45.3	3	1.9	3	1.9
	APR 20 mg BID		163	106	65	6	3.7	5	3.1
	APR 30 mg BID		162	96	59.3	4	2.5	12	7.4
	APR 20 mg BID	Week 52	234	159	67.9	11	4.7	12	5.1
	APR 30 mg BID		234	163	69.7	12	5.1	19	8.1
PALACE 3	PBO	Week 24	168	83	49	9	5	10	6
	APR 20 mg BID		170	100	59	3	2	13	8
	APR 30 mg BID		167	104	62	6	4	12	7
	APR 20 mg BID	Week 52	241	160	66	13	5	22	9
	APR 30 mg BID		242	165	68	10	4	14	6

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE-related discontinuations	
				n	%	n	%	n	%
PSUMMIT-2	PBO	Week 16	104	57	54.8	5	4.8	8	7.7
	UST 45 mg Q12W		103	65	63.1	0	0	2	1.9
	UST 90 mg Q12W		104	63	60.6	1	1	2	1.9
	UST combined		207	128	61.8	1	0.5	4	1.9
	PBO	Week 24	104	66	63.5	5	4.8	11	10.6
	PBO/UST 45 mg		31	13	41.9	1	3.2	0	0
	UST 45 mg Q12W		103	73	70.9	0	0	2	1.9
	UST 90 mg Q12W		104	72	69.2	2	1.9	3	2.9
	UST combined		238	158	66.4	3	1.3	5	2.1
RAPID PSA	PBO	Week 24	136	92	67.6	6	4.4	2	1.5
	CZP 200 mg Q2W		138	94	68.1	8	5.8	4	2.9
	CZP 400 mg Q4W		135	96	71.1	13	9.6	6	4.4

Key: AE, adverse events; APR, apremilast; BID, twice daily; CZP, certolizumab; NR, not reported; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse events; SEC, secukinumab; UST, ustekinumab.

Notes: Bold and italic indicates calculated values.

Source: Clinical systemic literature review report[13]

Table 32: Safety data in biologic-naïve population

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE related discontinuations	
				n	%	n	%	n	%
SELECT-PsA 1	PBO	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	UPA 15 mg QD		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 40 mg EOW		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE related discontinuations	
				n	%	n	%	n	%
ACTIVE	APR 30 mg BID	Week 24	109	69	63.3	5	4.6	5	4.6
	PBO		109	73	67	3	2.8	10	9.2
	APR 30 mg BID	Week 52	206	144	69.9	10	4.9	17	8.3
ADEPT	PBO	Week 24	162	NR	NR	7	***4.3***	*1*	***0.6***
	ADA 40 mg Q2W		151	NR	NR	5	***3.3***	*3*	***2***
CHOICE	SEC 300 mg	Week 16	103	59	57.3	NR	NR	1	**1**
	SEC 150 mg		103	61	59.2	NR	NR	NR	NR
	PBO		52	27	51.9	NR	NR	NR	NR
EXCEED	SEC 300 mg	Week 52	426	330	77	32†	8	17	4
	ADA 40 mg Q2W		427	338	79	28†	7	32	7
Genovese 2007	PBO	Week 12	49	39	79.6	2	4.1	2	4.1
	ADA 40 mg Q2W		51	27	52.9	*1*	2	*1*	2
	ADA 40 mg Q2W	Week 24	97	53	54.6	*3*	3.1	*6*	6.2
GO-REVEAL	PBO	Week 14	113	NR	NR	NR	NR	4	3.5
	GOL 50 mg Q4W		146	NR	NR	NR	NR	2	1.36
	GOL 100 mg Q4W		146	NR	NR	NR	NR	2	1.36
	PBO	Week 24	113	67	59	7	6	NR	NR
	GOL 50 mg Q4W		146	99	68	3	2	NR	NR
	GOL 100 mg Q4W		146	95	65	4	3	4	3
	GOL 50 mg/100 mg Q4W		292	196	67	7	2	NR	NR
IMPACT	INF 5 mg/kg at 0, 2, 6 & 14 weeks	Week 16	52	38	73	1	2	2	***3.8***
	PBO		51	33	65	1	2	1	***2***
	INF 5 mg/kg at 0, 2, 6 & 14 weeks	Week 50	49	41	84	8	16	3	***4***
	PBO		50	44	88	6	12	4	***8***

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE related discontinuations	
				n	%	n	%	n	%
IMPACT-2	INF 5 mg/kg at 0, 2, 6 & 14 weeks	Week 24	150	100	67	13	9	6	4
	PBO		97	65	67	6	6	1	1
	INF 5 mg/kg at 0, 2, 6 & 14 weeks	Week 54	90	**76**	85	22	11.5	NR	NR
	PBO		83	NR	NR	NR	NR	NR	NR
Mease 2000	PBO	Week 12	30	NR	NR	1	***3.3***	NR	NR
	ETN 25 mg Q2W		30	NR	NR	0	0	NR	NR
Mease 2004	ETN 25 mg Q2W	Week 24	101	NR	NR	4	***3.9***	1	***0.9***
	PBO		104	NR	NR	4	***3.8***	1	***0.9***
Mease 2018	ABT-122 120 mg QW	Week 12	71	33	46.5	0	0	0	0
	ABT-122 240 mg QW		73	31	42.5	1	1.4	0	0
	ADA 40 mg EOW		72	38	52.8	0	0	0	0
	PBO		24	11	45.8	1	4.2	0	0
OPAL Broaden (NCT01877668)	PBO	Week 13	105	37	35	1	1	1	1
	TOFA 5 mg BID		107	42	39	3	3	3	3
	TOFA 10 mg BID		104	47	45	1	1	0	0
	ADA 40 mg Q2W		106	49	46	1	1	2	2
	PBO to TOFA 5 mg BID	Week 52	52	36	69	3	6	2	4
	PBO to TOFA 10 mg BID		53	34	64	4	8	2	4
	TOFA 5 mg BID		107	71	66	8	7	6	6
	TOFA 10 mg BID		104	74	71	4	4	3	3
	ADA 40 mg Q2W		106	76	72	9	8	4	4
PSUMMIT 1	PBO	Week 16	205	86	42	4	2	3	1.5
	UST 45 mg Q12W		205	82	40	4	2	1	0.5
	UST 90 mg Q12W		204	89	43.6	3	1.5	2	1

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE related discontinuations	
				n	%	n	%	n	%
	PBO	Week 24	205	102	49.8	5	2.4	7	3.4
	UST 45 mg Q12W		205	111	54.1	6	2.9	3	1.5
	UST 90 mg Q12W		204	106	52	3	1.5	3	1.5
SPIRIT H2H	IXE	Week 24	283	NR	NR	10	3.5	7	2.5
	ADA		283	NR	NR	24	8.5	13	4.6
	IXE	Week 52	283	209	73.9	12	4.2	12	4.2
	ADA		283	194	68.6	35	12.4	21	7.4

Key: AE, adverse events; ADA, adalimumab; APR, apremilast; BID, twice daily; BW, twice weekly; EOW, every other week; ETN, etanercept; GOL, golimumab; INF, infliximab; IXE, ixekizumab; NR, not reported; PBO, placebo; QD, once daily; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse events; SEC, secukinumab; UPA, upadacitinib; UST, Ustekinumab.

Notes: Bold and italic indicates calculated values

Source: Clinical systemic literature review report[13]

Table 33: Safety data in biologic-experienced populations

Trial name	Treatment	Timepoint	N	Any AEs		Any SAEs		AE related discontinuations	
				n	%	n	%	n	%
SELECT-PsA 2	PBO	Week 24	212	139	65.6	4	1.9	11	5.2
	UPA 15 mg		211	135	64	12	5.7	15	7.1
OPAL BEYOND	TOFA 5 mg BID	Week 13	131	72	55	1	1	2	2
	TOFA 10 mg BID		132	70	53	3	2	10	8
	PBO		131	58	44	3	2	5	4
	PBO to TOFA 5 mg BID	Week 26	66	40	61	2	3	2	3
	PBO to TOFA 10 mg BID		65	38	58	1	2	3	5
	TOFA 5 mg BID		131	93	71	5	4	5	4
	TOFA 10 mg BID		132	96	73	8	6	11	8
SPIRIT P2	PBO	Week 24	118	NR	NR	4	3	6	5
	IXE 80 mg Q4W		122	NR	NR	3	2	5	4
	IXE 80 mg Q2W		123	NR	NR	8	7	8	7

Key: AE, adverse events; BID, twice daily; IXE, ixekizumab; NR, not reported; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SAE, serious adverse events; TOFA, tofacitinib; UPA, upadacitinib.

Source: Clinical systemic literature review report[13]

Section B: Clarification on cost-effectiveness data

B1. Priority question. The company model assumes that the HAQ-DI benefit for responders to a specific bDMARD is maintained until patients stop taking the bDMARD. Please provide results from a scenario in which the HAQ-DI score for responders increases in line with the natural history of progression of untreated PsA from the end of the trial period onwards. Please also provide the model that generates these scenario results.

Company response:

After extensive consideration, AbbVie considers that the scenario requested in question B1 is not clinically plausible, based on clinical opinion, new long-term evidence for upadacitinib, and prior validation of the assumption. These factors are described in more detail below. Taken together, they provide a robust basis upon which to support the assumption of zero disease progression beyond the trial period, and in which HAQ-DI progression in line with natural history of untreated disease is clinically implausible. As such, AbbVie consider that the request is neither clinically plausible nor supported by evidence from upadacitinib or other comparators and is likely to provide more biased ICER estimates than the existing assumption.

1. <u>Clinical opinion</u>

Clinical validation of the request was sought on 22 January 2021 from a UK rheumatologist. The clinician considered that the proposed scenario lacks clinical plausibility; it was outlined that in a situation in which a patient is progressing in line with natural history for untreated PsA (i.e., a rate of 0.072), there is no scenario in which this patient would be maintained on treatment – they would be rapidly switched to an alternative advanced therapy. The expert did acknowledge that some HAQ-DI progression may occur while responding to treatment, as all people experience a decline in function with age that is captured by the HAQ-DI; this was explored by Sokka et al. (2006) within a rheumatoid arthritis population, in which HAQ-DI progression was observed to be largely age-related.[14] In this study, a very small HAQ-DI progression rate was observed, almost all of which was attributable to

individuals over the age of 70 years (patients with rheumatoid arthritis and controls). In contrast, the patient population modelled in the submitted analysis enter with a mean age of 51.5 years, based on the SELECT-PsA 1 and SELECT-PsA 2 populations, which were considered generalizable to the UK PsA population by UK clinicians during an Advisory Board meeting held in May 2020 (see Sections B.2.3.1.2 and B.2.3.2.2 of the company submission).[15] The mean age from SELECT-PsA 1 and SELECT-PsA 2 is also similar to the mean age of 49.4 years, reported in a study by Tillet et al. (2017) who identified PsA patients from the Clinical Practice Research Datalink – which contains anonymized longitudinal medical records for ~11.7 million individuals from UK primary care.[17] As such, the clinical expert considered that it is implausible to include any age-related HAQ-DI deterioration in this population, and furthermore that a rate of 0.072 based on the natural history of untreated disease was also considered implausible as patients would be swapped to an alternative therapy in such situations.

2. Long-term evidence demonstrating maintained HAQ-DI benefits in patients receiving upadacitinib for up to 56 weeks

Additional data describing the HAQ-DI change from baseline up to 56 weeks is now available for a proportion of patients in the upadacitinib trials, SELECT-PsA 1 and SELECT-PsA 2. These data are presented in Appendices Table 35 and Table 36 and Figure 3 and Figure 4 below, and suggest a maintenance of HAQ-DI response beyond the initial 12-week trial period. It is important to recognise the limitations in these data – patients receiving placebo crossed over to upadacitinib at Week 24, and (given the time constraints) no formal crossover analysis has been performed. Nonetheless, these data further highlight the implausibility of HAQ-DI progression in line with the natural history of untreated patients.

Figure 3: Change from baseline to Week 56 in HAQ-DI (SELECT-PsA 1, FAS, AO)

Key: ADA, adalimumab; AO, as observed; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; PBO, placebo; UPA, upadacitinib.

Notes: Grey dotted line denotes when patients randomized to PBO switched to UPA 15 mg (Week 24)

Source: SELECT-PsA 1 clinical study report.[1]

Figure 4: Change from baseline to Week 56 in HAQ-DI (SELECT-PsA 2, FAS, AO)

Key: AO, as observed; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; PBO, placebo; UPA, upadacitinib.
Notes: Grey dotted line denotes when patients randomized to PBO switched to UPA 15 mg (Week 24)
Source: SELECT-PsA 2 clinical study report.[3]

3. Validation of the assumption by the York assessment group in TA199

Finally, in NICE multiple technology appraisal 199 (TA199), in the first revision of the earlier PsA model and in recognition of the limited evidence available, the assessment group (the Centre for Reviews and Dissemination/Centre for Health Economics, University of York) performed an expert opinion elicitation study in order to validate the assumption that HAQ-DI benefit is maintained while patients remain on a specific bDMARD after the trial period. Expert opinion was obtained in the form of a spreadsheet-based elicitation exercise that was designed to generate estimates for four topics of interest: initial HAQ change, disease progression while responding to treatment, disease progression for the 3-months following a relapse and longer-term disease progression following withdrawal. The histogram approach was used in the elicitation whereby a discretized numerical scale was pre-defined, and experts were asked to place 20 crosses on a frequency chart, representing their beliefs about the distribution of a particular quantity; each cross represented 5% of the distribution. Questionnaire responses were received from five experts. Regarding the

estimation of disease progression while responding to treatment, four out of the five experts believed that HAQ progression for responders would be negative, that is patients would continue to improve over time while receiving biologics.

In addition, the assessment group further explored the available evidence and highlighted observational evidence from national biologics registers which suggested that HAQ and health utility remain stable for PsA patients while on biologics. Gulfe (2009) analysed data from 574 patients in Southern Sweden between May 2002 and December 2008 and found health utilities remained largely unchanged for PsA over 7 years.[16] Considering the expert elicitation exercise and observational evidence in parallel, the TA199 assessment group assumed that HAQ-DI benefit is maintained for patients responding to biological treatment, i.e.- the rate of change of HAQ-DI for patients on biological therapies was zero, in its base case model.

AbbVie acknowledges the limitations of relying on this approach, given that the assessment group only considered tumour necrosis factor α (TNF-α) inhibitors (as they were the only available therapies at the time) and the sources of data are now fairly old. Nonetheless, the assumption has been consistently applied through recent appraisals in PsA, including for non-TNFα inhibitors and by the York assessment group again in the second update to the model in TA445 in 2017.

B2. Priority question. Please provide supporting evidence for the following assumptions: (i) the HAQ-DI benefit for responders to a specific bDMARD is maintained until patients stop taking that bDMARD and (ii) any increase in HAQ-DI score following the trial period for responders to bDMARDs is the same for all bDMARDs.

Company response:

With regard to part (i) of this question, justification for the assumption that response to a specific bDMARD is maintained until discontinuation is included in the answer to B1, above. For part (ii), evidence in support of a similar maintenance of HAQ-DI score amongst responders is limited, given the lack of head-to-head data in PsA. Nonetheless, the Week 56 HAQ-DI data collected in SELECT-PsA 1 and presented in the response to question B1 above demonstrates that ADA provides a similar

trend to UPA. In addition, the model does capture differences in HAQ-DI response as described in Section B.3.3.2 of the company submission, such that the HAQ-DI benefit of each treatment is specific to that treatment and conditional on PsARC response (PsARC response is also treatment specific). AbbVie believes that to subsequently assume a different rate of progression for different treatments would introduce greater uncertainty, and therefore in the absence of better evidence we have applied a common assumption across all comparators.

The clinical expert considered this approach to be most appropriate and highlighted the clinical heterogeneity of PsA in terms of patient characteristics and treatment response. As described above, the alternative scenario proposed by the ERG is not clinically plausible and does not align with UK clinical practice, while we have provided additional evidence to support the precedent assumption.

Section C: Textual clarification and additional points

Quality assessment

C1. Please clarify whether the quality assessments of the SELECT-PsA 1 and SELECT-PsA 2 trials, and the other trials included in the NMAs, were performed independently by two reviewers.

Company response:

Quality assessment for all trials in the NMA, with the exception of SELECT-PsA 1 and SELECT-PsA 2, were performed independently by two reviewers. At the time of review, SELECT-PsA 1 and SELECT-PsA 2 were not publicly available and could not assessed within the same sample. Regardless, a formal quality assessment for SELECT-PsA 1 and SELECT-PsA 2 trials has been conducted, and is described in Section B.2.5 of the company submission.

C2. The results of a quality assessment of studies included in the NMAs are shown in the CS, Appendix v2 (Table 15). Are these results based on the publications

referenced in the CS, Appendix v2 (Table 12), or were any additional data sources used?

Company response:

Yes, the results of the quality assessment of studies included in the NMA (reported in Table 15 of the CS appendix v2) were performed on the primary publications listed in Table 12 of the CS appendix v2. A number of linked publications associated with the primary publications were also captured in the clinical SLR, and these are described in Table 34 below; the linked secondary publication references refer to the reference list from the clinical SLR submitted alongside this response.

Table 34. List of primary publications for studies included in the NMA and their associated secondary references

Trial name (reference)	Population			Secondary publications references
	Mixed	Biologic naïve	Biologic experienced	
ACTIVE (1)		✓		(2-5)
ADEPT (6)		✓		(7-36)
CHOICE (54)		✓		-
FUTURE 2 (100)	✓	✓	✓	(101-149)
FUTURE 3 (150)	✓	✓	✓	(151)
FUTURE 4 (152)	✓	✓	✓	(153-155)
FUTURE 5 (156)	✓	✓	✓	(157-164)
Genovese 2007 (165)		✓		-
GO-REVEAL (168)		✓		(169-204)
IMPACT (205)		✓		(206, 207)
IMPACT-2 (208)		✓		(209-215)
Mease 2000 (216)		✓		(217)
Mease 2004 (218)		✓		(219-221)
Mease 2018 (223)		✓		(224, 225)
OPAL BEYOND (234)			✓	(235-239)
OPAL Broaden (240)		✓		(241-256)
PALACE 1 (257)	✓	✓	✓	(258-275)
PALACE 2 (276)	✓	✓	✓	(277)
PALACE 3 (278)	✓	✓	✓	(279-290)
PSUMMIT 1 (291)		✓		(292-310)
PSUMMIT-2 (311)	✓	✓	✓	(312-323)
RAPID PSA (324)	✓	✓	✓	(325-366)
SELECT-PsA-1 (367)		✓		-
SELECT-PSA-2 (368)			✓	-
SPIRIT H2H (369)		✓		(370-381)
SPIRIT- P1 (382)		✓		(383-443)
SPIRIT- P2 (444)			✓	(445-464)

Appendices

HAQ-DI data from at each treatment visit from baseline up to Week 56 is summarized for SELECT-PsA 1 in Table 35 and SELECT-PsA 2 in Table 36.

Table 35: Change from baseline to Week 56 in HAQ-DI (SELECT-PsA 1, FAS, AO)

	N	Baseline mean	Visit mean	Change from baseline		
				Within group LS mean (95% CI)[a]	Between group (UPA- ADA)	
					LS mean diff (95% CI)[a]	P-value[a]
Week 2						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	N	Baseline mean	Visit mean	Change from baseline		
				Within group LS mean (95% CI)[a]	Between group (UPA- ADA)	
					LS mean diff (95% CI)[a]	P-value[a]
Week 16						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36						
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44						

	N	Baseline mean	Visit mean	Change from baseline		
				Within group LS mean (95% CI)[a]	Between group (UPA- ADA)	
					LS mean diff (95% CI)[a]	P-value[a]
PBO to UPA 15 mg	[redacted]					
ADA 40 mg	[redacted]					
UPA 15 mg	[redacted]					
Week 56						
PBO to UPA 15 mg	[redacted]					
ADA 40 mg	[redacted]					
UPA 15 mg	[redacted]					

Key: ADA, adalimumab; AO, as observed; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; PBO, placebo; UPA, upadacitinib.

Notes: Patients randomized to PBO switched to UPA 15 mg at Week 24 and their data up to Week 24 are under PBO exposure.

[a] Within-group LS mean and 95% CI, and between group LS mean difference and 95% CI, and nominal p-value are based on mixed-effect model repeated measurement analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.

* Statistically significant at 0.05 level.

Source: SELECT-PsA 1 clinical study report.[1]

Table 36: Change from baseline to Week 56 in HAQ-DI (SELECT-PsA 2, FAS, AO)

	N	Baseline mean	Visit mean	Within-group LS mean (95% CI)[a]
Week 2				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 8				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 12				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 16				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 20				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 28				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 32				

	N	Baseline mean	Visit mean	Within-group LS mean (95% CI)[a]
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 36				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 44				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Week 56				
PBO to UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]

Key: AO, as observed; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire - Disability Index; LS, least squares; PBO, placebo; UPA, upadacitinib.

Notes: Patients randomized to PBO to UPA 15 mg switched to UPA 15 mg at Week 24 and their data up to Week 24 are under PBO exposure.

[a] Within-group LS mean and 95% CI, and between group LS mean difference and 95% CI, and nominal p-value are based on mixed-effect model repeated measurement analysis with unstructured variance-covariance matrix, including treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) as fixed factors and the continuous fixed covariate of baseline measurement.

Source: SELECT-PsA 2 clinical study report.[3]

References

1. AbbVie. Clinical Study Report M15-572. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 2020.

2. Bretz F, Maurer W, Brannath W and Posch M. A graphical approach to sequentially rejective multiple test procedures. *Statistics in medicine*. 2009; 28(4):586-604.

3. AbbVie. Clinical Study Report M15-554. A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease-Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. 2020.

4. Mease P, Lertratanakul A, Anderson J, et al. Upadacitinib for Psoriatic Arthritis Refractory to Biologics: SELECT-PsA 2. *Ann Rheum Dis*. 2020.

5. Koch G. Comments on 'Current issues in non-inferiority trials' by Thomas R. Fleming. *Stat Med*. 2008; 27(3).

6. Althunian TA, de Boer A, Groenwold RH and Klungel OH. Defining the noninferiority margin and analysing noninferiority: an overview. *British journal of clinical pharmacology*. 2017; 83(8):1636-42.

7. FDA. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials. Accessed: 25 Jan 2021.

8. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2005; 52(10):3279-89.

9. Genovese M, Mease P, Thomson G, et al. Safety and Efficacy of Adalimumab in Treatment of Patients With Psoriatic Arthritis Who Had Failed Disease Modifying Antirheumatic Drug Therapy. *The Journal of Rheumatology*. 2007; 34(5):1040-50.

10. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis*. 2017; 76(1):79-87.

11. Mease P, Hall S, FitzGerald O, et al. OP0216 efficacy and safety of tofacitinib, an oral janus kinase inhibitor, or adalimumab in patients with active psoriatic arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (CSDMARDS): a randomised, placebo-controlled, phase 3 trial. BMJ Publishing Group Ltd, 2017.

12. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. *Arthritis Research & Therapy*. 2016; 18(1):1-12.

13. AbbVie. Systematic literature review of clinical evidence in the management of patients with moderate-to-severe psoriatic arthritis. 2020. Data on File.

14. Sokka T, Kautiainen H, Hannonen P and Pincus T. Changes in Health Assessment Questionnaire disability scores over five years in patients with rheumatoid arthritis compared with the general population. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2006; 54(10):3113-8.

15. AbbVie. Upadacitinib in psoriatic arthritis HTA advisory board. May 2020 2020. Data on File.

16. Gülfe A, Kristensen LE, Saxne T, et al. Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden. *Annals of the Rheumatic Diseases*. 2009.

17. Tillett W, Charlton R, Nightingale A, et al. Interval between onset of psoriasis and psoriatic arthritis comparing the UK Clinical Practice Research Datalink with a hospital-based cohort. Rheumatology. 2017; 56(12):2109-13.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

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 extends much further than that of the traditional 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 psoriasis or psoriatic arthritis to communicate with one another via online forums on their own websites (~14,000 registered users), and Social Media (~6,500 registered users on closed Facebook group). The main Psoriasis Association website averages 45,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to "raising awareness" include Twitter (~12,000 followers) and Instagram (~7,250 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.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	Yes – Abbvie - £1,500 corporate membership, £6,500 core funding, £5,000 emergency COVID-19 support Amgen – £1,500 corporate membership, £8,500 emergency COVID-19 support Eli Lilly – £1,500 corporate membership, £5,000 emergency COVID-19 support Janssen – £412.50 honorarium, £5,000 emergency COVID-19 support, £10,000 core funding UCB – £1,500 corporate membership, £2,500 emergency COVID-19 support, £2,193.91 matched fundraising

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.	
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 (519,922 visitors in 2020) helpline (1892 enquiries in 2020) online forums (15,829 registered users in 2020) social media channels (including Facebook Group (this is a closed group with 6,881 registered users in 2020), Twitter (13,197 followers in 2020) and Instagram (10,344 followers in 2020) 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 psoriatic arthritis and are part way through supporting a Priority Setting Partnership on psoriatic arthritis specifically.
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 (and 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. Many people with psoriatic arthritis have a level of skin involvement also. A patient explains "***If today's pain doesn't bring you to your knees, tomorrow's rashes will cripple you with self-awareness***."

	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. A patient explains **"In 2019, about 20 years after the initial (skin) diagnosis, I was also diagnosed with psoriatic arthritis. This diagnosis was the result of 2 years of toe pains and swelling, limping, multiple doctors visits, test and scans."** 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. A patient explains **"Four years ago I became so ill with the arthritis I couldn't walk and went to the Rheumatologist in desperation…four years on, and now aged 55, I am managing my psoriasis and my psoriatic arthritis and am able to do more and have restarted the Couch to 5K! How happy this makes me is immeasurable."** 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 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. However, the concern regarding the limit of biologics available to individual patients in many areas may prevent earlier access to the more targeted therapies. 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.
8. Is there an unmet need for patients with this condition?	Yes – sadly no one treatment yet works for all patients over their lifetime, and so new treatments are required in order to treat PsA as this experience of a 38 year old patient illustrates – "**10 years (after psoriasis diagnosis) I started getting pains in my feet to the point I could not walk down the stairs without struggling. I went to the doctors to be told it was gout and given medication for it. A couple of years later I moved to a different area and had to change doctors. The pains in my feet hadn't changed so I went and spoke to a doctor who specialised in skin problems. The doctor referred me to the arthritis clinic at the hospital. The doctor looked at my joints and feet and said "yes you have psoriatic arthritis", and started me on a drug called methotrexate. This meant having blood tests every two weeks because of the side effects, but they were affecting my liver and kidneys so they stopped them and moved me on to a drug called sulfasalazine, but I had to stop them because the orange dye kept on giving me bad headaches.**"

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	For many, a once daily oral / tablet medication is much more preferable than a twice daily tablet, or injection / infusion.
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.
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.	People with a fear of injections, or who do not wish to go to hospital for regular infusions would benefit perhaps from using this therapy first. However, people who have a difficulty swallowing tablets may prefer an injectable therapy. Therefore it is important to consider both patient choice and clinician expertise and experience when prescribing any therapy.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
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
- There are currently few treatments available to treat psoriatic arthritis over the life time, and so an extension to the treatment armoury is definitely needed
- Oral / tablet medication is preferable to injections for many people

• 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

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

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

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	Living with psoriatic arthritis can vary enormously. Many people are able to manage their condition adequately and live life that is minimally impacted. For others the disease is a complete blight with every aspect of their life affected. It is also not obvious which individuals will have disease course that is stable, as the condition flairs and remits in unpredictable patterns.

experience when caring for someone with the condition?	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. 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: *“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?	As a JAK inhibitor, upadacitinib offers a different target, which is administered as an oral treatment, therefore there are less issues regarding storage and the need to self-inject, which some patients may see as an advantage over other similar class therapies, particularly if they have dexterity issues, which given psoriatic arthritis often affects the hands and fingers and or have a phobia of needles and injections.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with any treatment the risk and benefit will be of most concern to patients, in the trial data there were reported cases of herpes zoster and a few malignancies in the higher dosage regime. Patients are willing to accept adverse events, if the benefit of a therapy is substantial, although an ACR2O improvement may not be recognised by patients as being that particularly significant.
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.	Those who are unable to self-inject may find an oral treatment more beneficial than similar pathway/class self-administered injectable therapies.

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

Professional organisation submission

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society for Rheumatology**

3. Job title or position	**Consultant rheumatologist** [redacted]
4. Are you (please tick all that apply):	**yes** an employee or representative of a healthcare professional organisation that represents clinicians? **yes** a specialist in the treatment of people with this condition? **yes** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society for Rheumatology is the leading UK specialist charitable medical society for rheumatology and musculoskeletal care professionals. It is funded by membership subscription from health professionals in the UK and abroad, rheumatology conferences and training courses.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The British Society for Rheumatology is responsible for four disease patient registers across the UK**.** These registries include the BSR biologics registries in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis. These are funded by contractual arrangements between pharmaceutical companies, BSR and academic institutions responsible for the operational and academic elements of the registries. A wide variety of pharmaceutical companies are involved in supporting these registries including: Amgen, Eli Lily and Company and Abbvie. We also receive funding for events from these relevant companies: Abbvie, Accord Healthcare, Amgen, Biogen, Celgene, and Eli Lily and Company.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to control joint and entheseal inflammation in order to prevent progression of joint damage, pain and disability

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	There are a number of different measures of treatment response (reduction in clinical inflammation) used in psoriatic arthritis. These include: Reduction in swollen and tender joint counts (66/68) A common level of clinical evaluation of well controlled PsA disease is the minimal disease activity (MDA) MDA is achieved if 5 of the following criteria are met (see bracketed information below): Patient Global Activity VAS [0–100]: (Score ≤20) Patient pain VAS [0–100]: (Score ≤15) HAQ-DI [0–3]: (Score ≤0.5) Tender joint count [0–68]: (Score ≤1) Swollen Joint count [0–66]: (Score ≤1) PASI [0–72] or BSA [0–100]: (Score ≤1 or ≤3%, respectively) Leeds enthesitis index (LEI) [0 - 6]: (Score ≤1) Evaluation of psoriatic arthritis should include a broad evaluation of clinical features as described in: (Ogdie A et al J Rheumatol 2017; 44:697–700; doi:10.3899/jrheum.170150) Defining Outcome Measures for Psoriatic Arthritis: A Report from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) - Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis (PsA) Core Set working group, who recently published the updated 2016 psoriatic arthritis (PsA) core domain set, a set of disease features that should be measured in all clinical trials

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The number of available biologic treatment options for patients with psoriatic arthritis (PsA) unresponsive to DMARDs is lower than in some other inflammatory conditions (such as rheumatoid arthritis). NICE approved PsA treatments include some of the anti-TNF therapies, two anti-IL17 (secukinumab/ixekizumab), one anti IL-12 (ustekinumab), one JAK1/3 inhibitor (tofacitinib) and apremilast. An additional effective JAK inhibitor for use in psoriatic arthritis would provide an extremely useful additional option for patients (particularly those who have aversion to needles as many of the above options are injectable)
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	NSAIDs and DMARDs (methotrexate, sulfasalazine en, leflunomide and occasionally ciclosporin) Corticosteroids (predominantly intramuscular / intraarticular) If patients are poorly controlled on standard DMARD therapy, then they become eligible for biologic/small molecule therapy which include: Anti TNF therapy (etanercept, adalumimab, etc), two anti-IL17 (secukinumab/ixekizumab), one anti IL-12 (ustekinumab), one JAK1/3 inhibitor (tofacitinib) and apremilast.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE TAs NICE clinical guidelines for spondyloarthritis (and psoriasis for some situations) BSR guideline for psoriatic arthritis *https://academic.oup.com/rheumatology/article/52/10/1754/1792324* BSR guideline for DMARDs EULAR guideline for psoriatic arthritis http://ard.bmj.com/content/early/2015/12/07/annrheumdis-2015-208337

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is reasonably well defined There are nuances within the anti-TNF NICE TA which are sometimes overlooked / not appreciated by some rheumatologists (such as patients being able to remain on anti-TNF if they are proven skin psoriasis responders (on PASI) even if they are sub-optimally responding from an arthritis perspective). There is a generalised issue internationally with rheumatoid arthritis severity scores (such as DAS-28) being used in PsA – where they frequently fail to reflect true disease activity and are not validated.
• What impact would the technology have on the current pathway of care?	This technology would be an additional option to the post DMARD biologic/small molecule therapies and would probably fit in alongside these in the current care pathways. An additional choice of an effective oral therapy (probably similar to Tofacitinib and more effective than Apremilast) would be useful for patients with poor hand function and needle phobia.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There are differences between JAK inhibitors regarding effect and side effect profiles – related to the proportions of JAK1/2/3 and TYK2 that they suppress. However, in practice it is likely that Upadacitinib would be used in a similar way to current Tofacitib in psoriatic arthritis
• How does healthcare resource use differ between the technology and current care?	No change
• In what clinical setting should the technology be used? (For example,	Secondary care general rheumatology clinics Specialist psoriatic arthritis / spondyloarthritis clinincs

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No change from current skill levels or facilities required for other small molecule drugs used in psoriatic arthritis
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – for patients unresponsive to DMARDs, anti-TNF and possibly tofacitinib
• Do you expect the technology to increase length of life more than current care?	Yes – poorly controlled inflammatory arthritis not only causes pain, joint damage and disability - but also has an impact on patient health more globally (including increases in heart attacks, strokes and probably cancer). Controlling the inflammation related to PsA is likely to reduce cardiovascular morbidity and mortality
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – poorly controlled inflammatory arthritis causes pain, joint damage and disability These impacts on a wide variety of patient measures of quality of life including: pain, fatigue, work stability, social functioning, psychological health and body image.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	For patients with PsA failing DMARDs, who also have parallel issues with injectable administration of medicines (needle phobia or poor hand function), then having an additional effective oral medication to control PsA would be very beneficial.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Almost identical use to currently used tofacitinib in terms of expertise, monitoring and acceptability

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that there will be similar rules to the NICE response criteria in PsA for anti-TNF, tofacitininb and the other NICE approved biologic agents
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	JAK inhibitors do improve skin psoriasis as well as arthritis - so there will be additional benefits to patients skin psoriasis, which are not particularly well reflected in QALY calculations (if these are based on EQ5D). Softer benefits (such as improvements in fatigue) may not be captured well by EQ5D and hence QALYs Oral medications will not require the same level of infrastructure (sharps bins, regular homecare deliveries etc.)
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is a useful additional JAK inhibitor medicine, but it is not particularly more innovative than the already established and prescribed tofacitinib. However, this will not be quite the same as other 'me too' introduction / launches of medication. Response rates and side effect profiles can be more heterogeneous in JAK inhibitors as a group, as there are differences between the differing JAK inhibitors related to the amount of JAK1/2/3 and TYK 2 inhibition.

• Is the technology a 'step-change' in the management of the condition?	This is a useful additional JAK inhibitor, but it is not a step change
• Does the use of the technology address any particular unmet need of the patient population?	No more than tofacitinib (unless patients are non responders or have experienced side effects with this medication). It is likely to be more effective than Apremilast the alternative oral small molecule approved by NICE in PsA
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Increased infection risk – may precipitate higher frequency of infection and / or more severe infections in some individuals (this is a similar risk to the majority of immune modulating medications used to control PsA) JAK inhibitors including upadacitinib can cause: a) lipid levels to raise, which long term could increase cardiovascular risks if not acted upon b) herpes infection re-activation – although this would usually be dermatological re-activation, more serious systemic infection could occur c) increased DVT/PE risk which can be life threatening Upadacitinib specifically does appear to increase CK levels (muscle inflammation) in a small percentage of recipients – this tends to be transient in most (which suggests that it might long term in some, which could cause long term myalgia or theoretically even impaired muscle function if not acted upon)

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Generally, yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Many of the trials were of sufficient duration to provide some data on long term outcome (1-2 years)
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Too early to tell at this point as upadacitinib is not widely used in the UK and RA related NICE approval has only been granted in late 2020 The other JAK inhibitor (Tofacitinib) is growing in popularity amongst clinicians due to relative ease of administration and benefit for skin psoriasis
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None apparent
21b. Consider whether these issues are different from issues with current care and why.	None apparent
Key messages	

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

- Upadacitinib would be a useful addition to the treatment options for PsA patients unresponsive to DMARDs
- Measurement of response could include a reduction in swollen and tender joint counts (66/68) and the minimal disease activity (MDA)
- JAK inhibitors may precipitate reactivation of Herpes infections, raise lipids, initiate drug induced muscle inflammation and cause DVT/Pes. None of these side effects occur more commonly in PsA patients (prior to upadacitinib administration) than in the general population.
- For patients with PsA and difficulty administering injectable medications, upadacitinib will be a useful addition to present therapeutic options.
- It may be worth considering mirroring the nuances within the anti-TNF NICE TA 199 (including an option that proven skin psoriasis responders (on PASI) could continue therapy even if they are sub-optimally responding from an arthritis perspective).

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.

……

ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR133071

Completed 25 February 2021
Updated 17 March 2021

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Katherine Edwards, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Marty Chaplin, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Sophie Beale, Associate Senior Researcher, LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Tosin Lambe, Health Economic Modeller, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Nicola Goodson, Consultant Rheumatologist, Liverpool University, NHS Foundation Trust

Correspondence to: Katherine Edwards, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 25 February 2021. Updated 17 March 2021

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 133071

Acknowledgements: The authors would like to thank Dr Laura Coates, Associate Professor and NIHR Clinical Scientist, University of Oxford, Oxford, who provided feedback on a draft version of 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

Declared competing interests of the authors:

Dr Goodson has received reimbursement for attending a symposium from Novartis Pharmaceuticals Ltd, AbbVie and Janssen, as well as consultancy fees from Novartis Pharmaceuticals Ltd, UCB and Janssen. She has also received fees for speaking from AbbVie, hospitality fees from Pfizer, AbbVie, UCB, Novartis Pharmaceuticals Ltd and Janssen, and funds for research from Novartis Pharmaceuticals Ltd

Dr Coates has received reimbursement for attending a symposium from Janssen and AbbVie, as well as consultancy fees from AbbVie, Amgen, BMS, Boehringer, Ingelheim, Celgene, Domain, Gilead, Janssen, Lilly, Novartis, Pfizer, Serac and UCB. She has also received fees for speaking and hospitality from AbbVie, Amgen, BMS, Biogen, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and UCB, fees for organising education from UCB, and funds for research from AbbVie, Amgen, Celgene, Gilead, Janssen, Lilly, Novartis, Pfizer and UCB

This report should be referenced as follows: Edwards K, Mahon J, Chaplin M, Fleeman N, Beale S, Boland A, Lambe T, Dundar Y, Marsden A and Goodson N. Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]: A Single Technology Appraisal. LRiG, University of Liverpool, 2021

Contributions of authors:

Katherine Edwards	Project manager, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Nigel Fleeman	Critical appraisal of the clinical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Summary of the economic evidence
Yenal Dundar	Critical appraisal of the company's search strategies
Ashley Marsden	Critical appraisal of the company submission
Nicola Goodson	Clinical advice and critical appraisal of the clinical evidence

Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC	Appraisal committee
ACR	American College of Rheumatology
AE	Adverse events
bDMARD	Biologic disease-modifying anti-rheumatic drug
BSC	Best supportive care
CI	Confidence interval
CS	Company submission
csDMARD	Conventional-synthetic disease-modifying anti-rheumatic drug
CSR	Clinical study report
CT	Continuous treatment period health state
DMARD	Disease-modifying anti-rheumatic drug
eMIT	Electronic market information tool
EQ-5D-3L/5L	EuroQol-five dimensions-three levels/five levels
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
JAK	Janus kinase
mg	Milligrammes
MIMS	Monthly index of medical specialities
MOA	Mechanisms of action
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PAS	Patient Access Scheme
PASI	Psoriasis Area and Severity Index
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PSS	Personal Social Services
QALY	Quality adjusted life years
SAE	Serious adverse event
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TNF	Tumour necrosis factor
TP	Treatment period

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes an ERG scenario and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the ERG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICERs. Sections 1.3 to 1.6 explain the key issues identified by the ERG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the ERG.

All the issues outlined in this report represent the views of the ERG and are not the opinion of NICE.

1.1 Overview of the ERG's key issues

Summary of key issues

Issue	Summary of issues	Report sections
1	Clinical effectiveness evidence gaps	Section 2.3 and Section 3.2
2	Limited direct clinical effectiveness evidence	Section 2.3 and Section 3.2
3	Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs	Section 3.5.3 and Section 3.5.4
4	Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs	Section 3.5.3 and Section 3.5.4
5	Company model structure is simple and does not wholly reflect the real-world setting	Section 6.1
6	Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC	Section 6.1.1
7	Mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model	Section 6.2
8	Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment	Section 6.2.2
9	Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice	Section 6.3

HAQ-DI=Health Assessment Questionnaire-Disability Index; NMA=network meta-analysis; PsARC=Psoriasis Arthritis Response Criteria; TNF=tumour necrosis factor

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- improving quality of life by reducing levels of disability associated with psoriatic arthritis (PsA), as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
- length of life is not affected by treatment.

Overall, the technology is modelled to affect costs by:

- reducing the costs of treating disability associated with PsA.

The modelling assumptions, explored by the company (sensitivity and scenario analyses) that have the greatest effect on the ICERs per QALY gained are:

- constant annual discontinuation rate applied to all patients
- model time horizon.

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Clinical effectiveness evidence gaps

Report section	Section 2.3 and Section 3.2
Description of issue and why the ERG has identified it as important	There are a number of evidence gaps. No clinical effectiveness evidence is available: a. from the NMAs, for patients who had received one prior csDMARD, one of the sub-populations described in the final scope issued by NICE. Evidence for this sub-population was available from the SELECT-PsA 1 trial (for [redacted] of patients). This sub-population was not addressed in the company submission b. to support the assumption that the level of effectiveness of bDMARDs/tsDMARDs observed in the biologic-naïve population is the same for patients in whom TNF-alpha inhibitors are contraindicated or not tolerated c. to support the use of upadacitinib to treat the biologic-experienced population who have received prior treatment with a tsDMARD (apremilast or tofacitinib). Results (from subgroup analyses of SELECT-PsA 2 trial data) are available for patients who received prior TNF-alpha inhibitors or IL-17s are available d. by presence or severity of psoriasis in the company submission. However, company cost effectiveness results are presented by presence of concomitant psoriasis (no psoriasis, mild to moderate, moderate to severe) as determined by using a combination of BSA and PASI
What alternative approach has the ERG suggested?	a. No alternative approach. In NHS clinical practice, patients receive at least two csDMARDs before being offered a bDMARD/tsDMARD and previous NICE AC's have concluded that efficacy of bDMARDs/tsDMARD is not affected by number of prior csDMARDs b. No alternative approach. The ERG considers this assumption is appropriate c. No alternative approach. No data are available d. No alternative approach. The ERG alternative cost effectiveness results are also presented by disease severity
What is the expected effect on the cost effectiveness estimates?	The effect of these issues on cost effectiveness is not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for further information

BSA=body surface area; AC=Appraisal Committee; b=biologic; cs=conventional synthetic; DMARD=disease modifying anti-rheumatic drug; ERG=Evidence Review Group; PASI=Psoriasis Area and Severity Index; TNF=tumour necrosis factor; ts=targeted synthetic

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Limited direct clinical effectiveness evidence

Report section	Section 2.3 and Section 3.2
Description of issue and why the ERG has identified it as important	The SELECT-PsA 1 trial (biologic-naïve/contraindicated population) provides direct evidence for a comparison of the efficacy of upadacitinib versus adalimumab and of upadacitinib versus placebo. No direct evidence is available to allow comparison of upadacitinib with eight out of nine comparators listed in the final scope issued by NICE The SELECT-PsA 2 trial (biologic-experienced population) provides direct evidence for a comparison of upadacitinib versus placebo (assumed to represent BSC). No direct evidence is available to allow comparison of upadacitinib with five of the six comparators listed in the final scope issued by NICE
What alternative approach has the ERG suggested?	The ERG has not suggested an alternative approach. The company has carried out Week 12 NMAs to generate clinical effectiveness results for upadacitinib versus all the comparators listed in the NICE final scope (except certolizumab pegol as a comparator for the biologic-experienced population) Clinical advice to the ERG is that adalimumab is commonly the first bDMARD prescribed after at least two csDMARDs
What is the expected effect on the cost effectiveness estimates?	The effect of these issues on cost effectiveness is not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for further information

BSC=best supportive care; ERG=Evidence Review Group; NMA=network meta-analysis

Issue 3 Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs

Report section	Section 3.5.3 and Section 3.5.4
Description of issue and why the ERG has identified it as important	The company Week 12 NMAs have generated indirect evidence to allow comparisons of the clinical effectiveness of upadacitinib versus all the comparators listed in the final scope issued by NICE There are several sources of heterogeneity between the studies included in the Week 12 NMAs; this heterogeneity was accounted for by using random effect models The credible intervals around the observed effect point estimates were often wide and, therefore, it is not possible to draw definitive conclusions about the relative efficacy of upadacitinib from the company Week 12 NMA results
What alternative approach has the ERG suggested?	The company's approach was methodologically appropriate. There is no alternative approach that could be taken that would reduce the uncertainty around the company Week 12 NMA results
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness is not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for further information

ERG=Evidence Review Group; NMA=network meta-analysis

Issue 4 Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs

Report section	Section 3.5.3 and Section 3.5.4
Description of issue and why the ERG has identified it as important	The company's Week 12 biologic-experienced NMAs included evidence for all relevant comparators except certolizumab pegol. It was not possible to account for between trial heterogeneity due to the small number of trials in the biologic-experienced network. Furthermore, as the credible intervals around the observed effect point estimates were often wide, it is not possible to draw definitive conclusions about the relative efficacy of upadacitinib from the company Week 12 NMA results
What alternative approach has the ERG suggested?	The company's approach was methodologically appropriate. There is no alternative approach that could be taken that would reduce the uncertainty around the company Week 12 NMA results
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness is not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion for further information

ERG=Evidence Review Group; NMA=network meta-analysis

1.5 The cost effectiveness evidence: summary of the ERG's key issues

Issue 5 Company model structure is simple and does not wholly reflect the real-world setting

Report section	Section 6.1
Description of issue and why the ERG has identified it as important	The company model structure is a simplification of NHS clinical practice and does not take into account the complexity that arises from having multiple treatment options that may be prescribed in different sequences
What alternative approach has the ERG suggested?	The ERG has not suggested an alternative approach. There are insufficient robust clinical effectiveness data available to populate a more realistic model
What is the expected effect on the cost effectiveness estimates?	Failure to account for complexity in the company model means that company cost effectiveness results are unlikely to reflect the true cost effectiveness of upadacitinib in a real-world setting
What additional evidence or analyses might help to resolve this key issue?	None

Issue 6 Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC

Report section	Section 6.1.1
Description of issue and why the ERG has identified it as important	HAQ-DI is the main driver of company cost effectiveness results. However, for the following comparators, HAQ-DI conditional on PsARC results were not available from the company Week 12 NMAs and were therefore sourced from previous NICE TAs: • biological-naïve population: CZP, IXE, SEC (150mg and 300mg), TOF • biologic-experienced population: IXE, SEC 300mg, TOF. Using results from different sources without appropriate adjustments adds uncertainty to the company cost effectiveness results
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost effectiveness estimates?	High level of uncertainty around cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	None

CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire-Disability Index; IXE=ixekizumab; mg=milligrams; NMA=network meta-analysis; PsARC=Psoriasis Arthritis Response Criteria; SEC=secukinumab; TA=technology appraisal; TOF=tofacitinib

Issue 7 Mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model

Report section	Section 6.2.1
Description of issue and why the ERG has identified it as important	The company model does not reflect change in HAQ-DI conditional on PsARC score as described in the company submission (and as described in previous NICE technology appraisals)
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness results is not known
What additional evidence or analyses might help to resolve this key issue?	The company modelling approach should be changed to match the description in the company submission, or vice versa

HAQ-DI=Health Assessment Questionnaire-Disability Index; PsARC=Psoriasis Arthritis Response Criteria

Issue 8 Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment

Report section	Section 6.2.2
Description of issue and why the ERG has identified it as important	The company has not presented a scenario where the effect of HAQ-DI increases for patients who respond to a bDMARD/tsDMARD whilst receiving treatment. The ERG considers that results from such a scenario would have been informative
What alternative approach has the ERG suggested?	The ERG asked the company to implement this scenario (clarification question B1)
What is the expected effect on the cost effectiveness estimates?	The effect on cost effectiveness results is not known
What additional evidence or analyses might help to resolve this key issue?	The results from this scenario would be informative

b=biologic; ERG=Evidence Review Group; DMARD=disease modifying anti-rheumatic drug; HAQ-DI=Health Assessment Questionnaire-Disability Index; PsARC=Psoriasis Arthritis Response Criteria; ts=targeted synthetic

Issue 9 Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice

Report section	Section 6.3
Description of issue and why the ERG has identified it as important	The ERG considers that, in NHS clinical practice, the TNF-alpha inhibitor-contraindicated population generally receive more than one line of treatment and BSC is generally not an appropriate first-line treatment option for this population
What alternative approach has the ERG suggested?	The ERG implemented a scenario where the TNF-alpha inhibitor-contraindicated population received two lines of treatment and BSC was not a comparator
What is the expected effect on the cost effectiveness estimates?	ERG scenario results (using PAS price for upadacitinib and list price for other drugs) did not alter the company's cost effectiveness conclusions for this population
What additional evidence or analyses might help to resolve this key issue?	None

BSC=best supportive care; ERG=Evidence Review Group; PAS=Patient Access Scheme; TNF=tumour necrosis factor

1.6 Summary of company and ERG's cost effectiveness results

The company's cost effectiveness results are shown in Table A (biologic-naïve population), Table B (biologic-experienced population) and Table C (TNF-alpha inhibitor-contraindicated population).

The ERG has only generated alternative cost effectiveness results for the TNF-alpha inhibitor-contraindicated population, these results are shown in Table D.

Table A Company fully incremental and pairwise deterministic base case results for biologic-naïve population (PAS price for upadacitinib)

Technologies/ Severity	Total		Incremental, versus adalimumab		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
Adalimumab	[redacted]	[redacted]	-	-	-	£19,322
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,322	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£57,118	£57,118*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	£229,092*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	Upadacitinib is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£365,044	£113,594*
Mild-to-moderate						
Adalimumab	[redacted]	[redacted]	-	-	-	£17,980
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£17,980	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£64,577	£64,577*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	£274,601*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	Upadacitinib is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£271,574	£112,907*
Moderate-to-severe						
Adalimumab	[redacted]	[redacted]	-	-	-	£12,701
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£12,701	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant

Technologies/ Severity	Total		Incremental, versus adalimumab		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£86,662	£86,662*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	£353,052*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by etanercept	Upadacitinib is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£110,772	£97,333*

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
ICER=incremental cost effectiveness ratio; N/A=not applicable; PAS=Patient Access Scheme; QALY=quality adjusted life years
Source: CS, Table 79

Table B Company fully incremental and pairwise deterministic base case results for biologic-experienced population (PAS price for upadacitinib)

Technologies/ severity	Total		Incremental, versus BSC		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£11,513
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£11,513	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated by upadacitinib	£424,592*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£194,345	£194,345*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ixekizumab	£416,712*
Mild-to-moderate						
BSC	[redacted]	[redacted]	-	-	-	£9,775
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£9,775	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated by upadacitinib	£788,986*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£191,874	£191,874*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ixekizumab	£384,703*
Moderate-to-severe						
BSC	[redacted]	[redacted]	-	-	-	£6,165
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£6,165	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£177,669	£177,669*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ixekizumab	£269,436*

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
BSC=best supportive care; ext=extendedly; ICER=incremental cost effectiveness ratio; N/A=not applicable; PAS=Patient Access Scheme; QALY=quality adjusted life years
Source: CS, Table 80

Table C Company fully incremental and pairwise deterministic base case results for TNF-alpha inhibitor-contraindicated population or not tolerated (PAS price for upadacitinib)

Technologies/ severity	Total		Incremental, versus BSC		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£16,931
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£16,931	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£10,151,112	£10,151,112*
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by secukinumab	Upadacitinib is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by secukinumab	Upadacitinib is dominant
Mild-to-moderate						
BSC	[redacted]	[redacted]	-	-	-	£10,492
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£10,492	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£6,330,422	£6,330,422*
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by secukinumab	Upadacitinib is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by secukinumab	Upadacitinib is dominant
Moderate-to-severe						
BSC	[redacted]	[redacted]	-	-	-	£8,809
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£8,809	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
ICER=incremental cost effectiveness ratio; N/A=not applicable; PAS=Patient Access Scheme; QALY=quality adjusted life years; TNF=tumour necrosis factor
Source: CS, Table 81

Table D ERG scenario: patients in whom TNF-alpha inhibitors are contraindicated: ustekinumab given as second-line treatment (PAS price for upadacitinib)

Technologies/ severity	Total costs (£)	Total QALYs	Incremental costs (£) versus upadacitinib	Incremental QALYs versus upadacitinib	ICER fully incremental (£/QALY)	Pairwise ICER of upadacitinib vs comparator (£/QALY)
No psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Mild-to-moderate psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Moderate-to-severe psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by upadacitinib	Upadacitinib is dominant

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
BSC=best supportive care; ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; N/A=not applicable; PAS=Patient Access Scheme; QALY=quality adjusted life years; TNF=tumour necrosis factor
Source: ERG

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on the use of upadacitinib (RINVOQ™) to treat active psoriatic arthritis (PsA) after inadequate response to disease modifying anti-rheumatic drugs (DMARDs). In this Evidence Review Group (ERG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission.

PsA is a heterogeneous disease with a highly variable clinical presentation that is typically characterised by coexisting progression of arthritis and psoriasis. Axial involvement, i.e., where inflammation progresses to the spine and causes chronic back pain, is present in 25% to 70% of cases.[1,2] Other manifestations that may be present, depending on the activity and severity of the disease, include:

- dactylitis: inflammation of the entire finger or toe (present in almost half of patients with PsA)[3]
- enthesitis: inflammation of the sites where tendons or ligaments insert into the bone (present in over a third of patients with PsA)[4]
- psoriasis: inflammation of the skin which manifests as small, red, flaky patches and often precedes joint inflammation;[5] this is the most common extra-articular symptom[6] (clinical advice to the ERG is that this is present in approximately 70% to 80% of patients with PsA)
- nail disease: pitting and depression of the nail plate surface (present in two-thirds of patients with PsA).[7]

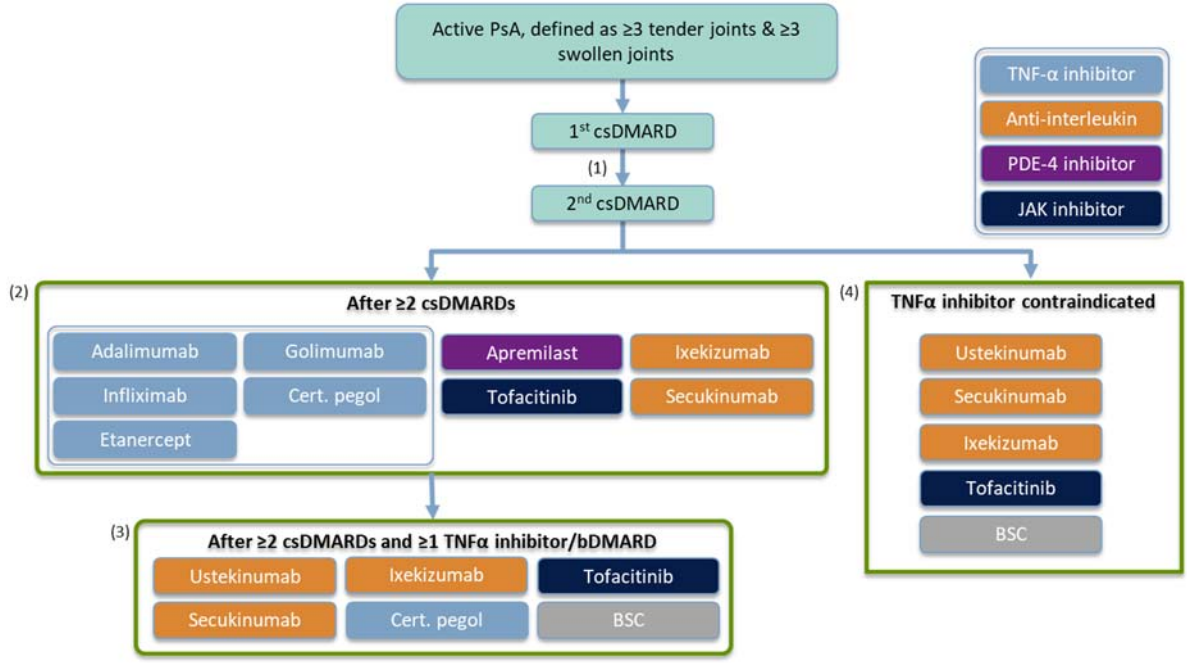
The multiple manifestations of PsA cause a combination of physical and psychological symptoms that contribute to significant reductions in health-related quality of life (HRQoL) and an inability to carry out daily activities.[8] Clinically active PsA leads to progressively more functional disability over time.[9] Compared with the general population, patients with PsA are more likely to have comorbidities such as cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, inflammatory bowel disease, osteoporosis, fibromyalgia, anxiety and depression.[10,11]

PsA is the second most common type of inflammatory joint disease (the most common is rheumatoid arthritis).[12] It affects women and men equally and the peak age of onset is between the ages of 30 and 50 years.[13] It has been estimated that, in the UK, prevalence of PsA is 0.19%[14] which, when applied to the entire adult UK population, equates to 123,006 cases of PsA.[15]

2.2 Company's overview of current service provision

2.2.1 Treatments in the pathway

The most recently updated clinical guidelines for the treatment of PsA were published in 2020 by the European League Against Rheumatism.[6] It is recommended that initial therapy should be with non-steroidal anti-inflammatory drugs (NSAIDs) or conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) for patients with polyarthritis and poor prognostic factors. If treatment goals are not met using csDMARDs, biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) can be initiated. NICE recommends the use of bDMARDs/tsDMARDs in adults with active and progressive PsA who have peripheral arthritis with ≥3 tender and ≥3 swollen joints, and when the disease has not responded to ≥2 csDMARDs, alone or in combination.[16,17] The bDMARDs/tsDMARDs recommended in the NICE pathway for the treatment of PsA are shown in Figure 1.



bDMARD=biological disease-modifying anti-rheumatic drug; BSC=best supportive care; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; cert. pegol=certolizumab pegol; JAK=Janus kinase; PDE-4=phosphodiesterase type 4; PsA=psoriatic arthritis; TNF-α=tumour necrosis factor
The numbers given in brackets represent the clinical sub-populations described in the final scope[18] issued by NICE

Figure 1 NICE treatment pathway for psoriatic arthritis

Source: CS, Figure 1

In line with the final scope[18] issued by NICE, the company describes four clinical sub-populations (CS, Section B.1.1):

- clinical sub-population 1: people with active PsA whose disease has not responded adequately to one csDMARD
- clinical sub-population 2: people with active PsA whose disease has not responded adequately to at least two csDMARDs
- clinical sub-population 3: people with active PsA whose disease has not responded adequately to csDMARDs and one or more tumour necrosis factor alpha (TNF-alpha) inhibitors
- clinical sub-population 4: people with active PsA in whom TNF-alpha inhibitors are contraindicated or not tolerated.

The company's proposed positioning of upadacitinib is as a treatment option for patients in clinical sub-populations 2, 3 and 4.

When prescribing a specific csDMARD for a patient, the decision is usually based on the nature and severity of the patient's symptoms. A patient's symptoms are assessed across six key areas: peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail psoriasis.[19]

Current treatments recommended by NICE for adults with active and progressive PsA who have peripheral arthritis (defined as ≥3 tender and ≥3 swollen joints), and who have not achieved adequate response to ≥2 csDMARDs are: TNF-alpha inhibitors (adalimumab, etanercept and infliximab [TA199],[20] certolizumab pegol [TA445],[21] and golimumab [TA220][22]); anti-interleukins (ixekizumab [TA537],[23] secukinumab [TA445][21] and ustekinumab [TA340],[24]); or tsDMARDs (apremilast [TA433][25] and tofacitinib [TA543][26]). Clinical advice to the ERG is that the choice of bDMARD or tsDMARD takes into account patient factors (including, pregnancy and history of cancer) and cost.

Guidance relating to treatment prescribing sequence is limited; ustekinumab is the only treatment that is specifically recommended by NICE as an option for patients who have had treatment with one or more TNF-alpha inhibitors.[24]

2.2.2 Number of patients eligible for treatment with upadacitinib

The company estimates that the number of patients eligible for treatment with upadacitinib will increase from [redacted] patients in Year 1 to [redacted] patients in Year 5, i.e., to approximately [redacted] of all patients with PsA (Document A, Table 12).

2.3 Critique of company's definition of decision problem

A summary of the decision problem outlined in the final scope[18] issued by NICE and addressed by the company is presented in Table 1. Each parameter is discussed in more detail in the text following Table 1 (Section 2.3.1 to Section 2.3.8).

Table 1 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Population	Adults with active PsA whose disease has not responded adequately to a previous DMARD therapy, or for whom DMARDs are not tolerated or contraindicated	As per scope	In line with NICE recommendations[20-26], in the NHS, patients are usually treated with ≥2 csDMARDs prior to receiving a bDMARD/tsDMARD. However, only approximately 35% of patients in the SELECT-PsA 1 trial had received ≥2 csDMARDs before receiving treatment with upadacitinib. Similarly, in the SELECT-PsA 2 trial, it is not clear if all patients had received ≥2 csDMARDs before receiving treatment with a bDMARD. Previous NICE Appraisal Committees[23,27] have considered that the efficacy of a bDMARD/tsDMARD is not influenced by number of prior csDMARDs
Intervention	Upadacitinib, alone or in combination with non-biological DMARDs	As per scope	SELECT-PsA 1 and SELECT-PSA 2 trial primary outcome results differentiated by concomitant treatment are presented in the CS
Comparator(s)	**Sub-population 1:** For people whose disease has not responded adequately to one csDMARD • Conventional DMARDs **Sub-population 2:** For people whose disease has not responded adequately to ≥2 csDMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab) • Apremilast	For people whose disease has not responded adequately to ≥2csDMARDs: • bDMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ixekizumab and secukinumab)	Clinical advice to ERG is that the listed comparators for each sub-population are the most relevant comparators for this appraisal Direct evidence is only available for one relevant active comparator (upadacitinib versus adalimumab, SELECT-PsA 1 trial). The company has been able to generate indirect evidence for all comparators for clinical sub-populations 2 and 3, except that no evidence has been provided for certolizumab pegol for clinical sub-population 3. The absence of NMA results for certolizumab pegol for clinical sub-population 3 is consistent with previous NICE Appraisals.[21,27] The company assumes that NMA results for clinical sub-population 2 are valid for clinical sub-population 4

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
	• Tofacitinib **Sub-population 3:** For those whose disease has not responded adequately to csDMARDs and one or more TNF-alpha inhibitors: • Ustekinumab • Secukinumab • Certolizumab pegol • Tofacitinib • Ixekizumab • Best supportive care **Sub-population 4:** For people in whom TNF-alpha inhibitors are contraindicated or not tolerated: • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Best supportive care	• Apremilast • Tofacitinib For those whose disease has not responded adequately to csDMARDs and one or more TNF-alpha inhibitors: • Ustekinumab • Secukinumab • Tofacitinib • Ixekizumab • Best supportive care For people in whom TNF-alpha inhibitors are contraindicated or not tolerated: • Ustekinumab • Secukinumab • Ixekizumab • Tofacitinib • Best supportive care	The company has not provided any evidence for clinical sub-population 1, however [redacted] of patients in the SELECT-PsA 1 trial make up this population

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • periarticular disease (for example enthesitis, tendonitis, dactylitis) • axial outcomes (for example, spinal pain and fatigue) • mortality • adverse effects of treatment • health-related quality of life	As per scope	The company has presented evidence for all relevant outcomes identified by NICE. Week 12 NMA results for clinical sub-populations 2 and 3 are available for the following outcomes: PsARC response, PASI 50/75/90 response, HAQ-DI score change conditional on PsARC response, and ACR 20/50/70 response. The company assumes that NMA results for clinical sub-population 2 are valid for clinical sub-population 4. Week 24 NMA results for these same outcomes are provided in the CS, Appendix D
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.	As per scope	The company has provided cost effectiveness results in terms of incremental cost per quality adjusted life year gained. Outcomes are assessed over a lifetime horizon and costs are considered from an NHS and PSS perspective

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	ERG comment
	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention or comparator technologies and subsequent treatments will be taken into account. For the comparators the availability and cost of biosimilars should be taken into consideration		
Subgroups	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	• Mechanism of action or number of previous treatments • Presence or severity of concomitant psoriasis (i.e., PASI75 in patients with ≥ 3% BSA-Ps [Section B.2.6])	The company has presented results for the following subgroups: number of prior csDMARDs (SELECT-PsA 1 trial), number of prior bDMARDs (SELECT-PsA 2 trial) and concomitant of csDMARDs (Yes/No) (SELECT-PsA 1 and SELECT-PsA 2) The company has not presented clinical effectiveness results by presence or severity of psoriasis; however, the company has presented cost effectiveness results by presence of concomitant psoriasis (none, mild, moderate or severe)
Special considerations including issues related to equity or equality	No equality issues are anticipated if upadacitinib is recommended for use by NICE	No equality issues are anticipated if upadacitinib is recommended for use by NICE	The company has not identified any equality issues and has not put forward a case for upadacitinib to be considered under NICE's End of Life treatment criteria[28]

bDMARD=biological disease-modifying anti-rheumatic drugs; BSA-Ps=body surface area-psoriasis; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; DMARD=disease-modifying anti-rheumatic drug; ERG=Evidence Review Group; HAQ-DI=Health Assessment Questionnaire – Disability Index; PASI=Psoriasis Area and Severity Index; PsA=psoriatic arthritis; PsARC=Psoriatic Arthritis Response Criteria; PSS=Personal Social Services; SJC=swollen joint count; TJC=tender joint count; TNF-alpha=tumour necrosis factor-alpha
Source: Final scope[18] issued by NICE; CS, Table 1

2.3.1 Sources of clinical effectiveness data

Intervention

The primary sources of clinical effectiveness evidence for upadacitinib are the SELECT-PsA 1[29] and SELECT-PsA 2[30] trials. Both trials assess the efficacy of two doses of upadacitinib (15mg and 30mg). However, the regulatory filing for upadacitinib in the UK is only based on the 15mg dose; therefore, the main focus of the CS (and this ERG report) is on the 15mg dose.

The SELECT-PsA 1 trial is a phase III, randomised, double-blind trial that compares the efficacy of upadacitinib (n=430) versus adalimumab (n=429) and versus placebo (n=423) in patients with active PsA and a history of inadequate response to at least one csDMARD. Clinical advice to the ERG is that adalimumab is frequently used in NHS clinical practice. No direct evidence is available to allow comparison of upadacitinib with eight out of nine comparators listed in the final scope[18] issued by NICE. The company uses data from this trial to support the use of upadacitinib in clinical sub-populations 2 and 4.

The SELECT-PsA 2 trial is a phase III, randomised, double-blind trial that compares upadacitinib (n=211) versus placebo (n=212) in patients with active PsA and a history of inadequate response to at least one bDMARD. No direct evidence is available to allow comparison of upadacitinib with five of the six comparators listed in the final scope[18] issued by NICE; placebo is assumed to represent best supportive care (BSC). The company uses data from this trial to support the use of upadacitinib in clinical sub-population 3.

Comparators

Direct evidence is only available for the comparison of upadacitinib versus adalimumab (SELECT-PsA 1 trial). The company has generated indirect evidence for the relative effectiveness of upadacitinib versus other relevant comparator treatments by carrying out network meta-analyses (NMAs). The company appears to have assumed that best supportive care can be represented by data from placebo arms.

2.3.2 Population

The focus of the CS is on clinical sub-populations 2, 3 and 4 (described in Section 2.2.1). These three sub-populations combined are a subset of the population described in the final scope[18] issued by NICE. Focusing on these three sub-populations is in line with the sub-populations considered in recent previous NICE STAs (TA543 [tofacitinib],[27] TA445 [certolizumab pegol and secukinumab],[31] and TA537 [ixekizumab].[23]

Clinical advice to the company (and the ERG) is that patients participating in the SELECT-PsA 1 and SELECT-PsA 2 trials are generally representative of patients with PsA treated in UK clinical practice.

Prior treatments

NICE recommendations state that patients should receive ≥2 csDMARDs before being treated with a bDMARD[20-24] or a tsDMARD.[25,26] In the SELECT-PsA 1 trial, [redacted]% of patients had received one prior csDMARD, [redacted] % had received two prior csDMARDs, and [redacted] % had received three or more prior csDMARDs (CS, p34). The company reports (CS, p35) that the inclusion of patients with ≥1 csDMARD in the SELECT-PsA 1 trial aligns with criteria commonly used in PsA trials. Previous NICE Appraisal Committees[23,27] have considered that the efficacy of a bDMARD/tsDMARD is not influenced by number of prior csDMARDs.

Clinical advice to the ERG is that following two prior csDMARDS, patients are usually started on treatment with a TNF-alpha inhibitor due to cost considerations. Patients may be switched to a different TNF-alpha inhibitor in the event of an adverse reaction, but in other cases of TNF-alpha inhibitor failure, patients would be switched to an anti-interleukin or a tsDMARD. Patients may also start treatment on tsDMARDs following two prior csDMARDs if the treatment was cost-equivalent to a biosimilar.

In the SELECT-PsA 2 trial, [redacted] % of patients had failed one prior bDMARD, [redacted] % had failed two prior bDMARDs, and [redacted] % had failed three or more prior bDMARDs, and [redacted] % of patients were intolerant to a prior bDMARD. In an observational study using Danish registry data, the rate of response to bDMARDs was shown to decline with every additional bDMARD treatment.[32] The post-hoc analyses of the SELECT-PsA 2 trial data (presented at the ACR Convergence 2020)[33] that explored aspects of prior bDMARD exposure on upadacitinib efficacy are discussed in Section 3.3.2.

2.3.3 Intervention

The intervention described in the final scope[18] issued by NICE is upadacitinib alone or in combination with csDMARDs. In the SELECT-PsA 1 trial, at baseline, only [redacted] of patients in the upadacitinib arm were receiving monotherapy; the remainder ([redacted] were also receiving a csDMARD. Of those taking any csDMARD, [redacted] were receiving methotrexate (MTX), [redacted] were receiving MTX plus another csDMARD, and [redacted] were receiving a csDMARD other than MTX (CS, Table 6). In the SELECT-PsA 2 trial, at baseline, just under half of patients were receiving a csDMARD ([redacted]). Of those taking any csDMARD, [redacted] were receiving MTX alone, [redacted] were receiving MTX+another csDMARD and [redacted] were receiving a csDMARD other than MTX (CS, Table 9).

An application for use of upadacitinib to treat PsA was filed to the European Medicines Agency on 1 June 2020. The Committee for Medicinal Products for Human Use issued a positive opinion for the use of upadacitinib for the treatment of psoriatic arthritis in December 2020. The European Commission has now issued a positive opinion on for the use of upadacitinib for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Upadacitinib may be used as monotherapy or in combination with MTX.[34]

Upadacitinib is an oral JAK inhibitor (a tsDMARD) that is administered once daily. The only other JAK inhibitor recommended by NICE for the treatment of PsA is tofacitinib (TA543).[27] Tofacitinib is associated with safety concerns that limit the eligible patient population in two ways.[35] First, in a post-marketing study, tofacitinib showed an increased risk of infection in patients aged over 65 years. Second, dose adjustment is required for patients with renal and hepatic impairment. In addition, tofacitinib may only be used in combination with MTX.[17,35]

2.3.4 Comparators

The company has presented clinical effectiveness evidence for clinical sub-populations 2 (and 4) for all the comparators listed in the final scope[18] issued by NICE. Whilst certolizumab pegol was identified as a comparator in the final scope[18] issued by NICE for clinical sub-population 3, the company did not consider data from the RAPID-PsA trial[36] (certolizumab pegol versus placebo) to be relevant to the decision problem as the trial excluded patients with primary failure to a previous TNF-alpha inhibitor (no response within the first 12 weeks). The company highlighted that excluding certolizumab pegol as a comparator for clinical sub-population 3 is consistent with the recent NICE technology appraisals of secukinumab and certolizumab pegol (TA445)[31] and tofacitinib (TA543).[27] The company has presented clinical effectiveness evidence for all other relevant comparators for clinical sub-population 3.

The company carried out NMAs for two sub-populations: (i) the biologic-naïve population, which the company considers reflects clinical sub-population 2 (and 4), and (ii) the biologic-experienced population, which the company considers reflects clinical sub-population 3. The ERG highlights that there is no trial evidence to demonstrate the effectiveness of bDMARDs/tsDMARDs specifically in patients who are known to be contraindicated to, or unable to tolerate, TNF-alpha inhibitors. It is, therefore, unclear whether it is appropriate to assume that efficacy results generated for clinical sub-population 2 (patients who are biologic-naïve) will be reflected in clinical sub-population 4 (patients who are contraindicated or unable to tolerate TNF-alpha inhibitors).

Data from mixed biologic-naïve (n=9)[36-44] and biologic-experienced (n=1)[45] populations were used for the Week 12 NMAs for some outcomes (Section 3.5). In these ten trials, if the overall trial population included fewer than 50% of patients who had received a prior biologic treatment, the company used data from the trial in the biologic-naïve NMAs; if the overall trial population included more than 50% of patients who had received a prior biologic treatment, the company used data from the trial in the biologic-experienced NMAs. The ERG considers that the company's approach to classifying biologic-naïve and biologic-experienced trials is a pragmatic approach to classifying the patient sub-populations.

2.3.5 Outcomes

The company has presented clinical effectiveness evidence for upadacitinib for all outcomes listed in the final scope[18] issued by NICE. The presented outcomes relate to disease activity, functional capacity, disease progression, periarticular disease, axial outcomes, mortality, adverse effects of treatment and HRQoL. Clinical advice to the ERG is that these are the most relevant outcomes for the clinical sub-populations considered in this appraisal.

The company has provided Week 12 (and Week 24) biologic-naïve and biologic-experienced NMA results for: proportion of patients achieving a response according to the Modified Psoriatic Arthritis Response (PsARC) criteria, proportion of patients achieving a response according to the Psoriasis Area Severity Index (PASI 50/75/90), a score change on the Health Assessment Questionnaire Disability Index (HAD-QI) conditional on PsARC response status, and proportion of patients achieving a response with the American College of Rheumatology (ACR 20/50/70) criteria.

2.3.6 Economics

As specified in the final scope[18] issued by NICE, the cost effectiveness of treatment was expressed in terms of incremental cost per quality adjusted life year (QALY). Outcomes were assessed over a lifetime time horizon and costs were considered from an NHS and Personal Social Services (PSS) perspective.

The sub-populations considered in the economic sections of the CS align with those described in the clinical section of the CS except that economics sub-population 1 equates to clinical sub-population 2, economics sub-population 2 equates to clinical sub-population 3 and economics sub-population 3 equates to clinical sub-population 4.

2.3.7 Subgroups

The company has presented ACR20 response at Week 12, results by number of previous treatments (prior csDMARDs [SELECT-PsA 1]; CS, Section B.2.7.1), prior bDMARD use

[SELECT-PsA 2], and background use of csDMARDs (CS, Section B.2.7.2). The company has not presented clinical evidence according to the presence or severity of concomitant psoriasis (PASI 75) in patients in ≥3% body surface area-psoriasis, however, the company has presented cost effectiveness results by severity of psoriasis (CS, Section B.3.3.3).

2.3.8 Other considerations

The company does not anticipate that a NICE recommendation for the use of upadacitinib in the NHS will lead to any equity issues.

The company highlights (CS, p113) that as upadacitinib is an oral treatment there is no requirement for any treatment administration training.

Clinical advice to the ERG is that, due to the coronavirus pandemic, some patients currently receiving a bDMARD for rheumatoid arthritis are being switched to treatment with JAK inhibitors including upadacitinib because of their short half-life and ease of administration. This approach was supported by the British Society of Rheumatology in 2020, during the first and second waves of the coronavirus pandemic.

Upadacitinib is available to the NHS at a Patient Access Scheme (PAS) discounted price. certolizumab pegol, golimumab, ixekizumab, secukinumab, ustekinumab, apremilast and tofacitinib and are all also available to the NHS at discounted PAS prices. Biosimilar prices for adalimumab, etanercept and infliximab are available.

The prices used in the company base case analysis are:

- public PAS prices: certolizumab pegol and golimumab
- confidential PAS price: upadacitinib
- Commercial Medicines Unit (CMU) price: adalimumab
- list prices: etanercept, infliximab, ixekizumab, secukinumab, ustekinumab, apremilast and tofacitinib.

The ERG considers that the company has (appropriately) not put forward a case for upadacitinib to be considered under NICE's End of Life treatment criteria.[28]

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence demonstrating the clinical effectiveness of upadacitinib versus the comparators listed in the final scope[18] issued by NICE have been provided (CS, Appendix D). The ERG did not find any relevant trials of upadacitinib in addition to those identified by the company. An assessment of the extent to which the systematic literature review carried out by the company was conducted in accordance with the LR*i*G in-house systematic review checklist is provided in Table 2. Overall, the ERG considers that the company's review was conducted to a good standard.

Table 2 ERG appraisal of the company's systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix v2 (Section D1.1, Table 11)
Were appropriate sources searched?	Yes	CS, Appendix v2 (Section D.1.1)
Was the timespan of the searches appropriate?	Yes	CS, Appendix v2 (Section D.1)
Were appropriate search terms used?	Yes	CS, Appendix v2 (Section D.1.1)
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix v2 (Section D.1.2, Table 11)
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix v2 (Section D.1.2)
Was data extracted by two or more reviewers independently?	Partial	CS, Appendix v2 (Section D1.2.2) Data were extracted by one reviewer and validated by a second senior reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix v2 (Section D.1.2.2)
Was the quality assessment conducted by two or more reviewers independently?	Yes	Clarification response to question C1
Were attempts to synthesise evidence appropriate?	Yes	See Section 3.2.5 and Section 3.5.3 for a discussion of the methods used by the company and the ERG's critique of those methods

ERG=Evidence Review Group
Source: LR*i*G in-house checklist

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

3.2.1 Included trials

The company identified two phase III RCTs that provided evidence for the clinical effectiveness of upadacitinib, namely the SELECT-PsA 1 trial and the SELECT-PsA 2 trial. The data presented in the CS are from the 24-week data cut-off dates of 13 December 2019 and 9 October 2019 for the SELECT-PsA 1 and SELECT-PsA 2 trials respectively. Both trials assess the efficacy of two doses of upadacitinib (15mg and 30mg). However, the licensed indication for upadacitinib for use in the NHS is only based on the 15mg dose; therefore, the main focus of the CS (and this ERG report) is on the 15mg dose.[34] The SELECT-PsA 1 and SELECT-PsA 2 trials are described in detail in the CS (Sections B.2.2 to B.2.5)

The ERG did not identify any other trials that directly compared upadacitinib versus the remaining comparators listed in the final scope[18] issued by NICE; therefore, the company performed indirect treatment comparisons through a series of network meta-analyses (NMAs). The NMAs were performed for two sub-populations: (i) biologic-naïve patients (clinical sub-populations 2 [and 4]), and (ii) biologic-experienced patients (clinical sub-population 3). Details of the comparator trials included in the NMAs are available from the NMA Technical Study Report.[46]

3.2.2 Characteristics of the SELECT-PsA 1 and SELECT-PsA 2 trials

The company has provided details of the designs of the SELECT-PsA 1 and SELECT PsA 2 trials (CS, Figure 2 and Figure 3) and details of key characteristics (CS, Table 4 and Table 7).

SELECT-PsA 1 trial

The SELECT-PsA 1 trial (n=1,705 enrolled patients) is an ongoing phase III, randomised, double-blind trial, evaluating upadacitinib versus adalimumab and versus placebo in adults with active PsA who have a history of inadequate response to at least one csDMARD. Patients in the SELECT-PsA 1 trial were randomised to one of five arms: upadacitinib 15mg, upadacitinib 30mg, adalimumab 40mg, placebo followed by upadacitinib 15mg, or placebo followed by upadacitinib 30mg.[29] Randomisation was stratified by extent of psoriasis (≥3% BSA or <3% BSA), concomitant use of at least one DMARD (Yes/No), presence of dactylitis, and presence of enthesitis. The trial is being conducted in 281 sites in 44 countries, including five sites (n=26 patients) in the UK, and is designed to capture a total treatment time of approximately 5 years. Following an initial 35-day screening period, the trial is divided into two treatment periods:

1. **Period 1** - a 56-week blinded treatment phase comparing upadacitinib versus adalimumab and versus placebo every other week. At Week 24, all patients who had been receiving placebo were switched to receive upadacitinib, regardless of their response to placebo. At the 13 Dec 2019 cut-off date, up to Week 24 of Period 1 had been completed.
2. **Period 2** – an ongoing long-term extension phase to evaluate the safety, tolerability and efficacy of upadacitinib in patients who completed Period 1.

The full analysis set (FAS) consists of all randomised patients from the trial who have received at least one dose of the study drug and includes 1,281 patients: upadacitinib 15mg (n=429), adalimumab (n=429) and placebo followed by upadacitinib (n=423). During the trial, patients were permitted to continue background treatment with up to two csDMARDs.

The primary outcome (patients achieving ACR20) is measured at Week 12. Results for ACR20 are also available at Week 24 for the FAS and pre-planned subgroups (demographic factors and baseline disease characteristics, including number of prior csDMARDs (≤1 or >1) and concomitant use of csDMARD use (Yes/No). See Section 3.3 for further details about the outcomes measured in the trial.

SELECT-PsA 2 trial

The SELECT-PsA 2 trial (n=642 enrolled patients) is an ongoing phase III, randomised, double-blind trial, evaluating upadacitinib versus placebo in adults with active PsA and a history of inadequate response to at least one bDMARD. Patients in the SELECT-PsA 2 trial were randomised to one of four arms: upadacitinib 15mg, upadacitinib 30mg, placebo followed by upadacitinib 15mg at Week 24, or placebo followed by upadacitinib 30mg at Week 24. Randomisation was stratified by extent of psoriasis (≥3% BSA or <3% BSA), concomitant use of at least one DMARD (Yes/No), and number of prior failed bDMARDs (1 vs >1). The trial is being conducted in 123 sites in 16 countries, including six sites (n=3 patients) in the UK and is designed to capture a total treatment time of approximately 3 years. After an initial 35-day screening period, the trial is divided into two treatment periods:

1. **Period 1** - a 56-week blinded treatment phase comparing upadacitinib versus placebo. At Week 24, all patients who had been receiving placebo were switched to receive upadacitinib, regardless of their response to placebo. At the 9 Oct 2019 cut-off date, up to Week 24 of Period 1 had been completed.

2. **Period 2** – an ongoing long-term extension phase intended to evaluate the safety, tolerability and efficacy of upadacitinib in patients who completed Period 1.

The FAS consists of all randomised patients who have received at least one dose of the study drug and includes 423 patients: upadacitinib 15mg (n=211), placebo followed by upadacitinib (n=212). During the trial, patients are permitted to continue stable background treatment with up to two csDMARDs.

The primary outcome (patients achieving ACR20) is measured at Week 12. Results for ACR20 are also available at Week 24 for the FAS and pre-planned subgroups (demographic factors and baseline disease characteristics, including the number of prior csDMARDs (≤1 or >1) and concomitant use of csDMARD (Yes/No). See Section 3.3 for further details about the outcomes measured in the trial.

3.2.3 Characteristics of patients in the SELECT-PsA 1 and SELECT-PsA 2 trials

Details of baseline patient and disease characteristics are provided in the CS (Sections B.2.1.3.2 and B.2.3.2.2). A summary of this information is presented in Table 3.

Table 3 Key SELECT-PsA 1 trial and SELECT-PsA 2 trial baseline patient and disease characteristics (FAS)

Category, mean (SD) or n (%)	SELECT-PsA 1			SELECT-PsA 2	
	UPA (n=429)	ADA (n=429)	PBO (n=423)	UPA (n=211)	PBO (n=212)
Patient characteristics					
Female	[redacted]	[redacted]	[redacted]	113 (53.6%)	120 (56.5%)
Age, years	[redacted]	[redacted]	[redacted]	53.0 (12.0)	54.1 (11.5)
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics					
TJC68	[redacted]	[redacted]	[redacted]	24.9 (17.3)	25.3 (17.6)
SJC66	[redacted]	[redacted]	[redacted]	11.3 (8.2)	12.0 (8.9)
≥3% BSA-Ps				130 (61.6%)	131 (61.8%)
PASI (for baseline ≥3% BSA-Ps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enthesitis (LEI>0)	[redacted]	[redacted]	[redacted]	133 (63.0%)	144 (67.9%)
Dactylitis (LDI>0)	[redacted]	[redacted]	[redacted]	55 (26.1%)	64 (30.2%

ADA=adalimumab; BSA-Ps=body surface area psoriasis; CSR=clinical study report; FAS=full analysis set; LDI=Leeds Dactylitis Index; LEI=Leeds Enthesitis Index; PASI=Psoriasis Area and Severity Index; PBO=placebo; PsA=psoriatic arthritis; SD=standard deviation; SJC=swollen joint count; TJC=tender joint count; UPA=upadacitinib
Source: CS, Table 5, SELECT-PsA 1 CSR,[29] SELECT-PsA 2 CSR[30] and Mease et al 2020[47]

The baseline patient and disease characteristics are similar and well-balanced across each of the arms within the SELECT-PsA 1 and SELECT-PsA 2 trials (Table 3). Clinical advice to the

ERG is that the baseline characteristics of patients from both trials are similar to the baseline characteristics of patients treated in UK clinical practice.

The ERG highlights that in the SELECT-PsA 1 trial, over two-thirds ([redacted]) of patients had only received one csDMARD prior to treatment with upadacitinib, while in the NHS patients typically receive ≥2 csDMARDs prior to receiving a bDMARD. Previous NICE Appraisal Committees[23,27] have considered that the efficacy of bDMARDs is not influenced by the number of prior csDMARDs.

The number of csDMARDs received by patients prior to enrolment in the SELECT-PsA 2 trial is unclear. In addition, while [redacted] of patients had previously failed one bDMARD, [redacted] had failed two prior bDMARDs, [redacted] had failed three or more prior bDMARDs, and the remaining [redacted] were intolerant to bDMARDs. The rate of response to bDMARDs has been shown to decline with every additional bDMARD treatment.[32]

3.2.4 Quality assessment of the SELECT-PsA 1 and SELECT-PsA 2 trials

The company conducted a quality assessment of the SELECT-PsA 1 trial and the SELECT-PsA 2 trial using the NICE Quality Assessment Tool,[28] which is based on the University of York Centre for Reviews and Dissemination guidance.[48] The ERG agrees with the company's conclusions that the SELECT-PsA 1 and SELECT-PsA 2 trials are well-designed and well-conducted. The company's assessments and ERG comments are provided in Appendix 1 (Table 35).

3.2.5 Statistical approach adopted for the analysis of data from the SELECT-PsA 1 and SELECT-PsA 2 trials

Information relevant to the statistical approach taken by the company to analyse data from the SELECT-PsA 1 and SELECT-PsA 2 trials has been extracted from the clinical study reports (CSRs),[29,30] the trial statistical analysis plans,[49,50] the trial protocols,[51,52] and the CS. A summary of the ERG checks of the pre-planned statistical approach used by the company to analyse data from the included trials is provided in Appendix 2 (Table 36). The ERG considers that the company's approaches to analysing data from the SELECT-PsA 1 and SELECT-PsA 2 trials were appropriate.

3.3 SELECT-PsA 1 trial and SELECT-PsA 2 trial efficacy results

In the SELECT-PsA 1 trial, [redacted] % and [redacted] % of patients had completed treatment up to Week 12 and Week 24, respectively. In the SELECT-PsA 2 trial, [redacted] % and 84.6% of patients had completed treatment up to Week 12 and Week 24, respectively.

3.3.1 Summary of results: FAS population

The primary endpoint of the SELECT-PsA 1 and SELECT-PsA 2 trials is ACR20 response rate at Week 12 for upadacitinib versus placebo. In both trials, the key secondary endpoints were ranked as part of the company's graphical multiple testing procedure; there were 14 ranked secondary endpoints in the SELECT-PsA 1 trial (CS, p30) and seven ranked secondary endpoints in the SELECT-PSA 2 trial (CS, p37). Each endpoint was only formally tested for statistical significance if the previously ranked endpoint result was statistically significantly different. A summary of results for each of these key endpoints, plus additional (exploratory) endpoints presented in the CS are provided in Table 4 and Table 5 for the SELECT-PsA 1 and SELECT-PsA 2 trials, respectively.

Table 4 Primary, secondary and additional endpoints reported in the CS for the SELECT-PsA1 trial

	Location in CS	Effect estimate (95% CI); p-value[a]	
		UPA vs PBO	UPA vs ADA
Primary endpoint: ACR20 response rate vs PBO at Week 12	pp51-52	[redacted]	-
Ranked key secondary endpoints[b]			
1. Change from baseline in HAQ-DI at Week 12	p55	[redacted]	-
2. sIGA of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16	pp55-56	[redacted]	-
3. PASI75 response at Week 16	pp56-57	[redacted]	-
4. Change from baseline in modified PsA SHS at Week 24	pp64-65[c]	[redacted]*	-
5. Percentage of patients with MDA at Week 24	pp57-58	[redacted]	-
6. Percentage of patients with resolution of enthesitis at Week 24	pp58-59	[redacted]	-
7. ACR20 non-inferiority vs ADA at Week 12	p59	-	[redacted]
8. Change from baseline in SF-36 PCS at Week 12	Company response to clarification letter, question A2	[redacted]	-
9. Change from baseline in FACIT-F at Week 12	pp59-60	[redacted]	
10. ACR20 superiority vs ADA at Week 12	p47	-	[redacted]
11. Percentage of patients with dactylitis resolution at Week 24	pp60-61	[redacted]	-
12. Pain superiority vs ADA at Week 12	p62	-	[redacted]
13. HAQ-DI superiority vs ADA at Week 12	p55		[redacted]
14. Change from baseline in SAPS at Week 16	Company response to clarification letter, question A2	[redacted]	-
Additional secondary endpoints reported in the CS			
PsARC at Week 12		[redacted]	[redacted]

	Location in CS	Effect estimate (95% CI); p-value[a]	
		UPA vs PBO	UPA vs ADA
PsARC at Week 20	pp63-64	[redacted]	[redacted]
PsARC at Week 24		[redacted]	[redacted]
ASDAS change from baseline at Week 24	pp66-67	[redacted]	[redacted]
BASDAI change from baseline at Week 24		[redacted]	[redacted]
Change from baseline in EQ-5D-5L index at Week 24	pp67-68	[redacted]	[redacted]
Change from baseline in EQ-5D-5L VAS at Week 24		[redacted]	[redacted]
Change from baseline in joint erosion score at Week 24	pp64-65	[redacted]	NR
Change from baseline in JSN Score at Week 24		[redacted]	NR

[a] P-values are only provided when the tests were conducted as part of the graphical multiple testing procedure
[b] All ranked secondary endpoints are for the comparison of UPA versus PBO unless otherwise stated
[c] Results in the CS were from a sensitivity analysis using an alternative approach to handling missing data, the ERG has presented results from the analysis approach that was pre-specified in the TSAP[50] and reported in the CSR[29] (Table 9)
* From the CSR
ACR=American College of Rheumatology; ADA=adalimumab; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D-5L=EuroQol-five dimensions-five levels; ERG=Evidence Review Group; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire Disability Index; JSN=joint space narrowing; LS=least squares; MD=mean difference; MDA=minimal disease activity; NR=not reported; PASI=Psoriasis Area Severity Index; PBO=placebo; PsARC=Psoriatic Arthritis Response Criteria; RRD=response rate difference; SAPS=Self-Assessment of Psoriasis Symptoms; SF-36 PCS=Short Form 36 Physical Component Summary; SHS=Sharp van der Heijde Score; sIGA=Static Investigator Global Assessment; UPA=upadacitinib; VAS=visual analogue scale
Source: CS, Table 13 to Table 24; CS, Appendix D, Table 23; Clarification letter response, question A1, question A2; SELECT-PsA 1 CSR,[29] Table 9

Table 5 Primary, secondary and additional endpoints reported in the CS for the SELECT-PsA 2 trial

	Location in CS	UPA vs PBO Effect estimate (95% CI); p-value[a]
Primary endpoint: ACR20 response rate at Week 12	pp68-69	RRD=32.8 (24.0 to 41.6); p<0.0001
Ranked key secondary endpoints		
1. Change from baseline in HAQ-DI at Week 12	p72	LS MD=-0.21 (-0.30 to -0.12); [redacted]
2. sIGA of psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16	pp72-73	RRD=27.6 (19.2 to 36.1); [redacted]
3. PASI75 response at Week 16	p73	RRD=36.3 (25.6 to 46.9); [redacted]
4. Change from baseline in the SF-36 PCS at Week 12	Appendix D, p82	[redacted]
5. Change from baseline in FACIT-F at Week 12	p74	[redacted]
6. Percentage of patients with MDA at Week 24	pp74-75	[redacted]
7. Change from baseline in SAPS at Week 16	Appendix D, p83	[redacted]
Additional secondary endpoints reported in the CS		
PsARC at Week 12	p75	[redacted]
PsARC at Week 20		[redacted]
PsARC at Week 24		[redacted]
ASDAS change from baseline at Week 24	pp75-76	[redacted]
BASDAI change from baseline at Week 24		[redacted]
Change from baseline in EQ-5D-5L index at Week 24	pp77-78	[redacted]
Change from baseline in EQ-5D-5L VAS at Week 24		[redacted]
Change from baseline in patient's assessment of pain at Week 24	pp76-77	[redacted]

[a] P-values are only provided when the tests were conducted as part of the graphical multiple testing procedure
ACR=American College of Rheumatology; ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D-5L=EuroQol-five dimensions-five levels; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI=Health Assessment Questionnaire Disability Index; MDA=minimal disease activity; PASI=Psoriasis Area Severity Index; PBO=placebo; PsARC=Psoriatic Arthritis Response Criteria; SAPS=Self-Assessment of Psoriasis Symptoms; SF-36 PCS=Short Form 36 Physical Component Summary; sIGA= Static Investigator Global Assessment; UPA=upadacitinib; VAS=visual analogue scale
Source: CS, Table 26 to Table 34, CS, Appendix D, Table 25

In the SELECT-PsA 1 trial, a statistically significant difference was observed for the primary endpoint and for the first nine ranked secondary endpoints. Eight of these endpoints compared upadacitinib to placebo, and the results for these endpoints favoured upadacitinib. One of these endpoints was a non-inferiority test for upadacitinib versus adalimumab in terms of ACR20 response at Week 12; upadacitinib was shown to be non-inferior to adalimumab. For the tenth ranked secondary endpoint, the multiplicity adjusted p-value indicated that upadacitinib was not statistically significantly superior to adalimumab (p=0.0815). As this test did not reach statistical significance, secondary endpoints ranked >10 were not formally tested as part of the company's graphical multiple testing procedure. For the remaining ranked secondary endpoints, the effect estimates for dactylitis resolution at Week 24, and Self-Assessment of Psoriasis Symptoms at Week 16 favoured upadacitinib in comparison to placebo, and the effect estimate for HAQ-DI at Week 12 favoured upadacitinib in comparison to adalimumab. There appeared to be little difference between upadacitinib and adalimumab in terms of pain at Week 12.

In the SELECT-PsA 2 trial, a statistically significant difference in favour of upadacitinib was observed for the primary endpoint and for all seven key ranked secondary endpoints.

3.3.2 Subgroup analyses of ACR20 at Week 12

SELECT-PsA 1 trial: number of prior csDMARDs

The CS focuses on the patients who have previously been treated with at least two csDMARDs. However, the eligibility criteria for the SELECT-PsA 1 trial specified that patients must previously have had an inadequate response to, or were intolerant to, treatment with at least one csDMARD. The company explored how treatment efficacy (ACR20) varied according to number of prior csDMARDs (≤1 versus >1) in a pre-specified subgroup analysis. Results are provided in Table 6. Response rates were consistent between the subgroups defined by prior csDMARD use, and also, the company's interpretation is in line with the opinion of previous NICE Appraisal Committees[23,27] (i.e., the efficacy of bDMARDs is not influenced by number of prior csDMARDs).

Table 6 SELECT-PsA 1 trial: ACR20 response rate at Week 12 by number of prior csDMARDs

	≤1 prior csDMARD			>1 prior csDMARDs		
	UPA (N=275)	**PBO (N=274)**	**ADA (N=288)**	**UPA (N=154)**	**PBO (N=149)**	**ADA (N=141)**
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% (95 % CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate difference (95% CI)						
UPA vs PBO	[redacted]			[redacted]		

Missing data approach: NRI
ACR=American College of Rheumatology; ADA=adalimumab; CI=confidence interval; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; NRI=non-responder imputation; PBO=placebo; UPA=upadacitinib; vs=versus
Source: CS, Table 36

SELECT-PsA 2 trial: number of prior bDMARDs (1 versus >1)

The number of prior bDMARDs (1 versus >1) was a pre-specified subgroup analysis of ACR20 from the SELECT-PsA 2 trial. Patients who were contraindicated to bDMARDs were not included in this analysis. As the number of previous treatments, and reason for previous treatment failure (i.e., due to lack of efficacy, intolerance or AEs) were listed as subgroup analyses of interest in the final scope[18] issued by NICE, the ERG has summarised the results from this subgroup analysis in Table 7.

Response rates for patients in the placebo arm were similar between those who had failed one bDMARD and those who had failed more than one bDMARD. The company states (CS, p80) that "upadacitinib 15mg demonstrated generally consistent efficacy in patients with inadequate response to one or multiple prior bDMARDs". However, the ERG notes that the benefit of treatment with upadacitinib versus placebo was numerically greater for patients who had only failed one prior bDMARD. It is difficult to draw firm conclusions about the effectiveness of upadacitinib versus placebo in these subgroups, as the subgroup analysis was not formally powered to detect statistically significant differences. Published results demonstrated that the rate of response to bDMARDs has been shown to decline with every additional bDMARD treatment.[32]

Table 7 SELECT-PsA 2 trial: subgroup analysis of ACR20 response rate at Week 12 by number of prior failed bDMARDs

	1 prior failed bDMARD		>1 prior failed bDMARDs	
	UPA (N=126)	PBO (N=135)	UPA (N=69)	PBO (N=59)
n	[redacted]	[redacted]	[redacted]	[redacted]
% (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Response rate difference (95% CI)				
UPA vs PBO	[redacted]		[redacted]	

Missing data approach: NRI
ACR=American College of Rheumatology; ADA=adalimumab; CI=confidence interval; bDMARD=biologic disease-modifying anti-rheumatic drug; NRI=non-responder imputation; PBO=placebo; UPA=upadacitinib; vs=versus
Source: CS, Table 37

The company (CS, pp80-81) also referred to the results of post-hoc analyses of the SELECT-PsA 2 trial that were presented at ACR Convergence 2020;[33] these analyses explored aspects of prior bDMARD exposure on upadacitinib efficacy in more depth. One analysis explored whether efficacy varied according to type of prior bDMARD received among those who had had an inadequate response to treatment with one bDMARD. A sub-population of interest in this appraisal is patients who have not responded to csDMARDs and at least one TNF-alpha inhibitor. Patients in the SELECT-PsA 2 trial may have had an inadequate response to bDMARDs other than TNF-alpha inhibitors, such as IL-17 inhibitors; it is therefore informative to consider how treatment efficacy varied according to type of prior bDMARD received.

The company stated (CS, p80) that similar efficacy was observed whether inadequate response was to a TNF-alpha inhibitor or to an IL-17 inhibitor. However, the ERG considers that the response rate differences for ACR20 at Week 12 for upadacitinib versus placebo suggest that patients who had had an inadequate response to a TNF-alpha inhibitor may experience greater benefit from treatment with upadacitinib (response rate difference: 47.6, 95% confidence interval [CI]: 34.0 to 61.1; n=74) compared to patients who had an inadequate response to an IL-17 inhibitor (response rate difference: 24.3, 95% CI: 3.3 to 45.2; n=42).

The company also referred to a post-hoc analysis (presented at ACR Convergence 2020[33]) that explored whether efficacy of upadacitinib versus placebo varied according to the number of bDMARD mechanisms of action (MOA) tried prior to enrollment (1 MOA and ≥ 2 MOAs), for patients who had had an inadequate response to at least two prior bDMARDs. In terms of ACR20 at Week 12, patients who had only had bDMARDs with the same MOA experienced greater treatment benefit for upadacitinib versus placebo (response rate difference: 40.8; 95% CI: 19.6 to 61.9) in comparison to patients who had tried bDMARDs with more than one MOA (response rate difference: 9.4; 95% CI: -12.8 to 31.7). These results should be interpreted with

caution due to the small number of patients included in the analyses (only 199 patients in total had experienced an inadequate response to treatment with at least two bDMARDs).

Concomitant use of csDMARDs in the SELECT-PsA 1 and SELECT-PsA 2 trials

The company has presented SELECT-PsA 1 and SELECT-PsA 2 trial ACR20 results according concomitant use of csDMARDs (Yes/No) (CS, Table 38). Results show that response rate differences for upadacitinib versus placebo were similar between patients currently receiving csDMARDs (SELECT-PsA 1: 34.8, 95% CI: 27.9 to 41.7, n=700; SELECT-PsA 2: 31.2, 95% CI: 18.1 to 44.2, n=198) and those not currently receiving csDMARDs (SELECT-PsA 1: 32.9, 95% CI: 17.9 to 47.9, n=152; SELECT-PsA 2: 34.3, 95% CI: 22.4 to 46.2, n=225). The ERG considers that these results provide evidence to support the hypothesis that upadacitinib is equally effective irrespective of whether it is used as a monotherapy or in combination with csDMARDs.

3.4 Patient reported HRQoL: EQ-5D-5L

Patient reported outcome data were collected as part of the SELECT-PsA 1 and SELECT-PsA 2 trials (see Section 3.3, Table 4 and Table 5). The ERG considers that, for this appraisal, the most important HRQoL data are those collected using the EQ-5D-5L questionnaire as these were used to populate the company economic model. The EQ-5D-5L questionnaire assesses patient health across five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety and depression) and measures level of severity on a 5-point scale.

Table 8 shows the change from baseline to Week 24 between upadacitinib and adalimumab (SELECT-PsA 1), and upadacitinib and placebo (SELECT-PsA 1 and SELECT-PsA 2) in EQ-5D-5L index scores.

Table 8 SELECT-PsA 1 and SELECT-PsA 2 trials: change from baseline in EQ-5D-5L index scores at Week 24

	SELECT-PsA 1			SELECT-PsA 2	
	UPA (N=387)	PBO (N=369)	ADA (N=387)	UPA (N=183)	PBO (N=167)
LS mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between group LS mean difference (95% CI); p-value[ǂ]					
UPA vs PBO	[redacted]			[redacted]	
UPA vs ADA	[redacted]			NA	

ADA=adalimumab; CI=confidence intervals; PBO=placebo; UPA=upadacitinib; LS mean=least squares mean; NA=not applicable
[a]nominal p-value
Source: CS, Table 25 and Table 35

At Week 24, in the SELECT-PsA 1 trial, treatment with upadacitinib was associated with greater improvements from baseline compared with adalimumab and compared with placebo. At Week 24, in the SELECT-PsA 2 trial, treatment with upadacitinib was associated with greater improvements from baseline compared with placebo.

3.5 ERG summary and critique of the indirect evidence

The primary objective of the company NMAs was to compare the relative efficacy of upadacitinib versus comparator treatments as measured by the following outcomes at Week 12:

- Proportion of patients achieving ACR20/50/70
- Proportion of patients achieving a PASI 50/75/90 response
- Proportion of patients achieving a PsARC response
- HAQ-DI score change conditional on PsARC response status (responder versus non-responder).

These outcomes were selected as they were considered to be important determinants of a clinically meaningful response (i.e., ACR20/50/70) or informed the company's economic modelling (PsARC response, PASI 50/75/90 response, and HAQ-DI score change conditional on PsARC response status). The company also conducted NMAs for these outcomes at Week 24. More trials reported Week 12 data than reported Week 24 data and results from Week 12 NMAs were selected to inform the company's economic model. The focus of the CS, and this ERG report, is therefore on the Week 12 NMAs. These NMAs were performed separately for two sub-populations:

- biologic-naïve population, defined as patients who had not previously been treated with a biologic therapy (assumed to represent clinical sub-populations 2 and 4)
- biologic-experienced population, defined as patients who had previously been treated with a biologic therapy (assumed to represent clinical sub-population 3).

3.5.1 Summary of trials included in the NMAs

The number of trials identified by the company's literature search for inclusion in the NMAs is unclear. Having examined the company's network diagrams (CS, Appendix D, Figure 2 to Figure 9), the ERG considers that 27 RCTs contributed data to the NMAs, with 24 RCTs contributing data to the biologic-naïve NMAs, and seven RCTs contributing data to the biologic-experienced NMAs. The ERG has not included the EXCEED trial[53] in this total as this trial is not shown in any of the company's network diagrams or in the company's list of studies included in the NMAs (CS, Appendix D, Table 13). However, the company's response to the clarification letter (question A4), and the details provided in the NMA Technical Study Report[46] suggest that the EXCEED trial[53] was included in the company's networks for ACR and PASI outcomes. The ERG therefore considers that the number of trials contributing data to the NMAs is unclear. In this ERG report, trial characteristics are considered for the 27 RCTs included in the company's networks of evidence (biologic-naïve: n=24; biologic-experienced: n=7).

A summary of key characteristics of the comparator treatment RCTs included in the company's NMAs has been provided by the company (CS, Appendix D, Table 13).

The biologic-naïve population NMAs included data from 24 RCTs: 19 phase III trials, one phase II trial, one phase IIIb/IV trial, one phase IV trial, and two trial reports did not specify a phase. All the included trials, with the exception of the SPIRIT-H2H trial[54] were placebo-controlled. The SPIRIT-H2H trial[54] compared ixekizumab Q2W, ixekizumab Q4W and adalimumab Q2W. Five trials (Mease 2018,[55] SPIRIT-H2H,[54] SELECT-PsA 1, SPIRIT-P1,[56] and OPAL-Broaden[37]) included adalimumab as an active comparator arm. The 24 trials provided efficacy data for the following treatments:

- upadacitinib (one trial)[29]
- etanercept (two trials)[57,58]
- adalimumab (seven trials)[29,37,54-56,59,60]
- infliximab (two trials)[61,62]
- golimumab (one trials)[63]
- certolizumab pegol (one trial)[36]
- ixekizumab (two trial)[54,56]
- secukinumab (five trials)[38-41,64]

- apremilast (four trials)[42-44,65]
- tofacitinib (one trial)[37]
- ustekinumab (two trials).[45,66]

The NMAs for the biologic-experienced population included data from seven phase III, placebo-controlled trials. The seven trials provided efficacy data for the following treatments:

- upadacitinib (one trial)
- ixekizumab (one trial)[67]
- secukinumab (three trial)[38,39,41]
- tofacitinib (one trial)[68]
- ustekinumab (one trial).[45]

The company highlights (CS, Appendix D, p35) that the trials that included biologic-experienced patients, included patients who had received different numbers of prior bDMARDs. Similarly, trials that included only biologic-naïve populations included patients who had had different numbers of prior csDMARD and NSAID. All trials, with the exception of the ACTIVE trial,[65] permitted the concomitant use of csDMARDs during the trial period; however, there were differences in the proportion of patients receiving concomitant csDMARDs between the included trials (ranging from 47% of patients who received concomitant MTX [Mease 2000 trial[58]] to 100% of patients who received concomitant csDMARDs [OPAL-Beyond trial[68]]). These three sources of heterogeneity are discussed in Section 3.5.6.

Baseline characteristics of the patients participating in the trials included in the biologic-naïve and biologic-experienced NMAs are provided in the NMA Technical Study Report[46] (Table 7 and Table 8). The company's comparison of patient demographic and baseline characteristics showed that patient demographic characteristics were similar; however, disease durations, prior treatments, degrees of concomitant plaque psoriasis and disease activity (for example, number of joints affected) varied. The ERG agrees with the company's assessment and considers that heterogeneity exists between the trials included in the company's NMAs.

3.5.2 Quality assessment of the trials included in the NMAs

The company conducted a quality assessment of the trials included in the NMAs using the NICE Quality Assessment Tool,[28] which is based on the University of York Centre for Reviews and Dissemination guidance.[48] The ERG considers that, overall, the trials that were included in the company's NMAs are of acceptable methodological quality. The company's quality assessments and ERG comments are presented in Appendix 1 (Table 35) and Appendix 3 (Table 37).

3.5.3 Methodological approach to the NMAs

The company NMAs were carried out using a Bayesian generalised linear model framework. The company assumed that data for each outcome of interest adhered to a specific distribution and applied an appropriate link function (Table 9).

Table 9 Distribution and link functions used for each NMA outcome

Outcome	Distribution	Link function
PsARC	Binomial	Logistic
PASI 50/75/90	Multinomial	Probit (used to jointly model PASI 50/75/90)
HAQ-DI change conditional on PsARC response	Normal	Linear
ACR 20/50/70	Multinomial	Probit (used to jointly model ACR 20/50/70)

ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire-Disability Index; NMA=network meta-analysis; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria
Source: CS, page 84

Data from trials with mixed populations

Ten trials[36-45] included in the company's NMAs recruited biologic-naïve and biologic-experienced patients but did not provide results stratified by sub-population. In these cases, the company used the overall population data in the biologic-naïve NMAs if <50% of patients had received prior biologic treatment and used the data in the biologic-experienced NMAs if ≥50% of patients had received prior biologic treatment. The ERG considers that this approach was reasonable despite being a source of heterogeneity. The company explored the impact of using data from mixed populations on the Week 12 NMA results by removing trials that recruited mixed populations from these NMAs.

Data for mixed populations were used in the Week 12 NMAs for the outcomes listed in Table 10. Only one trial[45] in the biologic-experienced Week 12 NMAs network included a mixed population.

Table 10 Week 12 NMA outcome results generated using data from mixed populations (biologic-naïve and biologic-experienced patients)

	PsARC	PASI	HAQ-DI change conditional on PsARC	ACR
Biologic-naïve Week 12 NMAs				
FUTURE 2[38]	✓			
FUTURE 3[39]		✓ (PASI 75/90)		
FUTURE 4[40]		✓ (PASI 75/90)		
FUTURE 5[41]		✓ (PASI 75/90)		
OPAL-Broaden[37]	✓	✓ (PASI 75/90)		✓ (ACR 20/50/70/)
PALACE 1[42]	✓	✓ (PASI 50/75)	✓	
PALACE 2[43]	✓	✓ (PASI 50/75)	✓	
PALACE 3[44]	✓	✓ (PASI 50/75)	✓	
RAPID-PsA[36]	✓			
Biologic-experienced Week 12 NMAs				
PSUMMIT 2[45]	✓			

ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire-Disability Index; NMA=network meta-analysis; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria
Source: adapted from NMA technical report,[46] Table 1 and Table 2

Timepoints for outcome assessments

For the biologic-naïve Week 12 NMAs, the majority of studies reported outcomes between Week 12 and Week 16. Outcome data from Week 14 and Week 16 were used where data from Week 12 were not reported. For the biologic-experienced Week 12 NMAs, the majority of studies reported outcomes at Week 12.

For the outcomes and trials provided in Table 11, Week 24 data were included in the Week 12 NMAs. The inclusion of Week 24 data in the company's Week 12 NMAs is a source of heterogeneity. No sensitivity analyses were performed to explore the impact of using Week 24 data in the Week 12 NMAs.

Table 11 Trials and outcomes for which Week 24 data were included in the biologic-naïve and biologic-experienced Week 12 NMAs

	PsARC	PASI	HAQ-DI change conditional on PsARC	ACR
Biologic-naïve Week 12 NMAs				
FUTURE 3[39]		✓ (PASI 75/90)		
Mease 2004[57]		✓ (PASI 50/75)		
PSUMMIT 1[66]	✓			
PSUMMIT 2[45]	✓			
PSUMMIT 1+2 pooled analysis[a]			✓	
SPIRIT-H2H[54]		✓ (PASI 75/90)		
Biologic-experienced Week 12 NMAs				
FUTURE 2[38]		✓ (PASI 75/90)		
PSUMMIT 2[45]	✓		✓	

[a] PSUMMIT 1+2 is a pooled analysis of the PSUMMIT 1 and PSUMMIT 2 trials that was used to inform the biologic-naïve NMA for HAQDI change conditional on PsARC response,[69] as data for this outcome were not available from the individual trials
ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire-Disability Index; NMA=network meta-analysis; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria
Source: adapted from NMA Technical Study Report,[46] Table 1 and Table 2

PASI 50/75/90 and ACR20/50/70

Some trials[37-45,54-58,64,67,68] reported data for a subset of PASI 50/75/90 outcomes (i.e., PASI 75 was reported by all the trials included in the biologic-naïve and biologic-experienced Week 12 NMAs for PASI outcomes, whereas PASI 50 and PASI 90 were not reported by all trials [CS, Table 40 and Table 41]). However, as the PASI 50, PASI 75 and PASI 90 outcomes were modelled jointly, the company was able to produce results for all PASI outcomes for comparators for which only data for a subset of PASI outcomes were available from the included trials. The same is true for the ACR20/50/70 outcomes; some trials[38-40,42-44,54] reported data for a subset of ACR 20/50/70 outcomes (i.e., ACR20 was reported by all but one[54] of the trials included in the biologic-naïve Week 12 NMAs and by all trials included in the biologic-

experienced Week 12 NMAs for ACR outcomes, whereas ACR50 and ACR70 were not reported by all trials). ACR outcomes were also modelled jointly.

Model selection: biologic-naïve Week 12 NMAs

For the biologic-naïve Week 12 NMAs, the company considered applying fixed-effects and random-effects models, with and without an adjustment for baseline risk, referred to by the company as a "placebo response adjustment". A placebo response adjustment means that differences in the placebo response rate between trials are accounted for when modelling relative treatment effects.

The company examined model statistics (β, 1/τ, and Deviance Information Criteria [DIC]) to inform their decisions about whether to apply fixed-effects or random-effects models, and whether to apply the placebo response adjustment. The company also examined plots showing placebo response rates across the included trials for each outcome of interest (NMA Technical Study Report,[46] Figure 17 to Figure 21) to determine whether a placebo response adjustment was necessary.

The company concluded that a placebo response adjustment was required to capture treatment effect modification by placebo response rates for the outcomes of PsARC, PASI, and ACR, but was not required for the outcome of HAQ-DI score change (conditional on PsARC response). The ERG considers that the decisions made by the company on whether to use a placebo response adjustment were appropriate.

The company concluded that random-effects models were required (in addition to the placebo response adjustment) for PsARC, PASI, and ACR to capture residual between trial heterogeneity. For HAQ-DI score change (conditional on PsARC response), the company concluded that a fixed-effects model (with no placebo response adjustment) was sufficient to model this outcome. The company provided results from random-effects models (with no placebo response adjustment) for the outcome of HAQ-DI score chance conditional on PsARC response in response to clarification letter, question A7.

The company's sensitivity analyses that excluded data for mixed populations were conducted using the same models as were used for the base-case NMAs (i.e., random-effects models with placebo response adjustment for PsARC, PASI and ACR responses, and fixed-effects models for HAQ-DI score change conditional on PsARC response).

Model selection: biologic-experienced Week 12 NMAs

For the biologic-experienced Week 12 NMAs, the company implemented only fixed-effects models with no placebo response adjustment due to the sparsity of the networks. In the

biologic-experienced Week 12 NMAs, most treatments were connected within the network by a single trial. The company confirmed that it was therefore difficult to estimate the cross-trial (statistical) heterogeneity parameter (1/τ) in random-effects models, and it was also difficult to accurately estimate the extent to which placebo response rates modify the treatment contrast in placebo response adjusted models (company response to the clarification letter, question A5). The ERG considers that the company's rationale for implementing only fixed-effects models with no placebo response adjustments is reasonable. The company's clarification response included results from random-effects models (with no placebo response adjustment) for the biologic-experienced Week 12 NMAs.

The company's sensitivity analysis excluding data for mixed populations from the NMA for PsARC response was conducted using the same model as used for the base-case NMA (i.e., fixed-effects model with no placebo response adjustment).

3.5.4 Results from the company Week 12 NMAs

As relative rather than absolute effect estimates are used in the company's economic model, the ERG has presented key relative effect estimates generated by the company Week 12 NMAs for upadacitinib versus each comparator. Absolute effect estimates (for each individual treatment) are provided in the CS, Appendix D, Table 16 (biologic-naïve Week 12 NMAs) and Appendix D, Table 17 (biologic-experienced week 12 NMAs).

Biologic-naive Week 12 NMA results

The networks of evidence for each of the outcomes are provided in the CS (Appendix D, Figure 2 to Figure 5). A summary of relative effect estimates, for each outcome, for upadacitinib versus comparator treatments is provided in Table 12.

Table 12 Treatment effect estimates for upadacitinib versus comparators: biologic-naïve Week 12 NMAs

Comparator	ACR20 OR (95% CrI)	ACR50 OR (95% CrI)	ACR70 OR (95% CrI)	PASI 50 OR (95% CrI)	PASI 75 OR (95% CrI)	PASI 90 OR (95% CrI)	PsARC OR (95% CrI)	Difference in HAQ-DI cfb	
								PsARC responders (95% CrI)	PsARC non-responders (95% CrI)
PBO									
ADA									
APR									
CZP								-	-
ETN									
GOL									
INF									
IXE 80mg Q4W								-	-
SEC 150mg								-	-
SEC 300mg								-	-
TOF								-	-
UST									

Green shading indicates a statistically significant difference in favour of UPA; red shading indicates a statistically significant difference in favour of the non-UPA comparator
ACR=American College of Rheumatology; ADA=adalimumab; APR=apremilast; cfb=change from baseline; CRT=certolizumab pegol; CrI=credible interval; ETN=etanercept; HAQ-DI=Health Assessment Questionnaire-Disability Index; GOL=golimumab; INF=infliximab; IXE=ixekizumab; NMA=network meta-analysis; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria; PBO=placebo; Q2W=once every 2 weeks; Q4W=once every 4 weeks; SEC=secukinumab; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab
Source: CS, Figure 10 to Figure 13

For ACR response, results for upadacitinib versus each comparator were similar across the ACR outcomes (ACR20, ACR50, and ACR70). The ERG considers that the results for ACR20 are the most reliable as all trials (except the SPIRIT-H2H trial[54]) contributed data for this outcome.

For PASI response, results for upadacitinib versus each comparator were similar across the PASI outcomes (PASI 50, PASI 75, and PASI 90). The ERG considers that the results for PASI 75 are the most reliable as all trials contributed data for this outcome.

For the comparisons of upadacitinib versus placebo, adalimumab, apremilast and golimumab, PsARC responder status made little difference to the efficacy of upadacitinib in terms of change in baseline from HAQ-DI score. For other comparisons, namely upadacitinib versus ustekinumab, etanercept and infliximab, the change in baseline from HAQ-DI score associated with upadacitinib varied between PsARC responders and non-responders; it was not possible to assess these differences formally as these analyses were not powered to detect subgroup differences. For all of these comparisons, the relative efficacy (change in baseline from HAQ-DI score) of upadacitinib was better among PsARC non-responders.

Absolute effect estimates from the sensitivity analyses that excluded data from mixed populations are provided in the CS (Appendix D, Table 20). The ERG compared the absolute effect estimates generated by the company base case and sensitivity NMAs (CS, Appendix D, Table 16 and Table 20) and concluded that the inclusion of mixed data in the biologic-naive Week 12 NMAs had little impact on the observed results.

Results for some comparators were not available from the sensitivity analyses as these comparators were linked to the network solely by trials reporting data for mixed (biologic-naïve and biologic-experienced) populations, namely:

- **PsARC response**: apremilast, certolizumab pegol, secukinumab 150mg and secukinumab 300mg
- **PASI response and HAQ-DI score**: apremilast.

The company provided results from random-effects models for the HAQ-DI score conditional on PsARC response NMAs (company response to the clarification letter, question A7). The relative effect estimates generated by the random-effects models are very similar to those generated by the fixed-effects models, suggesting that the choice of fixed versus random-effects has little impact on the results of this NMA.

Biologic-experienced Week 12 NMA results

The networks of evidence for each of the outcomes are provided in the CS (Appendix D, Figure 6 to Figure 9). A summary of effect estimates for upadacitinib versus the included comparators for each outcome are provided in Table 13.

Table 13 Treatment effect estimates for upadacitinib versus comparators: biologic-experienced Week 12 NMAs

Comparator	ACR20 OR (95% CrI)	ACR50 OR (95% CrI)	ACR70 OR (95% CrI)	PASI50 OR (95% CrI)	PASI75 OR (95% CrI)	PASI90 OR (95% CrI)	PsARC OR (95% CrI)	Difference in HAQ-DI cfb	
								PsARC responders (95% CrI)	PsARC non-responders (95% CrI)
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
SEC 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green shading indicates a statistically significant difference in favour of UPA
ACR=American College of Rheumatology; cfb=change from baseline; CrI=credible interval; HAQ-DI=Health Assessment Questionnaire Disability Index; IXE=ixekizumab; NMA=network meta-analysis; PASI=Psoriasis Area and Severity Index; PsARC=Psoriatic Arthritis Response Criteria; PBO=placebo; Q2W=once every 2 weeks; Q4W=once every 4 weeks; SEC=secukinumab; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab
Source: CS, Figure 14 to Figure 17

For ACR response, results for upadacitinib versus each comparator were similar across the ACR outcomes (ACR20, ACR50, and ACR70). For PASI response, results for upadacitinib versus each comparator were similar across the PASI outcomes (PASI 50, PASI 75, and PASI 90). The ERG considers that the results for ACR20 and PASI 75 and are the most reliable ACR and PASI outcomes as all trials contributed data for these outcomes.

For upadacitinib versus placebo, PsARC responder status made little difference to change in baseline HAQ-DI score results. For upadacitinib versus ustekinumab, the efficacy of upadacitinib varied between PsARC responders and non-responders; it is not possible to assess this difference formally as the analysis was not powered to detect a subgroup difference. For this latter comparison, the relative efficacy of upadacitinib is better among PsARC non-responders.

Absolute effect estimates from the sensitivity analysis excluding PsARC data from PSUMMIT 2[45] (this trial was the only one conducted in a mixed population) are provided in the CS (Appendix D, Table 20). The ERG compared the absolute effect estimates from the base case and sensitivity NMAs for PsARC (CS, Appendix D, Table 17 and Table 20) and concluded that the inclusion of mixed population data had little impact on results. Results for ustekinumab were not available from the sensitivity analysis as ustekinumab is only linked to the biologic-experienced network by the PSUMMIT 2[45] trial.

The company provided results from random-effects models for the biologic-experienced Week 12 NMAs (company response to NICE clarification letter, question A7). The relative effect estimates generated by the random-effects models are very similar to those generated by the fixed-effects models, although the 95% credible intervals (CrIs) generated by the random-effect models are wider those generated by the fixed-effect models due to uncertainty around the heterogeneity parameter estimate. The ERG considers that if there is important heterogeneity between the trials included in the biologic-experienced Week 12 NMAs, random-effects models have been unable to accurately estimate and account for this heterogeneity due to the sparsity of the networks of evidence.

3.5.5 Comparison of direct and indirect evidence

The ERG compared the direct results from the SELECT-PsA 1and SELECT-PsA trials with the results from the NMAs. For three outcomes (ACR, PASI and PsARC), the effect measure reported in the SELECT-PsA 1 and SELECT-PsA 2 trials was the response rate difference, whereas the effect measure generated by the NMAs was an odds ratio. However, results from all analyses showed that the reported effect estimates consistently favoured upadacitinib

versus adalimumab and versus placebo. The effect measure reported by the SELECT-PsA 1 and SELECT-PsA 2 trials and the effect measure generated by the NMAs for HAQ-DI score was least squares mean difference; results from these sources were numerically comparable.

3.5.6 ERG interpretation of the results from the Week 12 NMAs

Results from comparisons of upadacitinib versus relevant treatments show that, for most outcomes, the CrIs around the observed effect point estimates are often wide and do not exclude the point of no effect. The company concluded for both the biologic-naïve and biologic-experienced Week 12 NMAs that "overall, upadacitinib 15mg showed broadly equivalent results compared to the current therapeutic options" (CS, p96 and p101). However, the ERG highlights that an absence of a statistically significant effect does not provide evidence of no effect and when the CrIs are wide it is not possible to draw conclusions about the relative efficacy of treatments. Furthermore, some statistically significant effects both for and against treatment with upadacitinib were observed (see Table 12 and Table 13).

There are various sources of heterogeneity between the trials included in the company's NMAs. For the biologic-naive Week 12 NMAs, the company was able to estimate (statistical) heterogeneity ($1/\tau$) and account for heterogeneity (where applicable) in their analyses. For the biologic-experienced Week 12 NMAs, the company was unable to accurately estimate (statistical) heterogeneity ($1/\tau$) due to the sparsity of the networks of evidence. The company therefore employed fixed-effects models for all outcomes in these NMAs.

The ERG considers that, if important heterogeneity exists between the trials included in the biologic-experienced Week 12 NMAs, random-effects models have been unable to accurately estimate and account for this heterogeneity. Identified possible sources of heterogeneity that affect the biologic-experienced NMA results are:

- different numbers of prior treatments (NSAID, csDMARD, bDMARDs)
- proportion of patients with concomitant use of csDMARD
- wide-ranging disease durations
- proportion of patients with concomitant plaque psoriasis
- disease activity (number of joints)
- the time-points at which outcomes were assessed (inclusion of Week 14 and Week 16 data in some of the Week 12 NMAs for the biologic-naïve population, inclusion of Week 24 data in some of the Week 12 NMAs for the biologic-experienced population)
- mixed populations (biologic-naïve and biologic-experienced).

3.6 Safety and tolerability results

3.6.1 Upadacitinib safety and tolerability data

SELECT-PsA 1 and SELECT-PsA 2 trial safety and tolerability (24 Week) data are presented in the CS (Section B.2.10), with additional data provided in Appendix F. Data are provided for treatment exposure and subsequent therapy, any AEs, treatment-emergent adverse events (TEAEs) in ≥5% of patients, TEAEs of special interest, TEAEs relating to treatment discontinuation, TEAEs with a reasonable possibility of being related to the study drug, and deaths.

The mean (standard deviation [SD]) duration of study drug exposure in the SELECT-PsA 1 trial was similar across all three arms: [redacted] days for upadacitinib, [redacted] days for adalimumab, and [redacted] days for placebo. The mean (SD) duration of exposure in the SELECT-PsA 2 trial was [redacted] days for upadacitinib and [redacted] days for placebo.

Overall, the AE profile of upadacitinib is similar for patients in the upadacitinib arms of the SELECT-PsA 1 and SELECT-PsA 2 trials. The AE profile of upadacitinib is also similar to the AE profile of adalimumab (SELECT-PsA 1) and placebo (SELECT-PsA 1 and SELECT-PsA 2). The main exception was that a higher rate of AEs related to blood creatine phosphokinase was experienced by patients treated with upadacitinib compared to patients treated with placebo in the SELECT-PsA 1 trial [redacted] versus [redacted] respectively). In addition, a lower proportion of patients treated with upadacitinib reported AEs related to hepatic disorder compared to patients treated with adalimumab [redacted] versus [redacted] respectively). Clinical advice to the ERG is that, while the duration of exposure is short, it is reassuring that there are no unexpected safety concerns associated with upadacitinib.

3.6.2 Upadacitinib versus comparator safety and tolerability data

Safety was not an outcome that was assessed in the company NMAs. In the clarification letter (question A10), the ERG requested evidence on the safety and efficacy of upadacitinib compared to the comparator drugs. In response to question A10, the company provided rates of AEs, SAEs and AEs resulting in treatment discontinuation that were reported in the comparator trials.

An analysis of Week 24 safety data showed that patients who were treated with upadacitinib and comparator drugs had similar rates of AEs, SAEs and AEs related to treatment discontinuation (biologic-naïve and biologic-experienced patients), with the following exceptions:

- treatment with upadacitinib was associated with a lower rate of AEs (SELECT-PsA 1: [redacted], SELECT-PsA 2: [redacted]), compared to all doses of secukinumab in the FUTURE-2[38] trial at Week 24 (secukinumab 75mg, 150mg or 300mg: 77.8%, 81.8% and 77.9% respectively)

- treatment with upadacitinib was associated with a lower rate of SAEs in both trials (SELECT-PsA 1: [redacted], SELECT-PsA 2: [redacted]) compared to secukinumab 75mg in the FUTURE-2[38] trial at Week 24 [12.1%])

The ERG highlights that the values from the FUTURE-2[38] trial are based on calculated values for Week 24 presented by the company in their clarification response (response to clarification letter, question A10, Table 31). The company does not provide details of how these values were calculated.

The ERG also highlights that the reported rates from the FUTURE-2[38] trial of AEs and SAEs for seckukinab are higher than were reported for secukinumab in the FUTURE-5 trial,[41] which is the only other trial of secukinumab for the mixed population with Week 24 safety data. Rates of any AEs, any SAEs and any AEs related to treatment discontinuation were similar in the tria FUTURE-5 trial[41] to the rates reported for patients treated with upadacitinib in the SELECT-PsA 1 and SELECT-PsA 2 trials.

Clinical advice to the ERG is that the AEs related to treatment with upadacitinib are likely to be similar to the AEs related to the comparator drugs listed in the final scope[18] issued by NICE. However, longer-term follow-up data from disease registries are required before definitive conclusions about the safety of upadacitinib can be reached.

4 COST EFFECTIVENESS EVIDENCE

The CS provides cost effectiveness evidence to support the use of upadacitinib to treat adults with active PsA. The two key components of the economic evidence presented in the CS are (i) a systematic review to identify relevant economic evidence for the current treatment options for adults with moderate-to-severe PsA and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 ERG critique of the company systematic literature review

The company searched for cost effectiveness studies to inform modelling decisions from inception of relevant databases to the date on which the searches were conducted: first search was carried out on 6 September 2019 and subsequent searches were carried out on 26 May 2020 and 3 September 2020. Details of these strategies have been provided by the company (CS, Appendix G). The search did not identify any previous cost effectiveness studies of upadacitinib in patients with moderate-to-severe PsA; however, 55 studies evaluating the cost effectiveness of different treatments for patients with PsA were identified. Seven of these studies are previous NICE Technology Appraisals (TA199,[70] TA220,[71] TA340,[24,72] TA433,[25] TA445,[21,31] TA537,[73] TA543[27]); the company used data and methods presented in these studies to inform their modelling decision approach.

The company also searched the literature to identify utility/HRQoL studies (CS, Appendix H) and studies containing cost and resource use data (CS, Appendix I). The company has provided a summary of studies reporting utility values (Appendix H, Table 57) and a summary of the studies reporting resource use or cost data (Appendix I, Table 75). An assessment of the extent to which the company's literature review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 14.

Table 14 ERG appraisal of company review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	Yes

ERG=Evidence Review Group
Source: LR*i*G in-house checklist

4.2 ERG conclusions

Searches carried out by the ERG did not identify any additional relevant studies. The ERG has no concerns about the methods used by the company to identify evidence to inform modelling decisions and is satisfied that there are no relevant economic studies of upadacitinib available.

4.3 ERG summary and critique of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist and Drummond checklist

Table 15 NICE Reference Case checklist

Element of health technology assessment	Reference case	ERG comment on the company's economic evaluation
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The company has applied discounting from the start of the model rather than from the start of the second year

ERG=Evidence Review Group; PSS=Personal Social Services; QALY=quality adjusted life years
Source: NICE Guide to the Methods of Technology Appraisal[28] and ERG comment

Table 16 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Insufficient evidence available from company NMAs to populate the model and therefore missing values drawn from a variety of sources. In addition, the company NMA results were generated using short-term data (12 Week) and there are some concerns about heterogeneity
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	The consequences of stopping treatment for patients who were deemed responders at 12 weeks (as demonstrated by changes in HAQ-DI) were not incorporated into the company model correctly
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	There was no discussion of the impact of increasing HAQ-DI whilst receiving treatment

ERG=Evidence Review Group; HAQ-DI=Health Assessment Questionnaire-Disability Index; NMA=network meta-analysis
Source: Drummond and Jefferson 1996[28] and ERG comment

4.3.2 Population

The company has considered three populations: biologic-naïve, biologic-experienced and TNF-alpha inhibitor-contraindicated. From this point on, in this report, all clinical sub-populations are referred to as populations (except when citing the decision problem). Patients in the biologic-naïve population receive two active treatment lines. However, patients in the TNF-alpha inhibitor-contraindicated population and in the biologic-experienced population only receive one active treatment.

Table 17 shows how the model populations were matched with the sub-populations specified in the final scope[18] issued by NICE. Three levels of psoriasis severity were considered for the

modelled populations. The baseline characteristics of the modelled populations are shown in Table 18.

Table 17 Sub-populations described in the final scope issued by NICE and sub-populations considered in the company model

Appraisal sub-populations	
Final scope[18] issued by NICE	**Company model**
Inadequate disease response to one csDMARD	Not considered
Inadequate disease response to ≥2 csDMARDs	Biologic-naïve population: eligible to receive two lines of active treatment
TNF-alpha inhibitors are contraindicated or not tolerated	TNF-alpha inhibitor-contraindicated population: eligible to receive one line of active treatment
Inadequate response to csDMARDs and ≥1 TNF-alpha inhibitors	Biologic-experienced population: eligible to receive one line of active treatment

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; TNF=tumour necrotic factor
Source: CS, Table 1

Table 18 Modelled baseline patient characteristics

	Biologic-naïve population and TNF-alpha inhibitor-contraindicated population	**Biologic-experienced population**
Median age (years)	[redacted]	
Percentage female (%)	[redacted]	
Mean weight (kg)	[redacted]	
Disease severity		
No psoriasis	PASI=[redacted]; HAQ-DI=[redacted]	PASI=[redacted]; HAQ-DI=[redacted]
Mild-to-moderate psoriasis	PASI=[redacted]; HAQ-DI=[redacted]	PASI=[redacted]; HAQ-DI=[redacted]
Moderate-to-severe psoriasis	PASI=[redacted]; HAQ-DI=[redacted]	PASI=[redacted]; HAQ-DI=[redacted]
Source	SELECT-PsA 1 trial	SELECT-PsA 2 trial

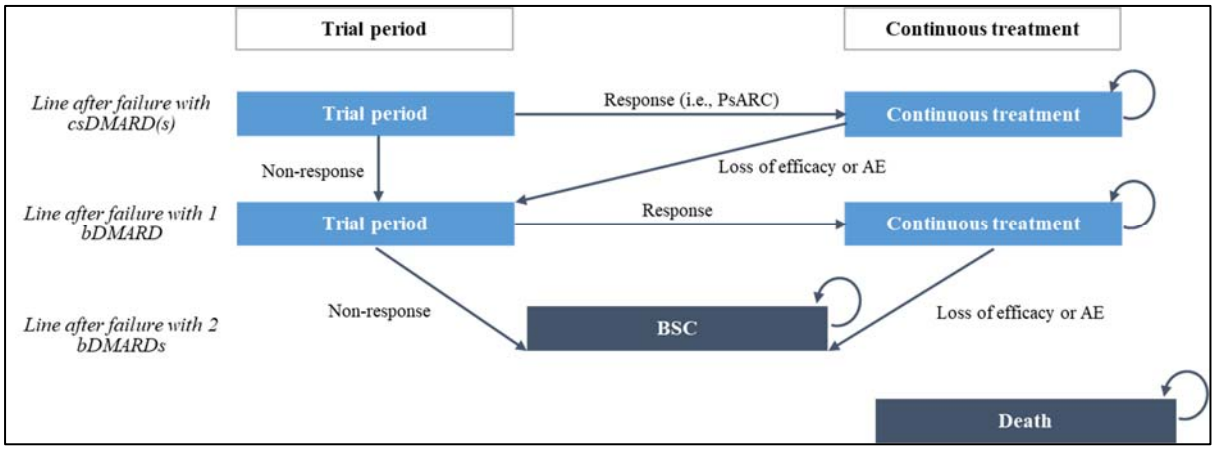
HAQ-DI=Health Assessment Questionnaire-Disability Index; PASI=Psoriasis Area and Severity Index
Source: CS, Section B.3.2.1 and Table 52

4.3.3 Model structure

The company has developed a de novo cost utility model in Microsoft Excel. The model is designed to capture both the costs and health outcomes associated with the joint (arthritis, HAQ-DI) and skin (psoriasis, PASI) components of PsA. It is a cohort-based Markov model comprising six mutually exclusive health states to represent transitions through a maximum of two active treatment lines. First-line refers to treatment after failure with csDMARDs, and second-line refers to treatment after failure with one bDMARD/tsDMARD The health states are: first- and second-line trial period (i.e., Treatment period [TP]-1 and TP-2), first- and

second-line continuous treatment (i.e., Continuous treatment period health state [CT]-1 and CT-2), best supportive care (BSC) and death. The trial periods (12 weeks duration) represent intervals during which patients' responses are assessed. Patients with adequate response progress to, and remain in, the continuous treatment period until treatment is discontinued or death.

The structure of the company model is shown in Figure 2. The company states (CS, Section B.3.2.2) that the model structure aligns with the second revision of the York Model that was used in TA445,[31] and which is now an accepted framework for modelling PsA.[27,31,73] Patients in the biologic-naïve population and TNF-alpha inhibitor-contraindicated population enter the model in the TP-1 health state whilst patients in the biologic-experienced population enter the model in the TP-2 health state.



BSC=best supportive care; bDMARD=biologic disease-modifying anti-rheumatic drug; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug
Note: Each trial period consists of three 4-week tunnel states

Figure 2 Structure of the company model

Source: CS, Figure 18

4.3.4 Interventions and comparators

The modelled intervention is oral upadacitinib (15mg) administered once daily. The comparators vary depending on the modelled populations (Table 19). The modelled dosing schedules for the comparator treatments are shown in Table 20.

Table 19 Modelled treatments by model population

Model population	First active treatment	Permitted second active treatment
Biologic-naïve population	• **Intervention**: upadacitinib • **Comparators**: adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab and tofacitinib	Ustekinumab
TNF-alpha inhibitor-contraindicated population	• **Intervention**: upadacitinib • **Comparators**: ixekizumab, secukinumab, tofacitinib and ustekinumab, BSC	None
Biologic-experienced population	• **Intervention**: upadacitinib • **Comparators***: ixekizumab, secukinumab, tofacitinib and ustekinumab, BSC	None

*Certolizumab pegol was listed as a comparator in the NICE scope,[74] but was not modelled for the biologic-experience population
BSC=best supportive care; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; TNF=tumour necrotic factor
Source: CS, Section B.3.2.3

Table 20 Modelled dosing schedules for comparator treatments

Treatment	Route	Dosing schedule
Adalimumab	SC	40mg every two weeks
Apremilast	Oral	Initial titration schedule (week 0 to week 2) then 30mg twice daily
Certolizumab pegol	SC	400mg at week 0, 2 and 4, then 200mg every 2 weeks
Etanercept	SC	25mg twice a week or 50mg every week
Golimumab	SC	50mg every month or 100mg every month (if body weight >100kg and no adequate clinical response to 50mg after 3 or 4 doses)
Infliximab	IV	5mg/kg at week 0, 2 and 6, then 5mg/kg every 8 weeks
Ixekizumab	SC	160mg at week 0, then 80mg every 4 weeks
Secukinumab	SC	150mg or 300mg at week 0, 1, 2, 3 and 4, then 150mg or 300mg every month
Tofacitinib	Oral	5mg twice daily
Upadacitinib	Oral	15mg once daily
Ustekinumab	SC	45mg at week 0 and 4, the 45mg every 12 weeks (90mg may be used if body weight >100 kg)

IV=intravenous; kg=kilogram; mg=milligram; SC=subcutaneous
Source: CS, Section B.3.2.3, Table 54

4.3.5 Perspective, time horizon and discounting

The company states that, in line with the NICE Reference Case,[28] the perspective of the model is the NHS and Personal Social Services (PSS). The cycle length in the company model is 1 week, the time horizon is 25 years, and costs and outcomes are discounted at 3.5% per annum.

4.3.6 Treatment effectiveness and extrapolation

The modelled measures of treatment effectiveness are PsARC response, time-to-treatment discontinuation rate, HAQ-DI and PASI 50/75/90 response. The model is primarily structured to reflect patients' progression through treatment lines using PsARC and annual discontinuation rate. Disease severity is captured within each treatment-related health state (i.e., TP health states and CT health states) using HAQ-DI and PASI 50/70/90.

The sources of all upadacitinib effectiveness evidence, with the exception of annual treatment discontinuation rate, that are used to populate the company model are the SELECT-PsA 1 and SELECT-PsA 2 trials. The company performed NMAs to generate effectiveness evidence for the comparison of upadacitinib versus all comparator treatments. The sources of the treatment effectiveness estimates used in the company model are shown in Table 21.

Table 21 Sources of treatment effectiveness estimates used in the company model

Population in company model	Source of treatment effectiveness estimate	Company justification
Biologic-naïve population	SELECT-PsA 1 trial and company biologic-naïve NMAs and other sources	Clinical advice received by the NICE AC that considered the use of ixekizumab in patients with active PsA (TA537[73]) was that the efficacy of a biologic therapy is the same irrespective of whether patients have had one or two prior csDMARDs
TNF-alpha inhibitor-contraindicated population		Clinical advice to the company was that the effectiveness of upadacitinib in the TNF-alpha inhibitor-contraindicated population is similar to the effectiveness of upadacitinib in the biologic-naïve population
Biologic-experienced population	SELECT-PsA 2 trial, company biologic-experienced NMAs and other sources	Results from a post-hoc analysis of the SELECT-PsA 2 trial data showed that the efficacy of treatment with upadacitinib in patients who had received one prior bDMARD is similar to the efficacy of treatment with upadacitinib in people that have received multiple prior bDMARDs

AC=Appraisal Committee; bDMARD=biologic disease-modifying anti-rheumatic drug; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; NMA=network meta-analysis; TA=technology appraisal; TNF=tumour necrotic factor
Source: CS, Section B.3.3

Modelling Psoriatic Arthritis Response Criteria

The company's model was populated with PsARC response rates generated by the company's Week 12 NMAs (Table 22), specifically:

- biologic-naïve population: random-effects model with placebo-response adjustment
- biologic-experienced population: fixed effects model (no placebo-response adjustment).

Table 22 PsARC response rates used in the company model (company NMA results)

Treatment	Biologic-naïve and TNF-alpha inhibitor-contraindicated populations (95% CrI)	Biologic-experienced population (95% CrI)
Upadacitinib	[redacted]	[redacted]
Adalimumab	[redacted]	–
Apremilast	[redacted]	–
Certolizumab pegol	[redacted]	–
Etanercept	[redacted]	–
Golimumab	[redacted]	–
Infliximab	[redacted]	–
Ixekizumab	[redacted]	[redacted]
Secukinumab 150mg	[redacted]▼	–
Secukinumab 300mg	[redacted]▲	68.6% (41.0% to 88.0%)*
Tofacitinib	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

*=extracted from the network meta-analysis results reported in the NICE Technology Appraisal of certolizumab pegol and secukinumab (TA445[31]) for treating active psoriatic arthritis after inadequate response to disease modifying antirheumatic drugs
▼=value for patients with no psoriasis or concomitant mild-to-moderate plaque psoriasis
▲=value for patients with concomitant moderate-to-severe plaque psoriasis
CI=confidence interval; mg=milligram; TNF=tumour necrosis factor
Source: CS, Table 56

Modelling HAQ-DI

Improvements in HAQ-DI over the trial period (ΔHAQ-DI) conditional on PsARC status were available from the company NMAs (Table 23). Summary trial results for changes in HAQ-DI conditional on PsARC status (responders and non-responders) were not available for certolizumab pegol, secukinumab, ixekizumab and tofacitinib, so these estimates were imputed using a similar approach to that used in a previous NICE Technology Appraisal (TA543[27]).

Patients within treatment-related health states (i.e., TP health states and CT health states) consist of responders and non-responders. The population in these health states is therefore the PsARC-weighted average of these two groups of patients. During the trial period (i.e., TP health states), all patients were assumed to experience an improvement in their baseline HAQ-

DI; responders accrued greater HAQ-DI benefit than non-responders. During the continuous treatment phase (CT health states), responders maintained their HAQ-DI improvement whilst non-responders gradually returned to their baseline HAQ-DI. The ERG highlights that this does not match the approach used in the company model (see Section 6.2.1 for details).

The annual rate (0.072) used to model return to baseline HAQ-DI score was based on a re-analysis of data from the Norfolk Arthritis Register (NOAR) study.[75,76]

Table 23 Change in HAQ-DI conditional on PsARC values used in the company model

Treatment	Biologic-naïve and TNF-alpha inhibitor-contraindicated populations (95% CI)		Biologic-experienced population (95% CI)	
	Responders	Non-responders	Responders	Non-responders
Upadacitinib 15mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	–	–
Apremilast	[redacted]	[redacted]	–	–
Certolizumab pegol*	[redacted]	[redacted]	–	–
Etanercept	[redacted]	[redacted]	–	–
Golimumab	[redacted]	[redacted]	–	–
Infliximab	[redacted]	[redacted]	–	–
Ixekizumab*	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150mg*	[redacted]▼	[redacted]▼	[redacted]	[redacted]
Secukinumab 300mg*	[redacted]▲	[redacted]▲	[redacted]	[redacted]
Tofacitinib*	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

*=imputed values
▼=value for patients with no psoriasis or concomitant mild-to-moderate plaque psoriasis
▲=value for patients with concomitant moderate-to-severe plaque psoriasis
CI=confidence interval; mg=milligram; TNF=tumour necrosis factor
Source: CS, Table 57

Modelling Psoriasis Area and Severity Index

Estimates of the proportions of patients achieving ≥50%, ≥75% and ≥90% relative improvement in PASI scores from baseline (i.e., PASI 50/75/90 respectively) that were generated by the company's NMAs are provided in the CS (Table 62). Similar to the HAQ-DI estimation approach, this group of outcomes was also specific to each treatment, conditional on PsARC status and patients were assumed to maintain their PASI whilst on treatment but gradually returned to their baseline PASI once treatment had stopped.

Modelling time to treatment discontinuation

In the company model, biologic-naïve patients stop receiving first-line treatment (i.e., transition from the CT-1 health state to the TP-2 health state) at a fixed annual rate of 0.165. The company considered that this fixed rate approach was consistent with the rates used in TA199[70] and TA445.[31] The original source of the fixed discontinuation rate (0.165) in the company model and the two previous NICE Technology Appraisals (TA199[70] and TA445[31]) was a systematic review conducted by Rodgers et al (Appendix 12, Table 62).[77]

Clinical advice to the company is that the annual discontinuation rates for the biologic-experienced population are higher than the annual discontinuation rates for the biologic-naïve population. Results from an analysis of Swiss rheumatoid arthritis registry data (Gabay 2015)[78] showed higher annual discontinuation rates for the biologic-experienced population compared with annual discontinuation rates for the biologic-naïve population (HR=1.24; 95% CI: 1.09 to 1.41). To estimate the fixed annual discontinuation rate for the biologic-experienced population, the company applied the annual discontinuation rate HR estimated by Gabay et al[78] to the fixed annual discontinuation rate for the biologic-naïve population (i.e., 0.165*1.24=0.205). The annual discontinuation rates used in the company model are shown in Table 24.

Table 24 Annual treatment discontinuation rates used in the company model

	CT-1 to TP-2	CT-2 to BSC
Biologic-naïve population	0.165	0.205
TNF-alpha inhibitor-contraindicated population	0.205	NA
Biologic-experienced population	NA	0.205

BSC=best supportive care; CT-1=first-line continuous treatment health state; CT-2=second-line continuous treatment health state; NA=not applicable TNF=tumour necrosis factor; NA=not applicable; TP-2=second-line trial period health state
Source: CS, Section B.3.3.4.2

General mortality cap

Age- and gender-specific mortality rates were taken from published national life tables for England and Wales,[79] using projections for 2017-19. Excess mortality risk attributable to PsA was implemented using a standardised mortality ratio of 1.05 that was obtained from TA537.[73]

4.3.7 Health-related quality of life

Modelling health state utility values in the company model

The HRQoL estimates used in the economic model were based on health state HAQ-DI and PASI values and EQ-5D-5L data collected as part of the SELECT-PsA 1 and SELECT-PsA 2 trials.

The company mapped SELECT-PsA 1 and SELECT-PsA 2 trial EQ-5D-5L questionnaire data to the UK EQ-5D-3L value set using a published crosswalk algorithm,[80] in line with the NICE position statement[81] on the valuation of EQ-5D-5L questionnaire scores. The company then used a regression-based method to estimate the relationship (i.e., coefficient) between utility values and HAQ-DI and PASI values. Separate regression models were fitted to the SELECT-PsA 1 trial data (for the biologic-naïve population and TNF-alpha inhibitor-contraindicated population) and the SELECT-PsA 2 trial data (for the biologic-experienced population) as shown in Table 25. The company applied the regression coefficients to the HAQ-DI and PASI values associated with each health state (CS, Table 68).

Table 25 Base case utility coefficients derived from the regression-based equations that were used to generate treatment-specific health state utility values

Independent variable	Biologic-naïve population and TNF-alpha inhibitor-contraindicated population Mean (SE)	Biologic-experienced population Mean (SE)
Intercept	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]
PASI	[redacted]	[redacted]

HAQ-DI=Health Assessment Questionnaire-Disability Index; PASI=Psoriasis Area and Severity Index; SE=standard error; TNF=tumour necrosis factor
Source: CS, Table 66

The approach taken by the company means that utility gains are assumed to increase linearly whilst patients are in TP health states and are in line with the HAQ-DI and PASI for those health states. Similarly, given that HAQ-DI and PASI in the CT health states are conditional on PsARC, the relevant health state utility values are conditional on PsARC, HAQ-DI and PASI.

Impact of adverse events on health-related quality of life

The impact of AEs on HRQoL was not captured in the economic model due to the uncertainty around the estimation of AE rates.

4.3.8 Resources and costs

The following categories of costs were included in the company model (CS, Section B.3.5):

- drug acquisition costs
- drug administration costs
- routine monitoring costs
- health state costs
- AEs costs

Drug acquisition costs

The drug acquisition costs used in the company model are presented in

Table 27. The unit cost of MTX was obtained from the drug and pharmaceutical electronic Market Information Tool (eMIT) database[82] whilst unit costs for other drugs were obtained from the Monthly Index of Medical Specialities (MIMS) database.[83] Unit drug costs for branded and biosimilar agents are available from MIMS and the eMIT. The company assumed equivalent efficacy for biosimilar and branded formulations of the same agent; therefore, the least expensive biosimilar pricing for treatments that had biosimilars (i.e., etanercept, infliximab and MTX were used in the base case.

In the base case analysis, the PAS price of upadacitinib and the CMU price of adalimumab were used. Ixekizumab, secukinumab, apremilast and tofacitinib are also available to the NHS at confidential PAS prices (these prices are not known to the company and, therefore, list prices for these drugs were used in the company base case analyses). Certolizumab pegol, golimumab and ustekinumab are also available to the NHS at discounted prices.[17] Descriptions of these discounts are provided in Table 26 and the drug acquisition costs used in the company model are provided in Table 27.

Table 26 Drug acquisition cost discounts used in the company model

Drug	Description of discount
Certolizumab pegol	First 3 months provided free of charge
Golimumab	100mg dose provided at the price as the 50mg dose
Ustekinumab	90mg dose provided at the same price as the 45mg dose

Source: CS, Section B.3.5.1.1

Table 27 Drug acquisition costs used in the company model

Drug	Cost per unit	Units required		% receiving MTX in combination*	Drug cost per 4-week cycle including cost of MTX	
		TP	CT		TP	CT
Upadacitinib 15mg🡻	[redacted]	84.0	364.0	70%	[redacted]	[redacted]
Upadacitinib 15mg🡹	[redacted]	84.0	364.0	39%	[redacted]	[redacted]
Adalimumab	[redacted]	6.0	26.0	64%	[redacted]	[redacted]
Apremilast	£9.82	126.0	728.0	5%	£546.75	£550.03
Certolizumab pegol	£357.50	9.0	26.0	32%	£0.17	£715.17
Etanercept	£82.00	24.0	104.0	49%	£643.76	£643.76
Golimumab	£762.97	3.0	12.0	45%	£763.21	£704.52
Infliximab	£377.00	15.0	32.5	70%	£1,885.37	£942.87
Ixekizumab	£1,125.00	4.0	13.0	28%	£1,500.14	£1,125.14
Secukinumab 150mg▼	£609.39	6.0	15.0	40%	£1,218.99	£562.72
Secukinumab 300mg▲	£609.39	12.0	24.0	40%	£2,437.77	£1,125.24
Tofacitinib	£12.32	168.0	728.0	63%	£690.36	£690.36
Ustekinumab	£2,147.00	2.0	4.3	20%	£1,431.44	£715.77
Methotrexate*	£0.04	N/A	156	N/A	£0.53	£0.53

*=methotrexate is used in combination with other treatment at a cost of £0.53 per 4-week treatment cycle
🡻=proportion of patients receiving methotrexate in combination with drug obtained from SELECT-PsA 1 trial
🡹=proportion of patients receiving methotrexate in combination with drug obtained from SELECT-PsA 2 trial
▼=values for patients with no psoriasis or concomitant mild-to-moderate plaque psoriasis in the biologic-naïve population
▲=values for patients with concomitant moderate-to-severe plaque psoriasis in the biologic-naïve population or tumour necrosis factor-alpha inhibitor-contraindicated population, and all patients in the biologic-experienced population
%=percentage; CT=continuous treatment period health state; mg=milligram; MTX=methotrexate; TP=treatment period health state
Source: CS, Table 70

Drug administration costs

The administration costs used in the company model are provided in Table 28.

Table 28 Drug administration costs

Route	Unit cost per administration	Source/service code
Subcutaneous	£42.00	PSSRU (2019):[84] nurse (GP practice) wage cost per hour
Intravenous	£183.54	NHS Reference Cost (2019):[85] SB12Z
Oral	£0.00	Assumption based on TA543[27] and TA537[73]

GP=general practice; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSSRU=Personal and Social Services Research Unit; TA=Technology Appraisal
Source: CS, Table 71

Routine monitoring cost

Modelled drug monitoring requirements (Table 29) were based on those used in a previous NICE Technology Appraisal (TA445[31,86]) and on expert opinion. The company states that resource use estimates align with the British Society of Rheumatology guideline.[87]

Table 29 Frequency of treatment monitoring resource use and associated unit cost

Service	Unit cost	NHS Reference Cost (2019)[85] code	Frequency	
			TP	CT
Rheumatologist visit	£143.49	WF01A	4	2
Full blood count	£2.79	DAPS05	8	4
Liver function test	£1.10	DAPS04	8	4
Urea and electrolyte	£1.10	DAPS04	8	4
ESR/CRP	£2.79	DAPS05	2	2
Chest X-ray	£30.59	DAPF	1	0
TB Heaf test/quantiferon	£58.24	WF01A	1	0
ANA test	£2.79	DAPS05	1	0
dsDNA test	£2.79	DAPS04	1	0

ANA=antinuclear antibody; CRP=C-reactive protein; CT=continuous trial period (annual); dsDNA=double strand deoxyribonucleic acid; ESR=erythrocyte sedimentation rate; GP=general practice; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSSRU=Personal and Social Services Research Unit; TA=Technology Appraisal; TB=tuberculosis; TP=treatment period
Source: CS, Table 73 and Table 74

Arthritis- and psoriasis-related healthcare costs

In line with previous appraisals (TA445[31] and TA543[27]) and consistent with the approach that the company used to estimate health state utility values in the economic model, health state costs were estimated based on HAQ-DI (arthritis measure) and PASI (psoriasis measure). This approach meant that arthritis- and psoriasis-related costs gradually increased over time for health state occupants.

A regression-based algorithm developed by Bansback (2006),[88] using data from rheumatoid arthritis patients in the UK, expressed resource use cost as a function of HAQ-DI. The parameters for that algorithm were obtained from TA543[27] (CS, Table 76) and then inflated to 2019 price year using the UK consumer prices index.[89]

The company considered that any cost estimate generated from the resource-use algorithm consists of both the cost of treatment and other healthcare costs. The company considered that, for treatment-related health states, a 15% reduction to the cost estimate generated by the resource-use algorithm would be appropriate.[77] The full cost from the resource-use algorithm was applied to the BSC health state because the 15% reduction that should have been applied was assumed to represent the costs of supportive medicines in that health state.

Values for psoriasis-related costs were taken from NICE TA543[27] (CS, Table 77) and inflated to 2019.[89] The values in NICE TA543[27] were based on data collected from Dutch patients with psoriasis who were treated with DMARDs (Hartman 2002[90]) using PASI 75.

Adverse event costs

The cost of AEs was not captured in the economic model due to the uncertainty around the estimation of AE rates.

5 COST EFFECTIVENESS RESULTS

The company has provided nine sets of cost effectiveness results; one set for each of the three PsA severity levels (no psoriasis, mild-to-moderate and moderate-to-severe) for each of the three populations that were considered in the company model.

5.1 Base case incremental cost effectiveness analysis results

The company's fully incremental and pairwise deterministic base case cost effectiveness analysis results for the biologic-naïve population, TNF-alpha inhibitor-contraindicated population and biologic-experienced population are provided in Table 30, Table 31 and Table 32, respectively.

Table 30 Fully incremental and pairwise deterministic base case results for the biologic-naïve population (PAS price for upadacitinib)

Technologies/ Severity	Total		Incremental, versus adalimumab		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
Adalimumab	[redacted]	[redacted]	-	-	-	£19,322
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,322	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£57,118	£57,118*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	£229,092*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	UPA is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£365,044	£113,594*
Mild-to-moderate psoriasis						
Adalimumab	[redacted]	[redacted]	-	-	-	£17,980
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£17,980	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant

Technologies/ Severity	Total		Incremental, versus adalimumab		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£64,577	£64,577*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	£274,601*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	UPA is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£271,574	£112,907*
Moderate-to-severe psoriasis						
Adalimumab	[redacted]	[redacted]	-	-	-	£12,701
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£12,701	N/A
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£86,662	£86,662*
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	£353,052*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by ETA	UPA is dominant
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	£110,772	£97,333*

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
ETA=etanercept; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life years; UPA=upadacitinib
Source: CS, Table 79

Table 31 Fully incremental and pairwise deterministic base case results for the TNF-alpha inhibitor-contraindicated population or not tolerated (PAS price for upadacitinib)

Technologies/ severity	Total		Incremental, versus BSC		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£16,931
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£16,931	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£10,151,112	£10,151,112*
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by SEC	UPA is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by SEC	UPA is dominant
Mild-to-moderate psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£10,492
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£10,492	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£6,330,422	£6,330,422*
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by SEC	UPA is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by SEC	UPA is dominant
Moderate-to-severe psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£8,809
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£8,809	N/A
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life years; SEC=secukinumab; UPA=upadacitinib
Source: CS, Table 81

Table 32 Fully incremental and pairwise deterministic base case results for the biologic-experienced population (PAS price for upadacitinib)

Technologies/ severity	Total		Incremental, versus BSC		Fully incremental ICER per QALY gained	Pairwise ICER per QALY gained, versus upadacitinib
	Costs	QALYs	Costs	QALYs		
No psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£11,513
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£11,513	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated by UPA	£424,592*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£194,345	£194,345*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by IXE	£416,712*
Mild-to-moderate psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£9,775
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£9,775	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated by UPA	£788,986*
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£191,874	£191,874*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by IXE	£384,703*
Moderate-to-severe psoriasis						
BSC	[redacted]	[redacted]	-	-	-	£6,165
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£6,165	N/A
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	UPA is dominant
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	£177,669	£177,669*
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by IXE	£269,436*

* South West quadrant ICER higher than £30,000 per QALY gained is considered cost effective
ext=extendedly; ICER=incremental cost effectiveness ratio; IXE=ixekizumab; PAS=Patient Access Scheme; QALY=quality adjusted life years; UPA=upadacitinib
Source: CS, Table 80

5.2 Probabilistic sensitivity analysis

The company base case probabilistic cost effectiveness results (pairwise) for the comparison of upadacitinib versus relevant comparators, by disease severity level, for the biologic-naïve population (CS, Figure 21 to Figure 23), TNF-alpha inhibitor-contraindicated population (CS, Figure 27 to Figure 29) and biologic-experienced population (CS, Figure 24 to Figure 26) are presented in the CS.

5.3 Deterministic sensitivity analysis

Results from the company's deterministic one-way sensitivity analyses for the comparison of treatment with upadacitinib versus relevant comparators showed that using the upadacitinib PsARC response rate upper and lower 95% CrI values in the model had the greatest impact on the magnitude of the company base case cost effectiveness results for the three biologic-naïve populations (CS, Figure 30, Figure 31 and Figure 32).

For treatment with upadacitinib versus relevant comparators in the three TNF-alpha inhibitor-contraindicated populations, using the upper and lower bound 95% CI for the fixed annual treatment discontinuation rate, had the greatest impact on the magnitude of the company base case cost effectiveness results (CS, Figure 36, Figure 37 and Figure 38).

For treatment with upadacitinib versus relevant comparators in the three biologic-experienced populations, using the upper and lower bound 95% CrI around the upadacitinib meant that the HAQ-DI change had the greatest impact on the magnitude of the company base case cost effectiveness results (CS, Figure 33, Figure 34 and Figure 35).

5.4 Scenario analyses

The company explored 18 alternative scenarios (CS, Table 83) for each modelled population. Treatment with upadacitinib was the preferred option (at a willingness to pay threshold of £30,000 per QALY gain) in all the scenarios, except when the time horizon was set to 5 years for the TNF-alpha inhibitor-contraindicated population (versus BSC) and biologic-experienced population (versus BSC) in patients with no psoriasis.

5.5 Model validation and face validity

The model structure, source data and assumptions were reviewed by an advisory board including health economic and clinical experts. Prior to submission a health economist not involved with model development reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

6 ERG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The company model structure is a simplification of NHS clinical practice, notably around treatment sequencing (including number of lines of treatment). In this appraisal, the number of treatment options (including BSC) that are available for the biologic-naïve, biologic-experienced and TNF-alpha inhibitor-contraindicated populations are nine, five and five, respectively. Published guidance relating to treatment sequencing is limited. Clinical advice to the ERG is that, in general, patients would be offered multiple bDMARDs/tsDMARDs based on their response and tolerance to individual treatments; they would not generally be offered one or two lines of treatment, as modelled by the company. Failure to account for treatment sequencing complexity in the company model means that company cost effectiveness results are unlikely to reflect the true cost effectiveness of upadacitinib in a real-world setting.

The ERG undertook the following activities to determine whether the company model produced cost effectiveness results that were consistent with the details about model structure and parameter values provided in the CS:

- cross-checking whether parameter values in the CS matched those used in the company model
- sense-checking the results generated by using extreme values of key model parameters
- algorithm checking
- checking PSA parameters.

With the exception of discounting and PSA (see
Table 33) and the algorithms relating to HAQ-DI progression after treatment discontinuation (discussed in Section 6.2.1), the ERG is satisfied that the company model algorithms and the parameter values used in the model reflect those in the CS. Further, the ERG has been able to reproduce the cost effectiveness results that are presented in the CS.

Summary details of the ERG's critique of the company model are provided in
Table 33.

Table 33 Summary of ERG company model critique

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Population	The model includes three clinical sub-populations (biologic-naïve, biologic-experienced and TNF-alpha inhibitor-contraindicated). This is in line with the final scope[18] issued by NICE	NA
Comparators	For the biologic-naïve and TNF-alpha inhibitor-contraindicated populations, the company has included relevant comparators in the model. However, the ERG considers that best supportive care is not a relevant comparator for the TNF-alpha inhibitor-contraindicated population For the biologic-experienced population, the company has appropriately not included certolizumab pegol as a comparator as the design of the Rapid-PsA[36] trial meant that data from that trial could not be included in the company NMAs	6.1
Treatment effectiveness	There was insufficient evidence available from the company NMAs to populate the model and therefore missing values were drawn from a variety of sources. In addition, the company NMA results were generated using short-term data (12 Week) and there are some concerns about heterogeneity	6.1.1
Patient pathway	The company has included two lines of treatment for the biologic-naïve population by assuming that this population will receive ustekinumab in the second-line setting. However, clinical advice to the ERG is that more than two therapies can be offered. The ERG considers that the evidence base to support the effectiveness of third- and subsequent lines of treatment is not robust The company has not attempted to include multiple lines of treatment for the biologic-experienced population after treatment with TNF-alpha inhibitor(s). However, clinical advice to the ERG is that subsequent lines of treatment can be offered. The ERG considers that the evidence base to support the effectiveness of third- and subsequent lines of treatment is not robust The company has not attempted to include two lines of treatment for the TNF-alpha inhibitor-contraindicated population. The ERG considers that it is likely that this population will receive more than one line of treatment and should be modelled using the same approach as is used to model multiple lines of treatment for the biologic-naïve population	NA NA 6.4
Modelling disease progression	Modelled HAQ-DI progression for responders differs from the description given in the CS and in previous submissions HAQ-DI progression ceases for responders whilst on biologic treatment. Clinical advice to the ERG is that responders might experience some level of HAQ-DI progression	6.2
Discontinuation rate	The company cost effectiveness results are most sensitive to annual treatment discontinuation rates. Whilst the values chosen by the company are the best available, the ERG considers that the evidence base for discontinuation rates is weak	6.2

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Utility values	The utility values used in the company model have been derived from the SELECT-PsA 1 and SELECT-PsA 2 trial data (EQ-5D-5L data were cross-walked to EQ-5D-3L).[80,81] This approach is in line with the NICE Reference Case[28] Using values from previous submissions would result in more favourable ICERs per QALY gained for upadacitinib versus any comparator	NA
Model costs	Clinical advice to the ERG is that modelled resource use levels are reasonable Appropriate unit costs are used	NA
Discounting	In the company model, discounting begins at the end of the first cycle, this is incorrect. Discounting should start at the beginning of the second year. It has not been possible for the ERG to correct this error as discounting is part of over 200 distinct formulas in the company model	NA
PSA	The company's PSA has been correctly implemented. However, the company has chosen to vary administration, monitoring and MTX costs; as these costs are known with certainty, they should not be varied in PSAs. Given that these costs account for less than 5% of the total costs for any treatment, the ERG considers that varying these costs will have a negligible impact on PSA results	NA
AEs	AEs are not included in the model. The ERG considers this to be an appropriate omission	NA

AE=adverse event; EQ-5D=EuroQol-5 dimensions; ERG=Evidence Review Group; MTX=methotrexate; NA=not applicable; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year
Source: LR*i*G in-house checklist

6.1.1 ERG critique of the clinical effectiveness evidence used in the company model

Company model cost effectiveness results are driven by PsARC response and HAQ-DI reduction conditional on PsARC and therefore the strength of the clinical effectiveness evidence for these outcomes is central to the credibility of the cost effectiveness results.

Biologic-naïve population

The ERG is satisfied that, for the biologic-naïve population, the company 12 Week NMAs produce results that can be used in the company model. For HAQ-DI change conditional on PsARC response, the main driver of cost effectiveness results, NMA results were not available for certolizumab pegol, ixekizumab, secukinumab (150mg and 300mg) and tofacitinib. For these treatments, the company used values from previously published NMAs[31,91] and summary-level trial results.[37,67,68] The ERG considers this approach is similar to carrying out a naïve comparison between trials and is not robust; it is not clear whether the potential bias from this simple approach results in under- or over-estimates of the effectiveness of treatments compared to upadacitinib. However, the ERG recognises that no other sources of HAQ-DI change conditional on PsARC response are available.

Biologic-experienced population

The ERG considers that, for the biologic-experienced population, the level of unaccounted for heterogeneity in the company Week 12 NMAs means that the NMA outputs used in the company model are not robust. For the biologic-naïve population, HAQ-DI change conditional on PsARC response Week 12 NMA results were not available for ixekizumab, secukinumab (300mg) and tofacitinib, and therefore the company used values from previously published NMAs. Although the company has made use of the best available evidence, robust estimates of the comparative efficacy of upadacitinib versus any comparator cannot be drawn for the biologic-experienced population.

6.2 ERG critique of the company model

The company's model is based on the 'York model'.[20,31] This model was first used to inform TA199[70] and was most recently updated to inform TA445.[31] During TA445,[31] the Assessment Group for that appraisal highlighted weaknesses in the model, notably around evidence on annual discontinuation rates, the natural history of disease progression and treatment sequencing. Whilst the company has taken all reasonable steps to update the evidence base, the weaknesses highlighted in TA445[31] remain and the issues relating to annual discontinuation rates and treatment sequencing have become more pronounced because the recommendations made in TA445[31] have increased the number of bDMARDs available to patients with PsA.

In addition to the uncertainties in the evidence base and the limitations relating to treatment sequencing, when reviewing the company's approach to generating cost effectiveness results and the company model, the ERG identified the following issues:

- there is a difference in the way that the company has modelled HAQ-DI progression after treatment for responders who stop treatment compared to how this is described in the CS and in previous submissions
- the company has not modelled HAQ-DI progression for responders whilst on treatment
- TNF-alpha inhibitor-contraindicated patients are only offered one line of treatment.

6.2.1 Modelled HAQ-DI (biologic-naïve and biologic-experienced populations)

The company states (CS, pp141-142) that, in line with the York model,[31] patients who respond to a bDMARD/tsDMARD (either first or second line), their HAQ-DI score is constant until this treatment is stopped, at which point it increases instantaneously to their baseline score. HAQ-DI then increases in line with natural history. This is shown in Figure 3. Whilst this is as described in the CS, this is not what happens in the company model.

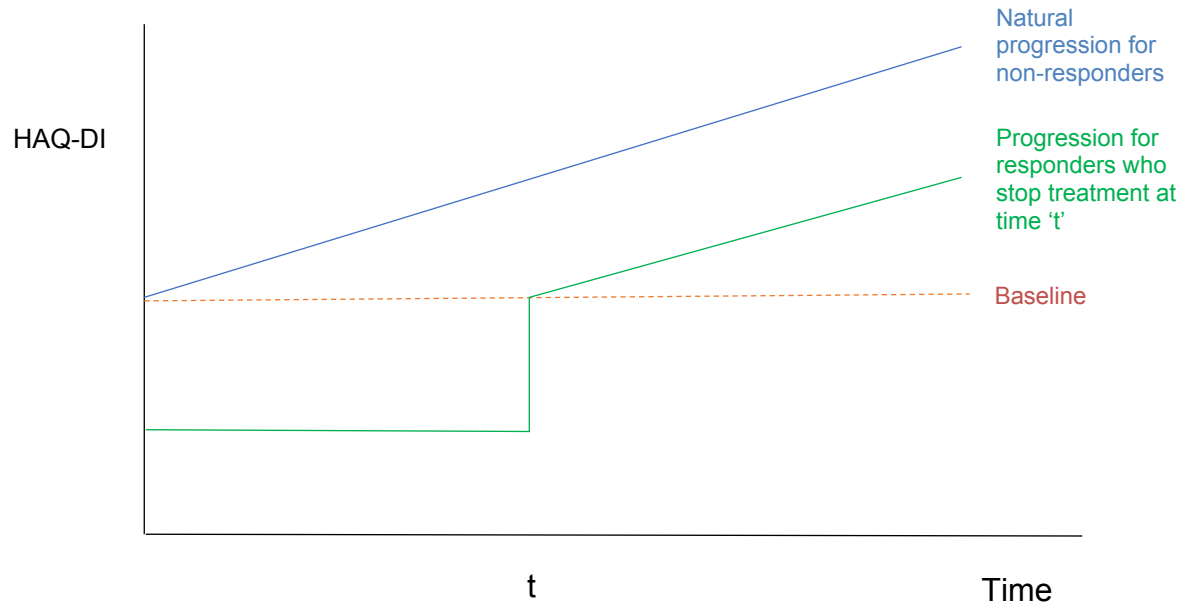


Figure 3 ERG's visual representation of company description of HAD-QI progression for responders and non-responders
Source: ERG

In the company model, when a responder to a bDMARD/tsDMARD stops (rather than switches) treatment, their HAQ-DI score increases instantaneously to a value that lies between their baseline value and the HAQ-DI score for non-responders to a bDMARD/tsDMARD whose HAQ-DI score has been increasing in line with natural history since the start of the model. The HAQ-DI score then converges asymptotically with the HAQ-DI score for non-responders. The company model HAQ-DI score trajectories for responders and non-responders over time are shown in Figure 4.

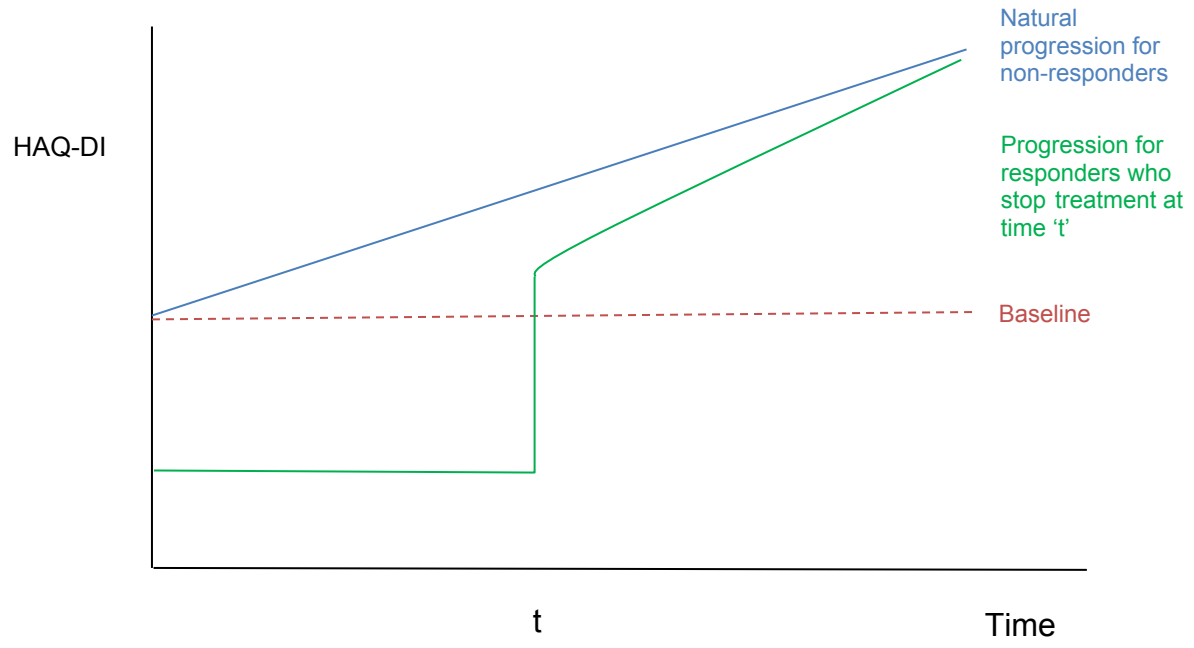


Figure 4 ERG's visual representation of company model HAD-QI progression for responders and non-responders
Source: ERG

The ERG did not correct the error in the company model as this would have required major re-modelling. It is very difficult to use MS Excel to accurately model HAQ-DI score change over time as described in the CS using a Markov framework. The size and direction of effect on the ICERs per QALY gained for upadacitinib versus any comparator for any population, if HAQ-DI had been modelled as described in the CS, cannot be determined.

6.2.2 HAQ-DI progression whilst on treatment

The company's approach to modelling HAQ-DI for patients receiving bDMARD/tsDMARD has been used in previous NICE technology appraisals[27,31,73] of active PsA. However, the ERG considers this approach is not without its limitations. For example, any differences in the long-term efficacy of specific treatments are ignored. Clinical advice to the ERG is that patients' arthritic symptoms will gradually increase over time even whilst receiving a bDMARD/tsDMARD, albeit at a slower rate than that of patients who do not respond to, or stop taking, a bDMARD/tsDMARD. Further, clinical advice to the ERG is that the rate of decline would correlate with the control of disease activity achieved with the bDMARD/tsDMARD.

The ERG asked the company (clarification question B1) to carry out a scenario analysis to show the effect of HAQ-DI score for responders increasing in line with natural history. The company did not provide this analysis. Clinical advice to the company was that this scenario

was implausible as, if a patient's HAQ-DI score was increasing in line with natural history whilst receiving a bDMARD/tsDMARD, then treatment would be stopped. In addition to clinical advice, the company cited three evidence sources to support HAQ-DI not increasing for patients who respond to a bDMARD/tsDMARD whilst receiving treatment:

- evidence from the SELECT-PSA 1 and SELECT-PSA 2 trials shows that 90% of total reduction in HAQ-DI occurred before Week 24 for upadacitinib and adalimumab, and the HAQ-DI score had not increased by Week 56
- results from a survey of clinicians (TA199,[20,70] published in 2010) showed that four out of five clinicians considered that treatment with a TNF-alpha inhibitor would continue to reduce HAQ-DI score for as long as the patient was on treatment
- results from an observational survey carried out in Sweden (Gulf 2009)[92] suggested that utility does not fall for up to 7 years if a patient is receiving a TNF-alpha inhibitor.

The ERG considers that the evidence sources cited by the company do not support not exploring the effect of HAQ-DI not increasing for patients who respond to a bDMARD/tsDMARD whilst receiving treatment:

- **SELECT-PsA 1 and SELECT-PsA 2 trials**: results are only available up to Week 56 and provide no evidence of benefit beyond that point
- **survey of clinical opinion in TA199[20] (TNF-alpha inhibitors)**: clinical opinion from the survey is not supported by the SELECT-PsA 1 and SELECT-PsA 2 trial evidence that shows a plateauing of benefit for upadacitinib and adalimumab after Week 44
- **Swedish observational study:**[92] as an observational study there is no way of knowing whether the lack of decline in utility would be mirrored in similar patients with PsA not receiving a bDMARD/tsDMARD.

The long-term relative efficacy of bDMARDs/tsDMARDs is key to determining their relative cost effectiveness. Whilst the ERG agrees that a scenario where the HAQ-DI score for responders to bDMARDs/tsDMARDs increases in line with natural history may be implausible, clinical advice to the ERG is that HAQ-DI score would increase for responders to bDMARDs/tsDMARDs over time and the evidence provided by the company does not show that this is not the case. The scenario proposed by the ERG would have allowed the importance of the company assumption that HAQ-DI score for responders to bDMARDs/tsDMARDs does not increase whilst on treatment to be explored.

6.3 TNF-alpha contraindicated population only offered one line of biologic therapy

The company has assumed that the TNF-alpha inhibitor-contraindicated population only receive one bDMARD/tsDMARD. Clinical advice to the ERG is these patients are offered more than one bDMARD/tsDMARD. For example, if a patient failed on secukinumab (an IL-17 inhibitor) they would be offered ustekinumab (an IL-23 inhibitor). Therefore, the cost effectiveness results for the TNF-alpha inhibitor-contraindicated population should be identical to the biologic-naïve population who received ustekinumab as a second-line treatment (after excluding TNF-alpha inhibitors as first-line treatment options).

6.4 Impact on the ICER of additional clinical and economic analyses presented by the ERG

The ERG has generated a set of results for the TNF-alpha inhibitor-contraindicated population. The company has assumed that this population only receives one line of treatment; however, clinical advice to the ERG is that it is more realistic to assume that, generally, this population will receive two lines of treatment, with the second line of treatment being ustekinumab (i.e., in line with the company approach to modelling treatment for the biologic-naïve population). The company included BSC as a comparator for this population; however, the ERG considers that this is not a relevant comparator as, in NHS clinical practice, patients are generally offered a bDMARD (other than a TNF-alpha inhibitor) or a tsDMARD as a first-line therapy.

The results generated by the ERG scenario are displayed in Table 34. The pairwise cost effectiveness results are identical to the biologic-naïve population who received ustekinumab as a second-line treatment (after excluding TNF-alpha inhibitors as first-line treatment options); however, the fully incremental results differ due to TNF-alpha inhibitors and BSC no longer being considered as relevant comparators. The results generated by the ERG for this population (before implementation of confidential discounted drug prices) do not change the company's conclusion that treatment with upadacitinib dominates all comparator treatments.

Table 34 TNF-alpha inhibitor-contraindicated population: ustekinumab given as second-line treatment (PAS price for upadacitinib)

Technologies	Total costs (£)	Total QALYs	Incremental costs versus upadacitinib	Incremental QALYs versus upadacitinib	ICER fully incremental (£/QALY)	Pairwise ICER of upadacitinib vs comparator (£/QALY)
No psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Mild-to-moderate psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Moderate-to-severe psoriasis						
Upadacitinib sequence	[redacted]	[redacted]	N/A	N/A	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant

*ICER per QALY gained is in the South West quadrant. An ICER per QALY gained in the South West quadrant should be interpreted in the opposite way to the North East quadrant i.e., higher ICERs per QALY gained mean treatments are more cost effective
ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: ERG

7 ERG CONCLUSIONS

7.1 Clinical conclusions

The ERG considers that the SELECT-PsA 1 trial (biologic-naïve population) and the SELECT PsA-2 trial (biologic-experienced) are good quality trials and the eligibility criteria and patient populations of both trials appear generalisable to patients with PsA treated in the NHS.

Direct efficacy and HRQoL evidence from the SELECT-PsA 1 trial and the SELECT-PsA 2 trial shows that treatment with upadacitinib is superior to placebo. In addition, evidence from the SELECT-PsA 2 trial shows that, for ACR20, treatment with upadacitinib is non-inferior to treatment with adalimumab.

There is no direct evidence available to demonstrate the clinical effectiveness of upadacitinib in patients following prior treatment with tsDMARDs (i.e., apremilast and tofacitinib).

There is no specific evidence to support the clinical effectiveness of upadacitinib versus relevant comparators for treating patients in the TNF-alpha contraindicated-population; the company has assumed the effectiveness of treatments for this population is the same as for the biologic-naïve population.

Clinical advice to the ERG is that the AEs associated with upadacitinib are likely to be manageable in NHS clinical practice and are similar to the AEs associated with the relevant comparator drugs.

The ERG considers that the company assessed all relevant outcomes in the Week 12 NMAs,

The company NMAs generated outcome results that were considered to be important determinants of a clinically meaningful response (i.e., ACR20/50/70) or informed the company's economic modelling (PsARC response, PASI 50/75/90 response, and HAQ-DI score change conditional on PsARC response status). The ERG considers that the company NMA methods were appropriate. The company's Week 12 biologic-naïve NMAs included evidence for all relevant comparators and between trial heterogeneity was accounted for by using random effect models. The company's Week 12 biologic-experienced NMAs included evidence for all relevant comparators except certolizumab pegol; however, it was not possible to account for between trial heterogeneity due to the small number of trials in the biologic-experienced network. Results from the company's Week 12 biologic-naïve NMAs are more reliable than results from the company's Week 12 biologic-experienced NMAs as it was possible to account for between trial heterogeneity in the Week 12 biologic-naïve NMAs.

For both the biologic-naïve and biologic-experienced populations, as CrIs around the observed effect point estimates are often wide, it is not possible to draw definitive conclusions about the relative efficacy of upadacitinib versus comparators for many outcomes.

7.2 Cost effectiveness conclusions

The company model structure is a simplification of NHS clinical practice and does not take into account the complexity that arises from having multiple treatment options that may be prescribed in different sequences. Failure to account for this complexity in the company model means that company model cost effectiveness results are unlikely to reflect the true cost effectiveness of upadacitinib in a real-world setting.

Results from the biologic-experienced Week 12 NMAs are more unreliable than results from the Week 12 biologic- naive NMAs and this should be taken into account when interpreting company cost effectiveness results.

HAQ-DI is the main driver of company cost effectiveness results. The conclusions that can be drawn from the cost effectiveness results generated by the company model are limited by the available HAQ-DI conditional on PsARC evidence.

The company model does not reflect HAQ-DI score as described in the CS (and as described in previous NICE TAs[23,27]). The impact of this error on cost effectiveness results is unclear. In addition, the ERG considers that a scenario where the effect of HAQ-DI increases for patients who respond to a bDMARD/tsDMARD whilst receiving treatment would have been informative.

The ERG considers that the TNF-alpha inhibitor-contraindicated population will receive more than one line of treatment and that BSC is not an appropriate first-line treatment option for this population. The ERG implemented a scenario where the TNF-alpha inhibitor-contraindicated population received two lines of treatment; results (using PAS price for upadacitinib and list price for other drugs) did not alter company conclusions.

The ERG has only generated alternative cost effectiveness results for the TNF-alpha inhibitor-contraindicated population as other changes would have involved substantial re-modelling (which is beyond the remit of the ERG) or could not be supported by the currently available clinical effectiveness evidence.

8 NICE END OF LIFE CRITERIA

The company has not made a case for treatment with upadacitinib to be considered under the NICE End of Life criteria.[93] The ERG considers that this is appropriate as treatment with upadacitinib does not increase life expectancy.

9 REFERENCES

1. Grinnell-Merrick LL, Lydon EJ, Mixon AM, Saalfeld W. Evaluating Inflammatory Versus Mechanical Back Pain in Individuals with Psoriatic Arthritis: A Review of the Literature. Rheumatology and Therapy. 2020:1-18.
2. Spondylitis Association of America. In Psoriatic Arthritis, Axial Involvement is Associated with More Severe Psoriasis. 2018; Available from: https://spondylitis.org/research-new/in-psoriatic-arthritis-axial-involvement-is-associated-with-more-severe-psoriasis/#:~:text=40%25%20of%20PsA%20patients%20will,to%20fusion%20within%20the%20vertebrate. Accessed 26 October 2020.
3. 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. Rheumatol Ther. 2016; 3:91-102.
4. Bagel J, Schwartzman S. Enthesitis and dactylitis in psoriatic disease: a guide for dermatologists. Am J Clin Dermatol. 2018; 19:839-52.
5. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. The New England journal of medicine. 2017; 376:957-70.
6. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M*, et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Annals of the Rheumatic Diseases. 2020; 79:700-12.
7. Zenke Y, Ohara Y, Kobayashi D, Arai S, Kishimoto M, Okada M*, et al.* Nail findings in patients with psoriatic arthritis: A cross-sectional study with special reference to transverse grooves. J Am Acad Dermatol. 2017; 77:863-7.
8. Cantini F, Niccoli L, Nannini C, Kaloudi O, Bertoni M, Cassara E. Psoriatic arthritis: a systematic review. International journal of rheumatic diseases. 2010; 13:300-17.
9. Coates LC. Impact of Psoriatic Arthritis from the Patient's Perspective in the Context of the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire: An Online Global Survey. 2018 ACR/ARHP Annual Meeting: ACR; 2018.
10. Magrey MN, Antonelli M, James N, Khan MA. High frequency of fibromyalgia in patients with psoriatic arthritis: a pilot study. Arthritis. 2013; Article ID 762921.
11. Husni ME. Comorbidities in psoriatic arthritis. Rheumatic Disease Clinics. 2015; 41:677-98.
12. Veale DJ. Psoriatic arthritis: recent progress in pathophysiology and drug development. Arthritis research & therapy. 2013; 15:224.
13. National Breast Cancer Foundation Inc. BRCA: The Breast Cancer Gene. 2020; Available from: https://www.nationalbreastcancer.org/what-is-brca. Accessed 11 February 2020.
14. 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. 2013; 52.
15. AbbVie. PsA Market Data. 2019.
16. National Institute for Health and Care Excellence. Spondyloarthritis in over 16s: diagnosis and management [NG65]. 2017; Available from: https://www.nice.org.uk/guidance/ng65. Accessed 2020 29 April 2020.
17. National Institute for Health and Care Excellence (NICE). NICE Pathways: Managing peripheral spondyloarthritis in adults. 2019; Available from: https://pathways.nice.org.uk/pathways/spondyloarthritis/managing-peripheral-spondyloarthritis-in-adults#content=view-index&path=view%3A/pathways/spondyloarthritis/managing-peripheral-spondyloarthritis-in-adults.xml. Accessed 27 April 2020.
18. National Institute for Health and Care Excellence (NICE). Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]. Published

date: October 2020. Available from: https://www.nice.org.uk/guidance/proposed/gid-ta10666/documents. Accessed January 2021.
19. AbbVie. RINVOQ in PsA Integrated Access Strategy. 2020.
20. National Institute for Health and Care Excellence. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [TA199]. 2018; Available from: https://www.nice.org.uk/guidance/ta199. Accessed 5 February 2021.
21. National Institute for Health and Care Excellence. Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs: Final appraisal determination. 2017; Available from: https://www.nice.org.uk/guidance/ta445/documents/final-appraisal-determination-document. Accessed 20 July 2020.
22. National Institute for Health and Care Excellence. Golimumab for the treatment of psoriatic arthritis. 2011; Available from: https://www.nice.org.uk/guidance/ta220. Accessed 5 February 2021.
23. National Institute for Health and Care Excellence. Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs [TA537]. 2018; Available from: https://www.nice.org.uk/guidance/ta537. Accessed 18 Nov 2020.
24. National Institute for Health and Care Excellence. Ustekinumab for treating active psoriatic arthritis [TA340]. 2017; Available from: https://www.nice.org.uk/guidance/ta340. Accessed 29 April 2020.
25. National Institute for Health and Care Excellence. Apremilast for treating active psoriatic arthritis [TA433]. 2017; Available from: https://www.nice.org.uk/guidance/ta433. Accessed 27 April 2020.
26. National Institute for Health and Care Excellence. Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [TA543]. Available from: https://www.nice.org.uk/guidance/TA543. Accessed 5 February 2021.
27. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA543]. Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID1220]. Committee Papers. 2018; Available from: https://www.nice.org.uk/guidance/ta543/documents/committee-papers. Accessed 27 April 2020.
28. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. Published date: April 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 20 July 2020.
29. AbbVie. Clinical Study Report M15-572. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 2020.
30. AbbVie. Clinical Study Report M15-554. A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease-Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. 2020.
31. National Institute for Health and Care Excellence (NICE). Multiple Technology Appraisal [TA445]. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs [ID579]. Committee papers. 2016; Available from: https://www.nice.org.uk/guidance/ta445/documents/committee-papers. Accessed 27 April 2020.
32. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG*, et al.* Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013; 65:1213-23.

33. Mease P, Lertratanakul A, Strober B, Tsuji S, Richette P, Lovan C*, et al.* Efficacy of upadacitinib in patients with psoriatic arthritis stratified by number of prior biologic disease-modifying antirheumatic drugs. American College of Rheumatology's All-Virtual Annual Meeting2020.
34. European Medicines Agency. Rinvoq: EPAR - Product information. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq. Accessed 18 February 2021.
35. European Medicines Agency. Xeljanz: EPAR - Product Information. Available from: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed 15 August 2019.
36. Mease P, Fleischmann R, Deodhar A, Wollenhaupt J, Khraishi M, Kielar D*, et al.* Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Annals of the Rheumatic Diseases. 2014; 74:423-41.
37. Mease P, FitzGerald O, Van der Heijdge D, Merola JF, Avila-Zapata F, Cieślak D*, et al.* Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med. 2017; 37:1537-50.
38. 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 (London, England). 2015; 386:1137-46.
39. 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 Res Ther. 2018; 20:47.
40. 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. Rheumatol Ther. 2019; 6:393-407.
41. Mease P, van der Heijde D, Landewé 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. Ann Rheum Dis. 2018; 77:890-7.
42. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD*, et al.* Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014; 73:1020-6.
43. Cutolo M, Myerson GE, Fleischmann RM, Lioté F, Díaz-González F, Van den Bosch F*, et al.* A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. J Rheumatol. 2016; 43:1724-34.
44. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J*, et al.* Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Ann Rheum Dis. 2016; 75:1065-73.
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. Ann Rheum Dis. 2014; 73:990-9.
46. AbbVie. Technical study report: network meta-analysis of treatments for moderately to severly active psoriatic arthritis. 2021.

47. Mease P, Lertratanakul A, Anderson J, Papp K, van den Bosch F, Tsuji S*, et al.* Upadacitinib for Psoriatic Arthritis Refractory to Biologics: SELECT-PsA 2. Ann Rheum Dis. 2020; 0:1-9.
48. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. CRD, University of York. 2009; Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 13 January 2021.
49. AbbVie. Statistical Analysis Plan, Study M15-554: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2 2019.
50. AbbVie. Statistical Analysis Plan, Study M15-572: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1 2019.
51. Abbvie. Clinical Study Protocol M15-572. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Non-Biologic Disease Modifying Anti-Rheumatic Drug (DMARD) – SELECT – PsA 1. 2018.
52. Abbvie. Clinical Study Protocol M15-554. A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – SELECT – PsA 2. 2019.
53. McInnes IB, Behrens F, Mease PJ, Kavanaugh A, Ritchlin C, Nash P*, et al.* Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet (London, England). 2020; 395:1496-505.
54. Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L*, et al.* A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020; 79:123-31.
55. Mease PJ, Genovese MC, Weinblatt ME, Peloso PM, Chen K, Othman AA*, et al.* Phase II Study of ABT-122, a Tumor Necrosis Factor- and Interleukin-17A-Targeted Dual Variable Domain Immunoglobulin, in Patients With Psoriatic Arthritis With an Inadequate Response to Methotrexate. Arthritis Rheumatol. 2018; 70:1778-89.
56. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL*, et al.* Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017; 76:79-87.
57. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P*, et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004; 50:2264-72.
58. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet (London, England). 2000; 356:385-90.
59. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH*, et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005; 52:3279-89.

60. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA*, et al.* Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol. 2007; 34:1040-50.
61. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U*, et al.* Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005; 52:1227-36.
62. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C*, et al.* Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005; 64:1150-7.
63. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J*, et al.* Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009; 60:976-86.
64. Nyugen. A Randomized, Placebo-Controlled Study Evaluating the Safety and Efficacy of Secukinumab in US Biologic-Naive Patients with Active Psoriatic Arthritis and Psoriatic Skin Lesions. 2019 ACR/ARP Annual Meeting 2019.
65. Nash P, Ohson K, Walsh J, Delev N, Nguyen D, Teng L*, et al.* Early and sustained efficacy with apremilast monotherapy in biological-naïve patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). Ann Rheum Dis. 2018; 77:690-8.
66. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C*, et al.* Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet (London, England). 2013; 382:780-9.
67. 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 (London, England). 2017; 389:2317-27.
68. Gladman D, Rigby W, Azevedo V, Behrens F, Blanco R, Kaszuba A*, et al.* Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. The New England journal of medicine. 2017; 377:1525-36.
69. Craig D, O'Connor J, Rodgers M, Smith A, Woolacott N. Ustekinumab for treating active and progressive psoriatic arthritis: A Single Technology Appraisal. Centre for Reviews and Dissemination, 2013. Available from: https://www.journalslibrary.nihr.ac.uk/programmes/hta/125801/#/. Accessed 26 January 2021.
70. National Institute for Health and Care Excellence (NICE). Psoriatic arthritis - etanercept, infliximab and adalimumab: Final Assessment Report [TA199]. 2009; Available from: https://www.nice.org.uk/guidance/ta199/documents/psoriatic-arthritis-etanercept-infliximab-adalimumab-review-acd-assessment-report3. Accessed 27 April 2020.
71. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA220]. Golimumab for Psoriatic Arthritis (manufacturer's submission). 2010; Available from: https://www.nice.org.uk/guidance/ta220. Accessed 27 April 2020.
72. National Institute for Health and Care Excellence (NICE). Psoriatic arthritis (active) - ustekinumab (Rapid Rev TA313): Committee papers. 2014; Available from: https://www.nice.org.uk/guidance/ta340/documents/psoriatic-arthritis-active-ustekinumab-rapid-rev-ta313-committee-papers-. Accessed 27 April 2020.

73. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal [TA537]. Ixekizumab for treating active psoriatic arthritis after DMARDs [ID1194]. Committee Papers. 2018; Available from: https://www.nice.org.uk/guidance/ta537/evidence/committee-papers-pdf-4913117821. Accessed 27 April 2020.
74. National Institute for Health and Care Excellence (NICE). Final scope for the appraisal of upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. National Institute for Health and Care Excellence; 2020; Available from: https://www.nice.org.uk/guidance/gid-ta10666/documents/final-scope. Accessed 2021 Februrary 06.
75. Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T*, et al.* Estimation of Psoriasis Area and Severity Index score for treatment responders in the decision model. NIHR Journals Library; 2011.
76. Morgan C, Lunt M, Bunn D, Scott DG, Symmons DP. Five-year outcome of a primary-care-based inception cohort of patients with inflammatory polyarthritis plus psoriasis. Rheumatology (Oxford). 2007; 46:1819-23.
77. 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 Technol Assess. 2011; 15:i-xxi, 1-329.
78. Gabay C, Riek M, Scherer A, Finckh A, physicians obotSc. Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. Rheumatology. 2015; 54:1664-72.
79. Office for National Statistics. National life tables: England and Wales (2017-2019). Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. Accessed 29 October 2020.
80. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012; 15:708-15.
81. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set. 2019; Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf. Accessed 27 April 2020.
82. National Health Service. Drugs and pharmaceutical electronic market information tool (eMIT). Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 27 August 2019.
83. Monthly Index of Medical Specialities (MIMS). Available from: http://www.mims.co.uk/drugs. Accessed 27 April 2020.
84. Curtis L, Burns A. Unit Costs of Health and Social Care 2019. Canterbury: University of Kent; 2018; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Accessed 19 April 2020.
85. UK Department of Health National Health Services (NHS). NHS Reference Costs 2017-2018. National Schedule of Reference Costs: The Main Schedule. Available from: https://improvement.nhs.uk/resources/reference-costs/. Accessed 27 April 2020.
86. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to diseasemodifying antirheumatic drugs: a systematic review and economic evaluation. Health Technology Assessment. 2017; 21.

87. Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S*, et al.* The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology. 2013; 52:1754-7.
88. Bansback N, Ara R, Barkham N, Brennan A, Fraser A, Conway P*, et al.* Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology. 2006; 45:1029-38.
89. Office for National Statistics. Consumer Prices Index, Special Aggregate: 06 Health. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l528. Accessed 20 April 2020.
90. Hartman M, Prins M, Swinkels OQ, Severens JL, De Boo T, Van Der Wilt GJ*, et al.* Cost-effectiveness analysis of a psoriasis care instruction programme with dithranol compared with UVB phototherapy and inpatient dithranol treatment. The British journal of dermatology. 2002; 147:538-44.
91. Ruyssen-Witrand A, Perry R, Watkins C, Braileanu G, Kumar G, Kiri S*, et al.* Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. RMD Open. 2020; 6:e001117.
92. Gülfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden. Annals of the Rheumatic Diseases. 2010; 69:352-7.
93. National Institute for Health and Care Excellence (NICE). Appraising life-extending, end of life treatments. NICE; 2009; Available from: https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2. Accessed 2 February 2021.

10 APPENDICES

10.1 Appendix 1: Quality Assessment

Table 35 Quality assessment for the SELECT-PsA 1 and SELECT-PsA 2 trials

Quality assessment item	Company assessment	ERG comment
Was randomisation adequate?	Yes, a 2:2:2:1:1 ratio (SELECT-PsA 1), or a 2:2:1:1 (SELECT-PsA 2)	Agreed
Was allocation adequately concealed?	Yes, using an IRT	Agreed
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline patient characteristics and disease activity were similar across treatment groups and reflected the intended study population	Agreed
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, blinded until the last patient completes the last visit of Period 1 An independent external DMC reviewed unblinded safety data at regular intervals during the study The blind was broken by AbbVie pharmacovigilance for 62 patients (SELECT-PsA 1)/ 36 patients (SELECT-PsA 2), for regulatory reporting reasons	Agreed.
Were there unexpected imbalances in dropouts between groups?	No, the mean durations of study drug exposure were similar between treatment arms	Agreed
Were any outcomes measured but not reported?	No, all measured outcomes were reported in the CSR	Agreed
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No ITT analysis was conducted. Efficacy analyses were conducted in the FAS population defined as all randomised patients who received at least one dose of study drug. Data management and patient withdrawals were handled appropriately (see Section 3.2.5)	Agreed. No ITT analysis was conducted. [redacted][29,30]

AO=as observed; CSR=Clinical Study Report; DMC=data monitoring committee; ERG=Evidence Review Group; IRT=interactive response technology; ITT=intention to treat; MI=multiple imputation; MMRM=mixed-effects model repeat measures; NRI=non-responder imputation; PsA=psoriatic arthritis
Source: SELECT-PsA 1 CSR[29] and protocol[50] SELECT-PsA 2 CSR[30] and protocol[49]

10.2 Appendix 2: ERG assessment of statistical approaches used to analyse SELECT-PsA 1 and SELECT-PsA 2 trial data

Table 36 ERG assessment of statistical approaches used to analyse SELECT-PsA 1 and SELECT-PsA 2 trial data

Item	ERG assessment	Statistical approach with ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	In both trials, efficacy analyses were carried out in the full analysis set (FAS) population, and safety analyses were carried out in the safety analysis set (SAS); both were defined as all randomised patients who received at least one dose of study drug. The ERG is satisfied that these populations were pre-specified in the TSAPs (SELECT-PsA 1 p12; SELECT-PsA 2 p10)
Was an appropriate sample size calculation pre-specified?	Yes	Study sample size calculations were pre-specified in the TSAPs (SELECT-PsA 1, pp10-11; SELECT-PsA 2, p9); the ERG is satisfied that these sample size calculations were appropriate
Were all protocol amendments made prior to analysis?	Partial	Protocol amendments are listed in the CSRs (SELECT-PsA 1, pp28-31; SELECT-PsA 2, pp25-28). The first data cut-off dates for the SELECT-PsA 1 and SELECT-PsA 2 trials were 13 December 2019 and 9 October 2019, respectively. In the SELECT-PsA 1 trial, all amendments were made prior to the date of the first data cut. These amendments were, therefore, not driven by results from the analyses. In the SELECT-PsA 2 trial, an additional sensitivity analysis and analyses of resolution of dactylitis and enthesitis at Week 24 (in which subjects who are rescued at Week 16 are treated as non-responders at Week 24) were added after finalisation of the TSAP. However, these analyses are clearly labelled as post-hoc analyses and the results can therefore be interpreted appropriately as exploratory analyses only.
Were all primary and secondary efficacy endpoints pre-defined and analysed appropriately?	Yes	In the CS, results are presented for the primary efficacy endpoint of both trials (ACR20 at Week 12) and various key secondary and additional secondary endpoints. Definitions and analysis approaches for these endpoints were pre-specified in the TSAPs (SELECT-PsA 1, pp27-39; SELECT-PsA 2, pp24-32). For both trials, the company performed statistical tests for the primary and key secondary endpoints using a graphical multiple testing procedure. This procedure was outlined in the TSAPs (SELECT-PsA 1, pp39-42; SELECT-PsA 2, pp32-33). For further information, see text that follows this table.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	In the CS, results are presented for EQ-5D-5L, SF-36 PCS, FACIT-F, and SAPS. Analytic approaches for these outcomes were pre-specified in the TSAPs (SELECT-PsA 1, pp29, 32-33, 36-38; SELECT-PsA 2, pp26, 28-32). In both trials, statistical testing of SF-36 PCS, FACIT-F, and SAPS was performed according to the graphical multiple testing procedure. Change from baseline in EQ-5D-5L was an additional secondary endpoint, and therefore no formal statistical testing was performed.

Item	ERG assessment	Statistical approach with ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data relating to exposure and AEs (including TEAEs, TEAEs of special interest, and TEAEs leading to treatment discontinuation) are presented in the CS (p103-111). The presented safety analyses were descriptive only, and were pre-specified in the TSAPs (SELECT-PsA 1, pp70-76; SELECT-PsA 2, pp56-62)
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data in the efficacy analyses is outlined in the TSAPs (SELECT-PsA 1, pp26-27; SELECT-PsA 2, pp23-24). For the data presented in the CS, one of three approaches were used to handle missing data: • Non-responder imputation (NRI) for binary endpoints: Subjects who prematurely discontinue from study drug were considered as non-responders for all subsequent visits after discontinuation, and subjects with any missing value at a specific visit were treated as non-responders for that visit. • Mixed-Effects Model Repeated Measures (MMRM) for continuous endpoints: Data collected after premature discontinuation of study drug were excluded. Data were imputed assuming that data were missing at random and using the method of restrictive maximum likelihood (REML). • As observed for radiographic endpoints in the SELECT-PsA 1 trial: No imputations performed for missing data. Subjects who did not have an evaluation on a scheduled visit were excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug or use of rescue medication, all observed data were used in the analysis. Missing safety data were not imputed. The ERG is satisfied that the approaches described were appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Results from subgroup analyses for ACR20 at Week 12 in the SELECT-PsA 1 and SELECT-PsA 2 trials for several demographic and baseline characteristics are presented in Appendix E to the CS (Table 26 and Table 27). Results are presented in the CS for specific subgroups of interest to this appraisal: i) number of prior csDMARDs (≤1 versus >1) in the SELECT-PsA 1 trial, ii) number of prior failed bDMARDs (1 versus >1) in the SELECT-PsA 2 trial, and iii) concomitant use of csDMARDs (Yes/No) in both the SELECT-PsA 1 and SELECT-PsA 2 trials. These subgroup analyses were all pre-specified in the TSAPs (SELECT-PsA 1, pp42-43; SELECT-PsA 2, p34). The results of sensitivity analyses for the endpoints of SHS, joint erosion score, and JSN score at Week 24 for the SELECT-PsA 1 trial are presented in Appendix D to the CS (Table 24). These analyses, which use linear extrapolation to impute missing data, were pre-specified in the SELECT-PsA 1 TSAP (pp38-39).

ACR=American College of Rheumatology; AE=adverse event; CSR=clinical study report; EQ-5D-5L=EuroQol-five dimensions-five levels; ERG=Evidence Review Group; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; SAPS=Self-Assessment of Psoriasis Symptoms; SF-36 PCS=Short Form 36 Physical Component Summary; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan

Source: CS, SELECT-PsA 1 and SELECT-PsA 2 CSRs,[29,30] SELECT-PsA 1 and SELECT-PsA 2 protocols,[51,52] SELECT-PsA 1 and SELECT-PsA 2 TSAPs,[49,50] and ERG comment

10.3 Appendix 3: Quality Assessment of trials included in the NMA analyses

Table 37 Quality assessment of trials included in the NMA analyses

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ACTIVE[65]	Unclear	Unclear	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Missing data using non-responder imputation
ADEPT[59]	Unclear	Yes; masking was done	Yes	Yes; double-blind	Unclear	Yes; enthesitis and dactylitis	Yes; ITT
ERG assessment (if different from company):		Unclear				Yes; enthesitis, dactylitis and FACIT-F	Yes; ITT. Missing data using non-responder imputation
CHOICE[64]	Unclear	Unclear	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Partial; ITT but methods for missing data unclear
FUTURE 2[38]	Yes; IVRS/IWRS	Yes; triple masking was done	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; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):		Yes, not clear if triple masking					Yes; ITT. Missing data imputed as non-response

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
FUTURE 3[39]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):	Yes; IRT	Yes; IRT					Yes; ITT. Missing values imputed as failures. Patient who did not achieve response based on joint count (week 16) imputed as non-responders
FUTURE 4[40]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):	Yes; IRT	Yes; IRT					Yes; ITT. Missing values imputed as non-responders
FUTURE 5[41]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):	Yes; IRT	Yes; IRT					Yes; ITT. Missing values and placebo patients rescued at week 16 imputed as non-responders
Genovese 2007[60]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):			Yes (mean CRP and % of patients with negative RF test greater in placebo)				Yes; ITT. Missing responders were counted as non-responders

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
GO-REVEAL[63]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT.
ERG assessment (if different from company):							Yes; ITT. For some whom ACR data was missing, the last observation was carried forward to week 14 or 24
IMPACT[61]	Unclear, investigator initiated	Unclear, investigator initiated	Yes, were generally similar, with a few exceptions	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):			Yes, some exceptions (mean CRP value)				Partial; methods unclear for handling missing data
IMPACT-2[62]	Yes; interactive patient allocation algorithm	Yes; interactive patient allocation algorithm	Yes	Yes; double-blind	Yes; the withdrawals, completers, and the specific reasons for withdrawal were reported.	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Subjects with missing ACR20 and PsARC data at week 14 and 20 considered as non-responders)

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Mease 2000[58]	Yes; block randomisation	Unclear	No; the groups were well balanced in all characteristics except that twice as many patients in the PBO group were receiving corticosteroids than in the ETN group, and in the groups evaluable for psoriasis, the PBO group had lower baseline PASI scores	Yes; double-blind	Unclear	No	Yes; ITT
ERG assessment (if different from company):							Partial; missing data methods not described)
Mease 2004[57]	Unclear	Unclear	Yes	Yes; double-blind	Unclear	Yes; SF-36 PCS and MCS	Yes; ITT
ERG assessment (if different from company):			Yes; well-matched except that slight predominance of women in placebo group, and men in etanercept group. Also, patients in etanercept group had more radiographic disease at baseline than placebo group			No	Yes; ITT. Use of last observation carried forward analysis for missing data

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Mease 2018[55]	Yes; IVRS or IWRS	Yes; IVRS or IWRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Missing values imputed as non-response)
OPAL-Beyond[68]	Yes; centralised automated randomisation system	Yes; centralised automated randomisation system	Yes	Yes; double-blind	Yes; the withdrawals, completers, and the specific reasons for withdrawal were reported.	No	Yes; ITT
ERG assessment (if different from company):			Yes, except the mean number of tender or painful joints				Yes; ITT. Missing values imputed as no response)
OPAL-Broaden[37]	Unclear	Yes; quadruple masking was done	Yes	Yes; double-blind	No		No; ITT
ERG assessment (if different from company):	Yes; automated web-based system	Yes, not clear if quadruple masking was done	Yes, except the mean LEI score, mean swollen joint count, and rate of MTX use			No	No
PALACE 1[42]	Unclear	Yes; quadruple masking was done	Yes	Yes; double-blind	Unclear	No	Yes; ITT

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ERG assessment (if different from company):		Yes, not clear if quadruple masking was done					Yes; ITT. Missing values were handled using the non-imputation rule
PALACE 2[43]	Unclear	Yes; quadruple masking was done	Unclear	Yes; double-blind	Unclear	No	Yes; ITT
ERG assessment (if different from company):		Yes, not clear if quadruple masking was done	Yes; balanced across treatment groups				Yes; ITT. Missing values were handled using the non-imputation rule
PALACE 3[44]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Missing values were handled using the non-responder imputation rule and LOCF
PSUMMIT 1[66]	Unclear	Yes; quadruple masking was done	Unclear	Yes; double-blind	Unclear	No	Unclear
ERG assessment (if different from company):	Yes; dynamic central randomisation (IVRS algorithm)	Yes, not clear if quadruple masking was done	Yes; well-balanced across groups				Yes; ITT. Missing data using LOCF

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
PSUMMIT 2[45]	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Missing data using LOCF for week 24 change in HAQ-DI, but otherwise not imputed.
RAPID-PsA[36]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	No	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Non-responder imputation used
SPIRIT H2H[54]	Yes; IWRS	Yes, assessors were blinded	Yes	No; open-label but blinded assessor	No	No	Yes; ITT
ERG assessment (if different from company):	Unclear	Unclear					Yes; ITT. Missing data imputed using modified baseline observation carried forward
SPIRIT- P1[56]	Yes; IVRS	Yes; IVRS	Yes	Yes; double-blind	Unclear; withdrawals not reported	No	Yes; ITT
ERG assessment (if different from company):							Yes; ITT. Missing data imputed using non-responder method

Study name Author (reference)	Was randomisation adequate?	Was allocation adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
SPIRIT- P2[67]	Yes; computer generated random sequence	Unclear	Yes	Yes; double-blind	Unclear; withdrawals not reported	No	Yes; ITT
ERG assessment (if different from company):			Yes, except for imbalances in concomitant MTX use and baseline SJC count				Yes; ITT. Missing data imputed as non-responders

ACR=American College of Rheumatology; BSA=body surface area; CRP=C-reactive protein concentration; ETN=etanercept; ERG=Evidence Review Group; FACIT-F=Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI=health assessment questionnaire-disability index; IRT=interactive response technology; ITT=intent to treat; IVRS=interactive voice response system; IWRS=interactive web response system; LEI=Leeds Index Score; LOCF=last observation carried forwards; MTX=methotrexate; PASI=Psoriasis Arthritis Severity Index; PBO=placebo; PsARC=Psoriatic Arthritis Response Criteria; RF=rheumatoid factor; SF-36 PCS/MCS=Short Form Health Survey 36-item physical component score/mental component score; 36; SJC=swollen joint count

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

'*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 9 March 2021** 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.

Issue 1 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, 15, 67, 88, and 95 – the wording around how HAQ-DI progression was modelled is potentially misleading and should be clearer	Please clarify that the ERG's critique relates specifically to how the *rebound* in HAQ-DI progression is modelled *for responders who subsequently discontinue treatment;* e.g.: [Page 10 and 15]: "Mismatch between description of HAQ-DI progression modelling following bDMARD/tsDMARD discontinuation for patients who responded to treatment at 12 weeks in the company submission and the approach implemented in the company model" [Page 15]: "The company model does not reflect change in HAQ-DI conditional on PsARC score following bDMARD/tsDMARD discontinuation for patients who responded to treatment at 12 weeks as described in the company submission (and as described in previous NICE technology appraisals)" [Page 67]: "Consequences of stopping treatment for patients who were deemed responders at 12 weeks (as demonstrated by changes in HAQ-DI) were not incorporated into the company model correctly" [Page 88]: "Modelled HAQ-DI progression following bDMARD/tsDMARD discontinuation for patients who responded to treatment at 12 weeks (biologic-naïve and biologic-experienced populations)"	Edit can avoid misleading reporting	The ERG has accepted one of the company's proposed amendments: [Page 67]: "Consequences of stopping treatment for patients who were deemed responders at 12 weeks (as demonstrated by changes in HAQ-DI) were not incorporated into the company model correctly" The ERG considers that the other proposed amendments are not required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 95 – the claim that our model differs from previous TAs in the modelling of HAQ-DI score progression for responders who discontinue treatment is potentially misleading	In the fourth paragraph of Section 7.2 (Page 95), the ERG states that the company model does not reflect HAQ-DI score as modelled in previous NICE TAs. However, the ERG also notes the difficulties of modelling this on Page 90, and we consider that it is likely that previous TAs also model HAQ-DI in the same way. Therefore, we consider it misleading to claim that our approach differs from previous TAs. Please update to: "The company has attempted to model HAQ-DI progression for responders who discontinue in line with previous NICE TAs, as described in the CS; however, due to challenges in modelling this within a Markov framework there may be different interpretations on how this should be implemented."	Edit can avoid misleading reporting	The ERG considers that this is not a factual inaccuracy; the proposed amendments have not been included in the text.
Page 30 – NICE STA precedence used to support submitting in a population narrower than the marketing authorisation	In the first paragraph of Section 2.3.2, please add ustekinumab [TA340], and ixekizumab [TA537] as examples of previous NICE STAs that have also focused on sub-populations excluding only 1 prior csDMARD.	Clarification/correction	Thank you for highlighting. The ERG has included ixekizumab [TA537]. However, it is less clear in ustekinumab [TA340] if patients with only 1 prior csDMARD were excluded from the analysis, therefore this example has not been included.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 – rate of response to bDMARDs with every additional bDMARD treatment	Please add reference to the post-hoc analysis of SELECT-PsA 2 that assessed more granular aspects of prior bDMARD exposure on upadacitinib efficacy. Compared to the overall population, upadacitinib 15 mg demonstrated generally consistent efficacy in patients with inadequate response to one or multiple prior bDMARDs, with similar efficacy observed whether inadequate response was to a TNF inhibitor or IL-17 inhibitor.	Clarification/correction	The ERG considers that this is not a factual inaccuracy. However, we have amended the text as follows: 'In an observational study using Danish registry data, the rate of response to bDMARDs was shown to decline with every additional bDMARD treatment.[32] The post-hoc analyses of the SELECT-PsA 2 trial data (presented at the ACR Convergence)[33] that explored aspects of prior bDMARD exposure on upadacitinib efficacy are discussed in Section 3.3.2.'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 and 76 – pricing used for adalimumab should be consistently reported	Please correct such that it is clear that the Commercial Medicine Unit (CMU) price of adalimumab, not the published list price, was used in the model; e.g. [Page 34]: Please delete adalimumab in the following bullet point "• list prices: **adalimumab**, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab, apremilast and tofacitinib" and clarify that the CMU price has been used. [Page 76]: Please delete adalimumab in the following sentence "The company assumed equivalent efficacy for biosimilar and branded formulations of the same agent; therefore, the least expensive biosimilar pricing for treatments that had biosimilars (i.e., etanercept, **adalimumab**, infliximab and MTX were used in the base case."	Edit can avoid potentially misleading reporting	Thank you for highlighting. The ERG has amended the text as suggested.
Table 19, Page 70 – certolizumab pegol should not be listed as a modelled comparator in the biologic-experienced population	In the table row for 'Biologic-experienced population', please remove certolizumab pegol from the list of comparators, as this was not modelled.	Clarification/correction	Thank you for highlighting. The ERG has amended the text as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 29, Page 78 – incorrect resource use frequencies reported	Please update the two 'frequency' columns with those reported in Table 73 of the company submission. The current frequencies reported are those used in NICE TA445, which have been modelled as a scenario analysis. In the submitted base case analysis, estimates based on clinical expert opinion obtained at the 22 May 2020 advisory board were used.	Reporting correction	Thank you for highlighting. The ERG has amended the table (as suggested) and corrected the text.
Table D, Page 21, page 92, table 34, page 93 – infliximab has erroneously been treated as a comparator; infliximab is not a relevant comparator for patients in whom TNF-alpha inhibitors are contraindicated	The ERG's scenario to model two lines of active treatment in the TNF-alpha inhibitor-contraindicated population includes infliximab as a comparator. Infliximab is not recommended by NICE and is not included in the NICE final scope for this population. Infliximab should therefore be removed as a comparator in the ERG's scenario analysis. [Page 93]: Please also amend the text in paragraph 3 to reflect the results once infliximab has been removed from the analysis "The results generated by the ERG for this population (before implementation of confidential discounted drug prices) do not change the company's conclusion that treatment with upadacitinib dominates all comparator treatments."	Edit can avoid incorrect/misleading reporting	Thank you for highlighting this. The ERG has amended the tables and text as suggested.

Issue 2 Minor edits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table C, Page 20 – missing asterisk in results table reporting	Please add asterisk to the ICER for secukinumab in the mild-to-moderate sub-population to denote that this is a south-west ICER.	Reporting clarity	Thank you for highlighting. The ERG has amended Table C (as suggested) and Table 31.
Page 30 – typographical error	In the second paragraph, please correct to: "upadacitinib (n=**429**)"	Correction	In this brief summary of the trial (p30), the patient numbers provided reflect those randomised to each of the trial arms. The number of patients randomised to the upadacitinib arm in the SELECT-PsA 1 trial was n=430. On p37, the ERG clarifies the numbers included in the full analysis set, which consist of n=429 patients in the upadacitinib arm. No changes made to the text.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 – typographical error	Please amend Section 2.3.3 to read: "Of those taking any csDMARD, [redacted] were receiving methotrexate (MTX), [redacted] were receiving MTX plus another csDMARD, and [redacted] were receiving a csDMARD other than MTX (CS, Table 6). In the SELECT-PsA 2 trial, at baseline, just under half of patients were receiving a csDMARD ([redacted]). Of those taking any csDMARD, [redacted] were receiving MTX alone, [redacted] were receiving MTX+another csDMARD and [redacted] were receiving a csDMARD other than MTX (CS, Table 9)"	Correction	The figures in the ERG report are correct. The differences in the percentages are due to different denominators being used by the company and the ERG. The company presented percentages based on the number of trial patients. The ERG calculated the percentages based on the number of patients receiving any csDMARD. No changes made to the text.
Page 32 – typographical error	In the first paragraph, please correct to: "Upadacitinib may be used as monotherapy **or** in combination with MTX."	Correction	Thank you for highlighting. The text has been amended as suggested.
Page 38 – typographical error	The mean PASI response in the adalimumab arm of SELECT-PsA 1 should read [redacted]	Correction	Thank you for highlighting. The text has been corrected as suggested.
Page 64 – typographical error	In the text for heading 4.1, please correct to: "ERG critique of the company systematic literature review"	Correction	Thank you for highlighting. The text has been corrected as suggested.
Page 94 – typographical error	In paragraph 2, please correct "ARC20" to "ACR20"	Correction	Thank you for highlighting. The text has been amended as suggested. This error has also been corrected on p34, p37 and p38.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Wednesday 28 April 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AbbVie**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

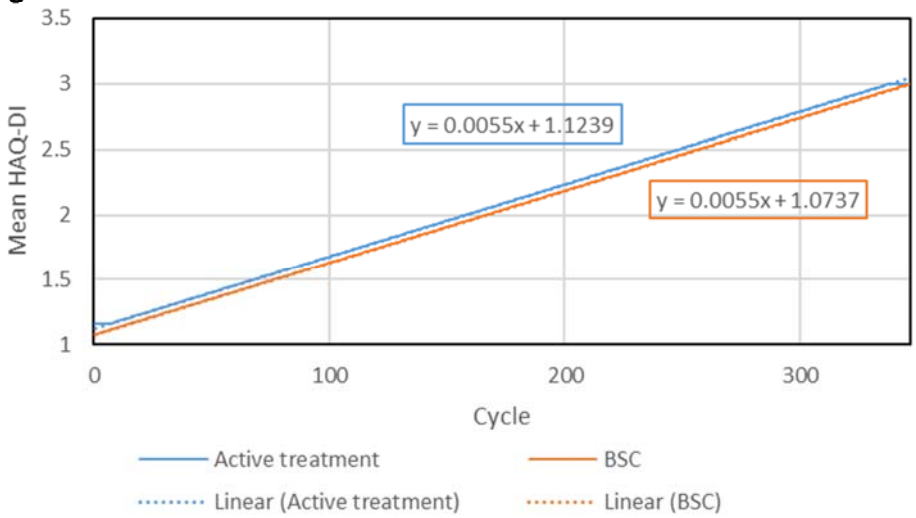
Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Clinical effectiveness evidence gaps	No	We thank the ERG for their assessment that there are no alternative approaches and that the approaches we have taken are appropriate. We recognise that there are a number of minor clinical effectiveness evidence gaps but we have accounted for these where possible, and clinical opinion provided to us suggests that these limitations are no different from those experienced in previous appraisals in PsA.
Key issue 2: Limited direct clinical effectiveness evidence	No	We recognise the limited direct clinical effectiveness evidence issue that is inherent to all appraisals with PsA, and thank the ERG for their assessment that no alternative approach is possible.
Key issue 3: Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs	No	We thank the ERG for their assessment that our NMA approach was methodologically appropriate and that there is no alternative approach that could have been taken to reduce uncertainty. We provided extensive sensitivity analyses to explore the assumptions and methods used in the biologic-naïve NMA, as follows: • Fixed vs. random-effects models • Fixed vs. random-effects model, with placebo-response adjustment • 24-week vs. 12-week data • Pooled vs. non-pooled data (when mixed bDMARD-naïve and -experienced populations were reported)

		These analyses allowed us to be confident that the relative effects of upadacitinib were broadly comparable to the relevant comparators across all included outcomes.
Key issue 4: Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs	No	We accept the perspective of the ERG that, while there are limitations inherent in the analysis, our approach was methodologically appropriate and that there is no alternative approach that could have been taken to reduce uncertainty. Due to the smaller number of comparators eligible for inclusion in the biologic-experienced NMA than the biologic-naïve network, the network is inherently constrained. Nonetheless, our approach and extensive sensitivity analyses allowed us to be confident that the relative effects of upadacitinib were broadly comparable to the relevant comparators across all included outcomes.
Key issue 5: Company model structure is simple and does not wholly reflect the real-world setting	No	We appreciate the opinion of the ERG that there is no alternative approach to developing a model that is more representative of NHS clinical practice. In the absence of suitable evidence to inform a true treatment sequencing model, the 'York' model provides an established, robust, and clinically validated framework that permits comparison between upadacitinib and previously reimbursed therapies. Furthermore, this model continues to be the basis of PsA NICE appraisals, including the ongoing appraisal of guselkumab (ID1658).
Key issue 6: Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC	No	We agree with the perspective of the ERG that no alternative data sources or approaches were possible here. In the face of limited data for HAQ-DI conditional on PsARC for a number of comparators, we took a pragmatic approach that allowed us to produce reasonable estimates and to generate ICERs for all comparators. While we accept that this introduces some uncertainty, we wished to provide the most complete analysis possible. The same approach was also performed and accepted by the committee in the recent appraisal of tofacitinib in PsA (TA543).

Key issue 7: Mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model	No	Firstly, we would like to note that it is not possible to reproduce the company's or the ERG's figures (Figures 3 and 4 in the ERG report) depicting the progression of HAQ-DI over time for non-responders, responders on treatment and responders discontinuing treatment because this is a schematic that aims to visually depict a patient's journey and is not based on the model traces. The approach used to model HAQ-DI over time is done so within the constraints of a Markov model, which we do acknowledge is a limitation, and uses formulae to 'imitate' tunnel states to track patients who discontinue active treatment and enter the BSC state over the model's time horizon. Given the precedent observed in prior PsA submissions – that is, Markov models have been used – we believe this to be appropriate and consistent with what has been done previously. The formula we are referring to is in column AH of the Trace sheets (mean HAQ-DI in BSC state), and works as follows: a) in the first part, the baseline HAQ-DI score is assigned to patients newly entering the BSC state, and b) in the second part of the formula, the baseline HAQ-DI adjusted by HAQ-DI deterioration is assigned to patients already in the BSC state. This part of the formula uses the previous cycle to determine both the patients already on BSC (column AD) and the previous HAQ-DI score (column AH). In the ERG's critique, it is noted that both the rebound effect and HAQ-DI progression after active treatment discontinuation is incorrectly implemented. We have therefore provided a response for each issue separately, to demonstrate why we do not consider some of the ERG's comments to be accurate. **<u>Rebound effect</u>** In the biologic-naïve population, the initial baseline values for HAQ-DI are specific to this population. When responding patients discontinue their first line of treatment, their second line consists of another line of active treatment – specifically, ustekinumab – and third line is assumed to be BSC. At this point,

		these patients are considered to be biologic-experienced. Therefore, when a patient's HAQ-DI reverts to baseline on entry into the BSC state, this baseline value represents the baseline of the biologic-experienced population, which is higher than the biologic-naïve population baseline (e.g., for the no-psoriasis subgroup, we move from 1.08 to 1.16 HAQ-DI score). We believe this to be a reasonable clinical assumption and is consistent with the treatment effects applied to ustekinumab as second-line treatment in the biologic-naïve population (these are populated with the NMA outcomes from the biologic-experienced population). To test that the correct HAQ-DI score is applied when patients revert to baseline, this can be done as follows, by removing the effect of progression: 1) Go to "Effectiveness" tab and then to "Change in HAQ-DI from baseline, conditional on PsARC response, by treatment and position in treatment sequence" section 2) We need to eliminate the effect of progression to check the baseline value at which patients are jumping from active treatment to BSC in an active treatment sequence. To do so, change "haqdi_deterioration" variable (cell E44) from 0.072 to 0 3) Go to "Trace_Seq_1bn" tab and locate "Mean HAQ-DI in BSC state". All values across all cycles in this column are 1.16 4) Run a true or false test to check all values are exactly the same 5) Next, test one of the biologic-experienced traces ("Trace_Seq_2be" for instance). In this case no 2L was modelled as patients transition from one active treatment to BSC. When the same test described above is repeated, the same observations will be obtained. **HAQ-DI progression after active treatment discontinuation** To test that HAQ-DI progression after active treatment discontinuation is correctly implemented, i.e., increases linearly at the same rate as non-responders, we again refer to column AH of the trace sheets, and in this case we need to eliminate the

		time component, since at each cycle patients could discontinue active treatment and move to BSC. To do this we need to track a given cohort of patients who enter the BSC state at the same time (i.e., timepoint t as per Figure 3 in the ERG report): 1) Go to "Transition Probs" tab and select a treatment option (in this example, we adjust the upadacitinib sequence) 2) Set rows 15:18 in column N to 0%, which will move all patients to the BSC state after completing the 12-week trial period of the active treatment (upadacitinib) 3) We also need to set rows 22:25 in column U to 0%, which will move all patients to the BSC state after completing the 12-week trial period of the 2nd line treatment (ustekinumab) 4) Next, go to the "Trace_Seq_1bn" tab and check the values for the column "Mean HAQ-DI in BSC state" (column AH). This column will show predicted outcomes for the specific cohort of patients who fail to achieve PsARC response following the trial periods for both active treatments (in the case of biologic-naïve group). Confirm that this column shows that HAQ-DI progresses linearly by 0.055. 5) If we now go to the "Trace_Seq_BSCbn" tab, without modifying anything we can observe the same linear progression of 0.055 in the "Mean HAQ-DI in BSC state" column In this way, we can observe how the "Mean HAQ-DI in BSC state" column presents cumulative values as patients can transition at any cycle into BSC, based on the constant discontinuation rate for active treatment sequences. This means that in any cycle at moment t, this column accounts for those patients entering BSC at moment t plus patients entering in previous cycles (t-1, t-2, and so on) and whose disease has already progressed for n cycles. This is illustrated in Figure 1, below, where the slopes are demonstrated to be equal at 0.055 for both treatment arms.

		Figure 1: Mean HAQ-DI in active treatment and BSC states  In summary, the test described above illustrates that, like the Markov trace for the BSC sequence, the Markov traces for the active comparator sequences reflect a linear trend in HAQ-DI when focusing on a specific cohort of patients who enter the BSC state in a given cycle. This is consistent with the conceptual diagram presented in our submission and aligns with the model conceptualisation presented in previous NICE TAs using the York model.
Key issue 8: Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment	No	In line with our response to the clarification questions, we consider that a scenario in which the HAQ-DI score for responders increases in line with natural history is 1) lacking in clinical plausibility, and 2) would represent a major divergence from the established 'York' model precedent that forms the basis of all recent PsA appraisals. In our clarification response we provided details of clinical opinion to us that this scenario is implausible, as patients experiencing progression at the natural history

		rate would be swapped to an alternative treatment due to lack of response. We also provided evidence to demonstrate that patients receiving upadacitinib do not experience any worsening of HAQ-DI up to week-56 after starting treatment. The ERG acknowledged in their report that their original request for a scenario in which patients that respond to treatment progress at the natural history rate may be implausible.
Key issue 9: Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice	No	We accept the perspective of the ERG that patients would generally receive more than one line of treatment in the TNF-alpha inhibitor-contraindicated population, and that BSC is generally not an appropriate first-line treatment option for this population. We consider the ERG's scenario results to be appropriate, and note that this scenario did not alter the cost-effectiveness conclusions for this population.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Discontinuation rate	N/A – raised by Technical Team during teleconference	No	During the technical engagement teleconference, the Technical Team noted an additional issue relating to the ongoing guselkumab PsA appraisal (ID1658), in which the manufacturer applied treatment-specific discontinuation rates to all treatments, with guselkumab having the lowest rate applied. This was considered by the committee to a) be biasing the cost-effectiveness results in favour of guselkumab, and b) inconsistent with the precedent established in prior PsA appraisals. We would like to clarify that the base-case results presented in our submission apply the standard 16.5% discontinuation rate established in the York models (TA199 and TA445). Two scenarios were presented in which this assumption is varied: 1) higher discontinuation rate for biologic-experienced population than biologic-naïve population from Gabay et al. 2015 (24% vs. 16.5%, respectively), and 2) use of a more recent source of discontinuation rate, from Fagerli et al. 2018. The results of these scenario analyses were not found to materially impact the base-case ICERs and did not impact the cost-effectiveness of upadacitinib. We also wish to note that the ERG report is unclear with relation to discontinuation rates applied in our base case. Table 24 of the ERG report (page 74) appears to suggest that the alternative discontinuation rate for the biologic-experienced

			population from Gabay et al. 2015 is applied in the base case. We would like to clarify that this not correct, and these values are only applied in a scenario, as described above.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Thank you for agreeing to give us your views on this treatment 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.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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

Please return this form by **5pm** on **Wednesday 28 April 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with active psoriatic arthritis and current treatment options	
About you	
1.Your name	**David Chandler**
2. Are you (please tick all that apply):	**X**☐ a patient with active psoriatic arthritis? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with active psoriatic arthritis? **X**☐ 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 below and provide answers where possible) X☐ Yes, my nominating organisation has provided a submission X ☐ I agree with it and **do not wish to** complete a patient expert statement X☐ Yes, I authored / was a contributor to my nominating organisations submission X ☐ 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/experience (e.g. 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
Living with the condition	
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.	
Current treatment of the condition in the NHS	
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 upadacitinib is given or taken, side effects of treatment etc), please describe these.	
Advantages of this treatment	
9a. If there are advantages of upadacitinib over current treatments on the NHS please describe these. For example, the impact 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 upadacitinib help to overcome/address any of the listed disadvantages of current treatment that	

you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of upadacitinib over current treatments on the NHS please describe these? For example, are there any risks with upadacitinib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from upadacitinib 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	

Equality	
12. Are there any potential equality issues that should be taken into account when considering active psoriatic arthritis and treatment? Please explain if you think any groups of people with active psoriatic arthritis 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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

Clinical expert statement & technical engagement response form

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The 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 to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Wednesday 28 April 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with active psoriatic arthritis and current treatment options	
About you	
1. Your name	**James Galloway**
2. Name of organisation	**King's College London / King's College Hospital NHS Foundation Trust**
3. Job title or position	**Reader / Honorary Consultant**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with active psoriatic arthritis ? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for active psoriatic arthritis	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop disease progression, reduce pain and fatigue, improve quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Responses are usually measured in terms of a reduction in the number of tender and swollen joints, accompanied by patient and clinician judgement that disease activity has improved. A common example of how this is presented is as a proportion of people achieving a 20% improvement across these domains (the ACR20 response).

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in active psoriatic arthritis ?	I would argue strongly that there is an unmet need in PsA. In contrast to RA, the number of available treatments is more limited, and we continue to struggle to control disease activity in patients who fail to response (or more commonly lose response after a period of time). In addition, currently our only available oral targeted therapy is tofacitinib – which has less convincing data for concurrent psoriasis.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	First line therapy for PsA remains DMARDs such as methotrexate, sulfasalazine and leflunomide. We would usually try two of these (often in combination, although combination strategies are less common in PsA than RA) – but if disease remained active despite these (i.e. 3 or more actively inflamed joints) we would escalate to a targeted therapy. The first line targeted therapy is driven by cost, and it is fair to say that currently it is adalimumab (usually biosimilar, although it depends on local price negotiations). If a TNFi fails or is contraindicated, then we will usually switch to a different class of therapy, such as IL-17i, IL12-23i or a JAKi. Factors that influence choice include severity of skin involvement, extra-articular manifestations (esp inflammatory eye or bowel disease – which would mean we avoid IL-17i), and patient preference – often linked to oral / injectable preferences and also dosing frequency.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance is available and is often supplemented by regional pathways.
• Is the pathway of care well defined? Does it vary or are there differences of opinion	Pathways are well defined, and whilst there are subtle regional differences (eg whether to use subcutaneous methotrexate), the variation is minimised by the clear NICE guideline. One point to note is that some centres offer combined clinics with dermatologists and rheumatologists working in partnership. This is very valuable for patients

between professionals across the NHS? (Please state if your experience is from outside England.)	with both skin and joint disease as the evidence base for the two phenotypes differs, and there are parallel NICE guidelines – and treatment should really focus upon the disease phenotype, using the appropriate guideline accordingly.
• What impact would the technology have on the current pathway of care?	The new technology (upadacitinib) would add an important opportunity for PsA patients. It will increase the number of people we can successfully achieve a state of disease remission for – with the long term impacts of reduce disease burden (fewer days off work, better quality of life, less cumulative disability and fewer joint replacement operations).
12. Will upadacitinib be used (or is it already used) in the same way as current care in NHS clinical practice?	I am not entirely sure I understand this question. The new technology would fit into the existing treatment pathways as an alternative targeted therapy option.
• How does healthcare resource use differ between upadacitinib and current care?	From a healthcare resource perspective – potential upadacitinib patients are already being reviewed frequently in clinic. If we are able to commence them on an effective treatment, this should actually diminish health care resource utilisation (acknowledging that administration of an oral medication is also less complex than s/c alternatives).
• In what clinical setting should upadacitinib be used? (For example, primary or secondary care, specialist clinics.)	Secondary care rheumatology services
• What investment is needed to introduce upadacitinib? (For example, for facilities, equipment, or training.)	No new facilities required. Rheumatology teams are already familiar with the drug from RA.

13. Do you expect upadacitinib to provide clinically meaningful benefits compared with current care?	This is a tricky question. I would not argue that upadacitinib is going to be superior to the other biologics (we only have head to head data for adalimumab), but rather that it will be comparable to existing options. It is likely, as we become familiar with the drug, that we will understand better the profile of the patient best suited to upadacitinib. However, what is definitely clear is that we continue to see substantial disease burden from PsA, and adding a drug that achieves ACR20 responses at a level of a TNFi (and with evidence for both articular and skin manifestations of the disease) is a substantial step forward for the PsA community.
• Do you expect upadacitinib to increase length of life more than current care?	Length of life is not normally an outcome we study in PsA thankfully.
• Do you expect upadacitinib to increase health-related quality of life more than current care?	Definitely – when compared to DMARD alone, I would anticipate substantial benefits in line with the evidence base from the clinical trials.
14. Are there any groups of people for whom upadacitinib would be more or less effective (or appropriate) than the general population?	There are potential advantages of upadacitinib for patients who struggle with injectable options. A population we may be more cautious in using upadacitinib are those at increased risk of zoster reactivation.
The use of the technology	
15. Will upadacitinib be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use	The oral preparation makes this an easier option for patients (and clinical teams) compared to injectable options.

(for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are no practical implications I can think of regarding use. Clinical screening is the same as we currently use for other drugs used for PsA.
16. Will any rules (informal or formal) be used to start or stop treatment with upadacitinib? Do these include any additional testing?	Treatment initiation will be based upon the NICE guidance (i.e. confirmation of active inflammatory joint disease on clinical assessment in patients who have failed standard DMARD therapy). Treatment cessation will be as per response criteria for other similar drugs – based upon PsARC.
17. Do you consider that the use of upadacitinib will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
18. Do you consider upadacitinib to be innovative in its potential to make a significant and substantial impact on health-related benefits	Yes. The crucial aspects of upadacitinib that bring novelty to the PsA field are the oral formulation and the novel mode of action.

and how might it improve the way that current need is met?	Considering the mode of action, upadacitinib has greater selectivity for the JAK pathways that we think are the strongest drivers of inflammation in PsA.
• Is upadacitinib a 'step-change' in the management of the condition?	I would say yes. I appreciate that steps come in varying sizes – and whilst the arrival of upadacitinib is perhaps not as seismic as when TNF inhibitors were launched, upadacitinib is certainly a very important advance. We are seeing evidence for JAK inhibition emerging across a broad range of disease areas – and as time progresses, we will learn better the nuance of these agents, understanding which patients are best suited. A crucial thing to appreciate is that upadacitinib is a small molecule inhibitor of the JAK pathway – implying that in due course patents will end, and we will have the potential of generic versions (with accompanying cost savings to the NHS).
• Does the use of upadacitinib address any particular unmet need of the patient population?	The major unmet need is in patients with refractory PsA, who have failed to respond (or lost response) to existing agents. However, a second factor to consider is the options for patients with a desire not to use injectable therapies to control their disease. Upadacitinib addresses both these unmet need areas.
19. How do any side effects or adverse effects of upadacitinib affect the management of the condition and the patient's quality of life?	The side effect profile of Upadacitinib, based upon the trial programmes, is excellent. The rates of serious adverse events are consistent with comparable therapy options available. Herpes zoster reactivation is reported with upadacitinib, although predominantly as a non-severe event. The issue of zoster is familiar to rheumatologists due to the existing availability of JAK inhibitors in RA, and whilst an important side effect, it is also one we have strategies to mitigate.
Sources of evidence	

20. Do the clinical trials on upadacitinib reflect current UK clinical practice?	Yes. The trial portfolio is highly relevant to UK practice, offering information about the key patient groups we treat (biologic naïve and experienced). In addition, trial inclusion criteria align to our existing criteria for other targeted therapies in PsA.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	To my mind, the primary endpoint (ACR response) in the trials is crucial. However, I would highlight that the secondary endpoints of skin responses, enthesitis, fatigue and function are very powerful metrics of improvement that carry enormous importance to people with PsA.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Based upon the legacy of PsA trials, and my clinical experience, I would agree that that the ACR20 responses described in the trials have excellent face validity, and correspond to long term clinical outcomes. This has been shown in longer term studies.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA543, T537 and TA445?	I am aware that the head to head trial has now been published in full – although I suspect the trial reports were made available to the TA submissions.
23. How do data on real-world experience compare with the trial data?	To date, real world data are limited in size. I think it is too early to look at real world data for PsA and Upadacitinib.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	None I can think of.
24b. Consider whether these issues are different from issues with current care and why.	Not applicable.
Topic-specific questions	

25. Would you expect HAQ-DI to increase over time in patients who respond to a bDMARD/tsDMARD whilst receiving treatment? If so, to what extent?	This is contentious. In RA, I would usually say yes. However, it is important to consider age. PsA cohorts are on average 5-10 years younger. Certainly in my clinics, PsA patients are typically much younger when their disease is active. As a result, natural progression of HAQ over time is much less of an issue. Between the ages of 60 and 70, there are well documented studies describing the natural decline of HAQ in the general population and in RA cohorts. However, between 40 and 50, changes are much less marked. My HAQ is currently zero, and I hope it remains zero for the next decade! In addition, in PsA, the total joint counts are generally lower than RA. Taking these factors into account, I would actually support a model with HAQ not increasing by time alone (assuming disease activity is controlled).
26. Would people for whom TNF-alpha inhibitors are contraindicated typically be offered more than one bDMARD/tsDMARD?	Definitely. It would be entirely inappropriate to leave someone with active PsA untreated. The evidence for traditional DMARDs in PsA is weak, and unfortunately drugs like methotrexate have limited benefits across the different domains of disease (skin, enthesis).

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Clinical effectiveness evidence gaps	The trial programme covers the key effectiveness questions of relevance.
Key issue 2: Limited direct clinical effectiveness evidence	There are head to head comparisons of upadacitinib and DMARD / TNFi, which is what I would expect for drugs coming through to approval.
Key issue 3: Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs	NMA models always need cautious interpretation. In particular, context around varying placebo responses need consideration. Although the NMA conditions comparisons on the placebo response, it is relevant to consider that the placebo responses vary for many reasons (background healthcare standards, patient expectation). Some of these factors will influence introduce potential for bias more than offers… However, that aside, I think the NMAs presented are actually very well prepared and comparable to others that I have reviewed send to NICE.

Key issue 4: Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs	No additional comments beyond key issue 3.
Key issue 5: Company model structure is simple and does not wholly reflect the real-world setting	I am not sure I would see this as a criticism. The company presented model is pragmatic – and I am not sure how much closer to the real world model it is feasible to achieve.
Key issue 6: Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC	This is consistent with previous PsA appraisals I believe.
Key issue 7: Mismatch between description of HAQ-DI modelling in the company submission and the approach	The issue here is around how the company have modelled the HAQ change over time. Neither model perfectly maps to real world experiences. Pages 87 / 88 of ERG report are what this refers to. I think some of this may be interpretation of the original model… and I may have misunderstood the original specification. Irrespective, I am not sure it really impacts ICER. The company model appears to be more conservative in design, so the impact of this difference would appear to actually disadvantage the models for upadacitinib.

implemented in the company model	
Key issue 8: Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment	I think this relates to page 90 of ERG report, and is also linked to the previous question on HAQ progression in responders. My understanding is that the modelling presented reflects what previous technology appraisals have worked from. In the upadacitinib trials, the mean age was 49.7 years, and so my view is that accepting stable HAQ is actually reasonable amongst responders.
Key issue 9: Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice	I think this issue is valid to raise – although alternative modelling scenarios are hard to construct.
Are there any important issues that have been missed in ERG report?	None I can think of.

PART 3 -Key messages

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

- Upadacitinib is an novel therapeutic – targeted the JAK pathway in a selective manner
- The clinical trials show impressive responses not only in articular disease, but also skin and entheseal disease – which is an important step change for JAKi in PsA
- The safety profiles are consistent with the RA experience and very acceptable
- The cost modelling has face validity, including the modelling of HAQ over time in responders
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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

Technical engagement response form

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Wednesday 28 April 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Rheumatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Clinical effectiveness evidence gaps	no	Evidence gaps do exist – but these don't detract more for this medication than for any other previous NICE TA review.
Key issue 2: Limited direct clinical effectiveness evidence	**No**	No additional data to comment on
Key issue 3: Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs	**No**	No additional data to comment on
Key issue 4: Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs	**no**	No additional data to comment on
Key issue 5: Company model structure is simple and does not wholly reflect the real-world setting	no	We agree that the company modelling of just 1-2 therapeutic options is simplistic and doesn't fully reflect real-life NHS clinical care. Presumption of Ustekinumab as second line therapy does not reflect actual clinical choices at this stage in particular.

Key issue 6: Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC	**no**	Different trials will inevitably collect PROMs such as HAQ-DI in a heterogeneous way. The effect of this would not differ majorly from other previous medication considered for a NICE TA in PsA
Key issue 7: Mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model	**yes**	This is a modelling issue and I am a clinician, not a modelling expert, and therefore adequately knowledgeable in this particular aspect to comment.
Key issue 8: Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment	**yes**	This is a modelling issue and I am a clinician, not a modelling expert, and therefore adequately knowledgeable in this particular aspect to comment. However, an increasing HAQ-DI (deterioration in function) in a patient responding to treatment would be an unusual scenario and usually related to a parallel co-morbidity deteriorating rather than being a pure psoriatic arthritis issue. To my mind this makes issue 8 more of theoretical interest than having any particular relevance to the real world
Key issue 9: Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice	**yes**	We agree that, in NHS clinical practice, the TNF-alpha inhibitor-contraindicated population generally receive more than one line of treatment and BSC is generally not an appropriate first-line treatment option for this population. However, as the ERG scenario results did not alter the company's cost effectiveness conclusions for this population, this does not appear to have affected the overall outcomes here.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

British Society for Rheumatology
Comments on the Technical Engagement Data Report

1. The data on upadacitinib having a stronger beneficial impact on over MDA, skin and joints than tofacitinib changes the previous BSR comment that upadacitinib would be seen as similar in efficacy to other available JAK inhibitors such as tofacitinib. This would suggest that on an evidence based medicine approach to clinical care, upadacitinib would be used preferentially to tofacitinib

2. The data on upadacitinib having a beneficial impact on axial inflammation in PsA (reducing BASDAI by 3.1 in 24 weeks) will have a large impact on clinical priorisation of upadacitinib in PsA
   The only other NICE TA approved medications with robust axial evidence of response are anti TNFs and anti IL17s
   30% of PsA patients have axial involvement. For this group upadacitinib would be used preferentially to the current NICE TA approved ustekinumab, tofacitinib and apremilast (but has a similar effect as the anti TNF and anti IL17 options).
   Similar to ustekinub, tofacitinib and apremilast, the data recently presented to the TA for guselkumab in PsA also did not provide evidence of efficacy in axial PsA.

3. As upadacitinib is a tablet, for patients with PsA and axial disease who happen to also have significant needle phobia or poor hand function, upadacitinib becomes a probable clinical therapeutic option of choice for this group (before use of anti TNFs or anti IL17s)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm on Wednesday 28 April 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Thank you for the opportunity to comment on this technical engagement document. We can confirm we have no comments at this time.		

NICE National Institute for Health and Care Excellence

TECHNICAL ENGAGEMENT RESPONSE FORM

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

ERG response to company response to technical engagement

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Clinical effectiveness evidence gaps	No	We thank the ERG for their assessment that there are no alternative approaches and that the approaches we have taken are appropriate. We recognise that there are a number of minor clinical effectiveness evidence gaps but we have accounted for these where possible, and clinical opinion provided to us suggests that these limitations are no different from those experienced in previous appraisals in PsA.
ERG response:		No additional comment
Key issue 2: Limited direct clinical effectiveness evidence	No	We recognise the limited direct clinical effectiveness evidence issue that is inherent to all appraisals with PsA and thank the ERG for their assessment that no alternative approach is possible.
ERG response:		No additional comment

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 3: Some uncertain indirect clinical effectiveness results: company Week 12 biologic-naïve NMAs	No	We thank the ERG for their assessment that our NMA approach was methodologically appropriate and that there is no alternative approach that could have been taken to reduce uncertainty. We provided extensive sensitivity analyses to explore the assumptions and methods used in the biologic-naïve NMA, as follows: • Fixed vs. random-effects models • Fixed vs. random-effects model, with placebo-response adjustment • 24-week vs. 12-week data • Pooled vs. non-pooled data (when mixed bDMARD-naïve and -experienced populations were reported) These analyses allowed us to be confident that the relative effects of upadacitinib were broadly comparable to the relevant comparators across all included outcomes.
ERG response:		No additional comment

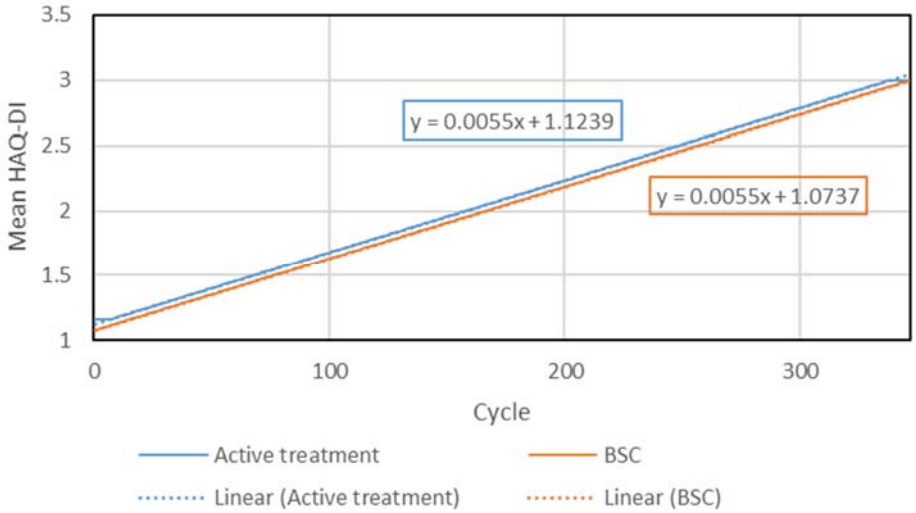
Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 4: Uncertain indirect clinical effectiveness results: company Week 12 biologic-experienced NMAs	No	We accept the perspective of the ERG that, while there are limitations inherent in the analysis, our approach was methodologically appropriate and that there is no alternative approach that could have been taken to reduce uncertainty. Due to the smaller number of comparators eligible for inclusion in the biologic-experienced NMA than the biologic-naïve network, the network is inherently constrained. Nonetheless, our approach and extensive sensitivity analyses allowed us to be confident that the relative effects of upadacitinib were broadly comparable to the relevant comparators across all included outcomes.
ERG response:		No additional comment
Key issue 5: Company model structure is simple and does not wholly reflect the real-world setting	No	We appreciate the opinion of the ERG that there is no alternative approach to developing a model that is more representative of NHS clinical practice. In the absence of suitable evidence to inform a true treatment sequencing model, the 'York' model provides an established, robust, and clinically validated framework that permits comparison between upadacitinib and previously reimbursed therapies. Furthermore, this model continues to be the basis of PsA NICE appraisals, including the ongoing appraisal of guselkumab (ID1658).
ERG response:		No additional comment

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 6: Clinical effectiveness data used to populate the company model are derived from different sources for HAQ-DI conditional on PsARC	No	We agree with the perspective of the ERG that no alternative data sources or approaches were possible here. In the face of limited data for HAQ-DI conditional on PsARC for a number of comparators, we took a pragmatic approach that allowed us to produce reasonable estimates and to generate ICERs for all comparators. While we accept that this introduces some uncertainty, we wished to provide the most complete analysis possible. The same approach was also performed and accepted by the committee in the recent appraisal of tofacitinib in PsA (TA543).
ERG response:		No additional comment
Key issue 7: Mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model	No	Firstly, we would like to note that it is not possible to reproduce the company's or the ERG's figures (Figures 3 and 4 in the ERG report) depicting the progression of HAQ-DI over time for non-responders, responders on treatment and responders discontinuing treatment because this is a schematic that aims to visually depict a patient's journey and is not based on the model traces. The approach used to model HAQ-DI over time is done so within the constraints of a Markov model, which we do acknowledge is a limitation, and uses formulae to 'imitate' tunnel states to track patients who discontinue active treatment and enter the BSC state over the model's time horizon. Given the precedent observed in prior PsA submissions – that is, Markov models have been used – we believe this to be appropriate and consistent with what has been done previously. The formula we are referring to is in column AH of the Trace sheets (mean HAQ-DI in BSC state), and works as follows: a) in the first part, the baseline HAQ-DI score

Key issue	Does this response contain new evidence, data or analyses?	Response
		is assigned to patients newly entering the BSC state, and b) in the second part of the formula, the baseline HAQ-DI adjusted by HAQ-DI deterioration is assigned to patients already in the BSC state. This part of the formula uses the previous cycle to determine both the patients already on BSC (column AD) and the previous HAQ-DI score (column AH). In the ERG's critique, it is noted that both the rebound effect and HAQ-DI progression after active treatment discontinuation is incorrectly implemented. We have therefore provided a response for each issue separately, to demonstrate why we do not consider some of the ERG's comments to be accurate. Rebound effect In the biologic-naïve population, the initial baseline values for HAQ-DI are specific to this population. When responding patients discontinue their first line of treatment, their second line consists of another line of active treatment – specifically, ustekinumab – and third line is assumed to be BSC. At this point, these patients are considered to be biologic-experienced. Therefore, when a patient's HAQ-DI reverts to baseline on entry into the BSC state, this baseline value represents the baseline of the biologic-experienced population, which is higher than the biologic-naïve population baseline (e.g., for the no-psoriasis subgroup, we move from 1.08 to 1.16 HAQ-DI score). We believe this to be a reasonable clinical assumption and is consistent with the treatment effects applied to ustekinumab as second-line treatment in the biologic-naïve population (these are populated with the NMA outcomes from the biologic-experienced population). To test that the correct HAQ-DI score is applied when patients revert to baseline,

Key issue	Does this response contain new evidence, data or analyses?	Response
		this can be done as follows, by removing the effect of progression: 1) Go to “Effectiveness” tab and then to “Change in HAQ-DI from baseline, conditional on PsARC response, by treatment and position in treatment sequence” section 2) We need to eliminate the effect of progression to check the baseline value at which patients are jumping from active treatment to BSC in an active treatment sequence. To do so, change “haqdi_deterioration” variable (cell E44) from 0.072 to 0 3) Go to “Trace_Seq_1bn” tab and locate “Mean HAQ-DI in BSC state”. All values across all cycles in this column are 1.16 4) Run a true or false test to check all values are exactly the same 5) Next, test one of the biologic-experienced traces (“Trace_Seq_2be” for instance). In this case no 2L was modelled as patients transition from one active treatment to BSC. When the same test described above is repeated, the same observations will be obtained. HAQ-DI progression after active treatment discontinuation To test that HAQ-DI progression after active treatment discontinuation is correctly implemented, i.e., increases linearly at the same rate as non-responders, we again refer to column AH of the trace sheets, and in this case we need to eliminate the time component, since at each cycle patients could discontinue active treatment and move to BSC. To do this we need to track a given cohort of patients who enter the BSC state at the same time (i.e., timepoint t as per Figure 3 in the ERG report): 1) Go to “Transition Probs” tab and select a treatment option (in this example,

Key issue	Does this response contain new evidence, data or analyses?	Response
		we adjust the upadacitinib sequence) 2) Set rows 15:18 in column N to 0%, which will move all patients to the BSC state after completing the 12-week trial period of the active treatment (upadacitinib) 3) We also need to set rows 22:25 in column U to 0%, which will move all patients to the BSC state after completing the 12-week trial period of the 2nd line treatment (ustekinumab) 4) Next, go to the "Trace_Seq_1bn" tab and check the values for the column "Mean HAQ-DI in BSC state" (column AH). This column will show predicted outcomes for the specific cohort of patients who fail to achieve PsARC response following the trial periods for both active treatments (in the case of biologic-naïve group). Confirm that this column shows that HAQ-DI progresses linearly by 0.055. 5) If we now go to the "Trace_Seq_BSCbn" tab, without modifying anything we can observe the same linear progression of 0.055 in the "Mean HAQ-DI in BSC state" column In this way, we can observe how the "Mean HAQ-DI in BSC state" column presents cumulative values as patients can transition at any cycle into BSC, based on the constant discontinuation rate for active treatment sequences. This means that in any cycle at moment t, this column accounts for those patients entering BSC at moment t plus patients entering in previous cycles (t-1, t-2, and so on) and whose disease has already progressed for n cycles. This is illustrated in Figure 1, below, where the slopes are demonstrated to be equal at 0.055 for both treatment arms.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Figure 1: Mean HAQ-DI in active treatment and BSC states  In summary, the test described above illustrates that, like the Markov trace for the BSC sequence, the Markov traces for the active comparator sequences reflect a linear trend in HAQ-DI when focusing on a specific cohort of patients who enter the BSC state in a given cycle. This is consistent with the conceptual diagram presented in our submission and aligns with the model conceptualisation presented in previous NICE TAs using the York model.
ERG response:		The ERG thanks the company for explaining how mean HAQ-DI changes over time in the model and agrees with the perspective of the company that it is not

Key issue	Does this response contain new evidence, data or analyses?	Response
		possible to replicate the progression of HAQ-DI described in the CS using a Markov framework. The ERG considers that the steps provided by the company do not show that the issues identified by the ERG in the company approach to HAQ-DI modelling do not exist. For example, as the company shows, removing any HAQ-DI progression will mean that all patients have a HAQ-DI that reverts to the baseline value on stopping treatment. However, once HAQ-DI progression is restored in the model, on stopping treatment a patient's HAQ-DI will rebound to a value that is a complex function of the patient's baseline HAQ-DI value, the HAQ-DI value for non-responders at the cycle the patient stopped treatment and the percentage of the treated cohort that has already stopped treatment. Removing progression from the model or making everyone stop treatment at 12 weeks removes the complexity in the model that causes the issues raised by the ERG. The ERG therefore considers that the mismatch between description of HAQ-DI modelling in the company submission and the approach implemented in the company model remains.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 8: Absence of modelling scenario to explore the effect of increasing HAQ-DI conditional on PsARC whilst responding to treatment	No	In line with our response to the clarification questions, we consider that a scenario in which the HAQ-DI score for responders increases in line with natural history is 1) lacking in clinical plausibility, and 2) would represent a major divergence from the established 'York' model precedent that forms the basis of all recent PsA appraisals. In our clarification response we provided details of clinical opinion to us that this scenario is implausible, as patients experiencing progression at the natural history rate would be swapped to an alternative treatment due to lack of response. We also provided evidence to demonstrate that patients receiving upadacitinib do not experience any worsening of HAQ-DI up to week-56 after starting treatment. The ERG acknowledged in their report that their original request for a scenario in which patients that respond to treatment progress at the natural history rate may be implausible.
ERG response:		No additional comment
Key issue 9: Treatment options for the TNF-alpha inhibitor-contraindicated population do not reflect current NHS clinical practice	No	We accept the perspective of the ERG that patients would generally receive more than one line of treatment in the TNF-alpha inhibitor-contraindicated population, and that BSC is generally not an appropriate first-line treatment option for this population. We consider the ERG's scenario results to be appropriate, and note that this scenario did not alter the cost-effectiveness conclusions for this population.
ERG response:		No additional comment

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Discontinuation rate	N/A – raised by Technical Team during teleconference	No	During the technical engagement teleconference, the Technical Team noted an additional issue relating to the ongoing guselkumab PsA appraisal (ID1658), in which the manufacturer applied treatment-specific discontinuation rates to all treatments, with guselkumab having the lowest rate applied. This was considered by the committee to a) be biasing the cost-effectiveness results in favour of guselkumab, and b) inconsistent with the precedent established in prior PsA appraisals. We would like to clarify that the base-case results presented in our submission apply the standard 16.5% discontinuation rate established in the York models (TA199 and TA445). Two scenarios were presented in which this assumption is varied: 1) higher discontinuation rate for biologic-experienced population than biologic-naïve population from Gabay et al. 2015 (24% vs. 16.5%, respectively), and 2) use of a more recent source of discontinuation rate, from Fagerli et al. 2018. The results of these scenario

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			analyses were not found to materially impact the base-case ICERs and did not impact the cost-effectiveness of upadacitinib. We also wish to note that the ERG report is unclear with relation to discontinuation rates applied in our base case. Table 24 of the ERG report (page 74) appears to suggest that the alternative discontinuation rate for the biologic-experienced population from Gabay et al. 2015 is applied in the base case. We would like to clarify that this not correct, and these values are only applied in a scenario, as described above.
ERG response:			The ERG agrees with the company that the alternative discontinuation rate for the biologic-experienced population is not applied in the base case.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Dear [redacted]

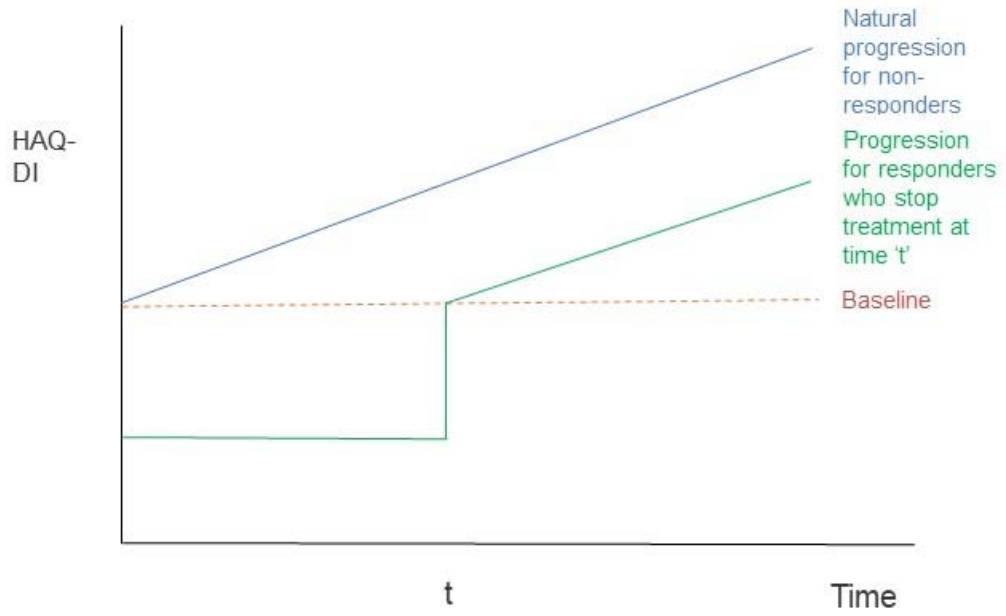
NICE technology appraisal committee D are in the process of appraising upadacitinib for psoriatic arthritis. As you will be aware the same basic model structure has been used throughout for this disease area and originated with York's assessment group model for TA199 Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. The last drug to be appraised in this disease area was TA711 Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs which was also reviewed by York ERG. With York's experience in this disease area we were hoping you would be able to help clarify an issue that has been identified in the current appraisal.

The current ERG have spotted a discrepancy in how HAQ-DI progression over time has been modelled. They noted that the company's description of how HAQ-DI progression over time is implemented in the *current* Excel model is not consistent with how it has actually been modelled (see below graphs for description of issue). This was raised with the company at engagement – they suggested the approach used to model HAQ-DI over time is done so within the constraints of a Markov model, which is a limitation, but they consider this to be appropriate and consistent with Markov models used in previous PsA submissions. The current ERG were wondering if this issue had occurred/been spotted in previous models in this disease area or if it is specific to this company's model. They suspect this error is limited to the current model, due to the fact that, in this model altering the discontinuation rates doesn't seem to have any effect on the model outcomes which is not consistent with previous topics. Gary and the ERG would appreciate a sense check on this as they did wonder if it had something to do with the fact this was run in excel and not R as some other PSA topics had used.

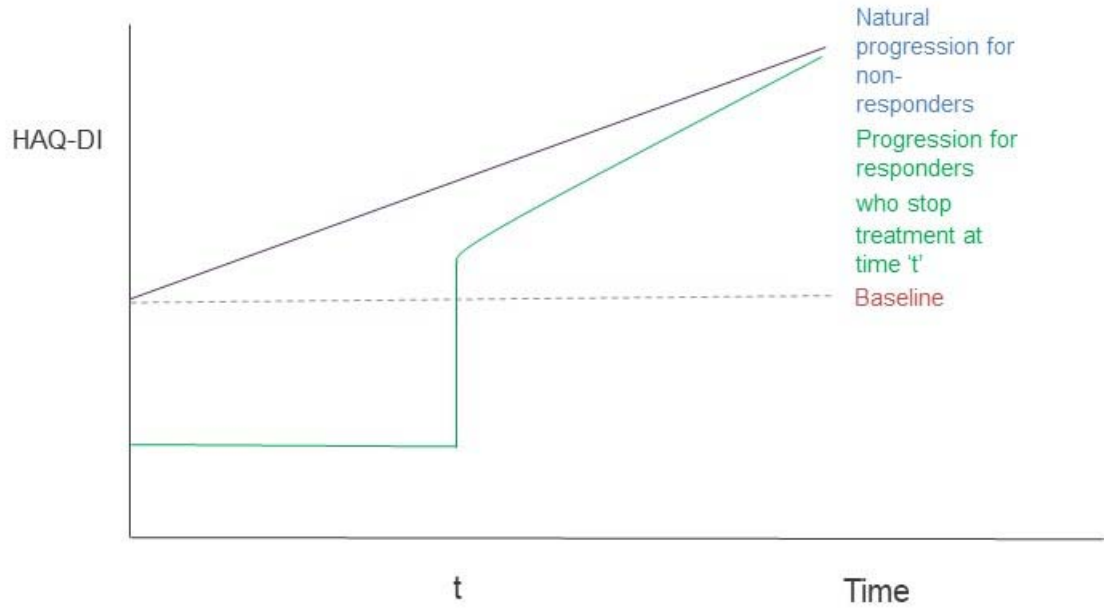
The NICE technical team would be grateful if someone from the ERG could double check to see if this problem occurred in the previous PsA models. We are due to take this topic to committee next **Thursday 12th August**. I appreciate this is a last-minute request, however if we could get a response before the committee that would be greatly appreciated.

We also attach 2 committee slides which describe the issue for further information.

1) How it is described as being modelled by the company as being consistent with the previous models in this disease area



2) How it is actually implemented in the current model



Kind regards,

[redacted]
Health Technology Assessment (HTA) Adviser – Technology Appraisals
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | M1 4BT | United Kingdom

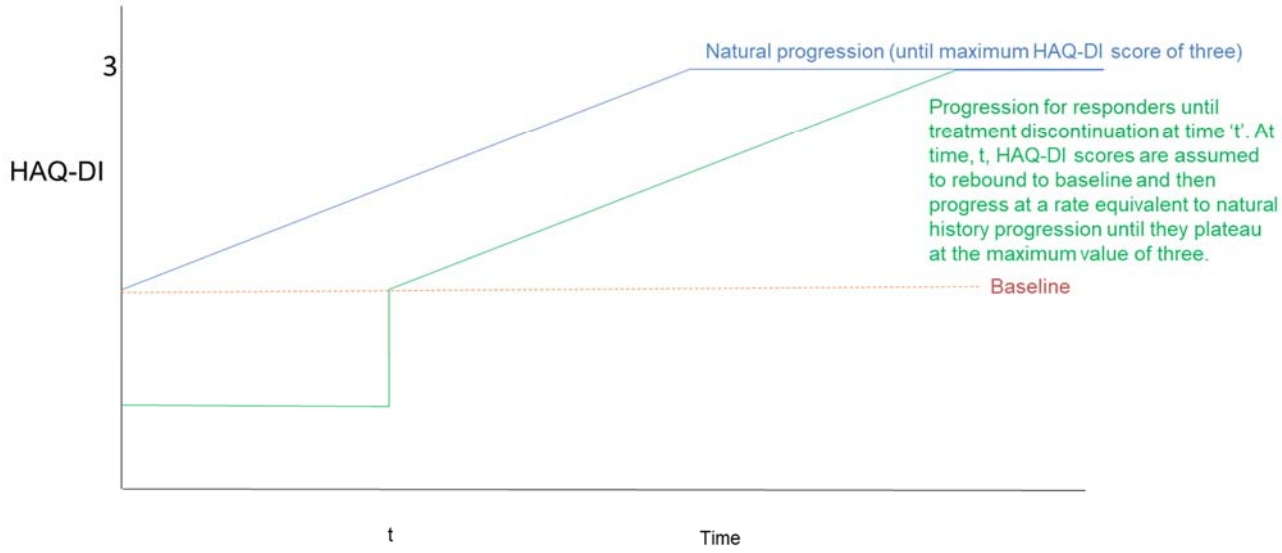
Dear [redacted],

I've looked into the query regarding the modelling of HAQ-DI progression over time based on experience with TA711 Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs and knowledge of the original York assessment group model.

In TA711 and previous York model, HAQ-DI score for bDMARD treatment responders is assumed to be constant and maintained throughout the duration of treatment. When patients move to final line therapy of BSC (non-responders to bDMARDs), HAQ-DI scores are assumed to rebound to baseline scores and then progress at a rate equivalent to natural history progression until they plateau at the maximum HAQ-DI value of three.

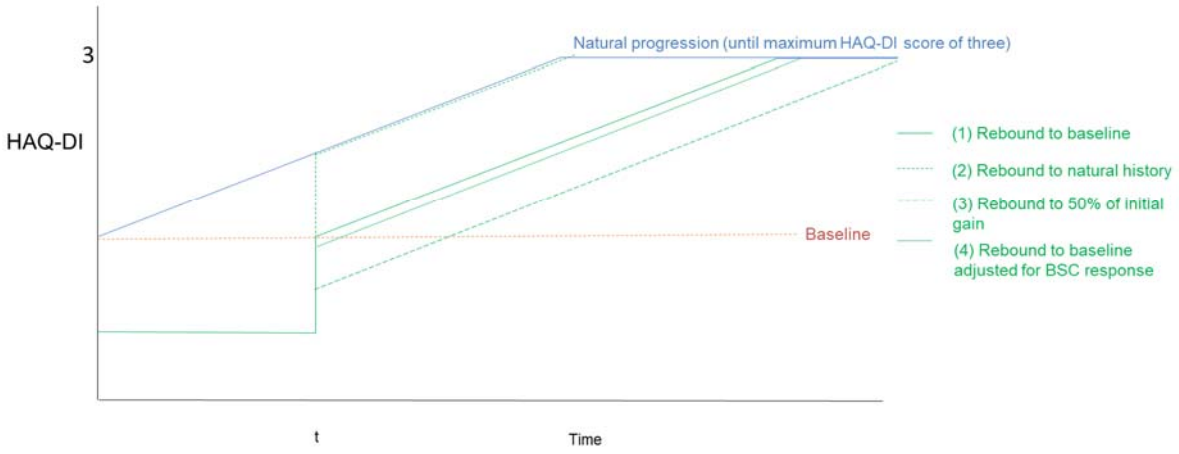
This is illustrated in Figure 1 below.

Figure 1



Alternative HAQ-DI rebound assumptions have also been considered in previous appraisals: rebound to natural history; rebound to a percentage of initial gain; and rebound to baseline adjusted for BSC response from NMA. These are illustrated in Figure 2 below.

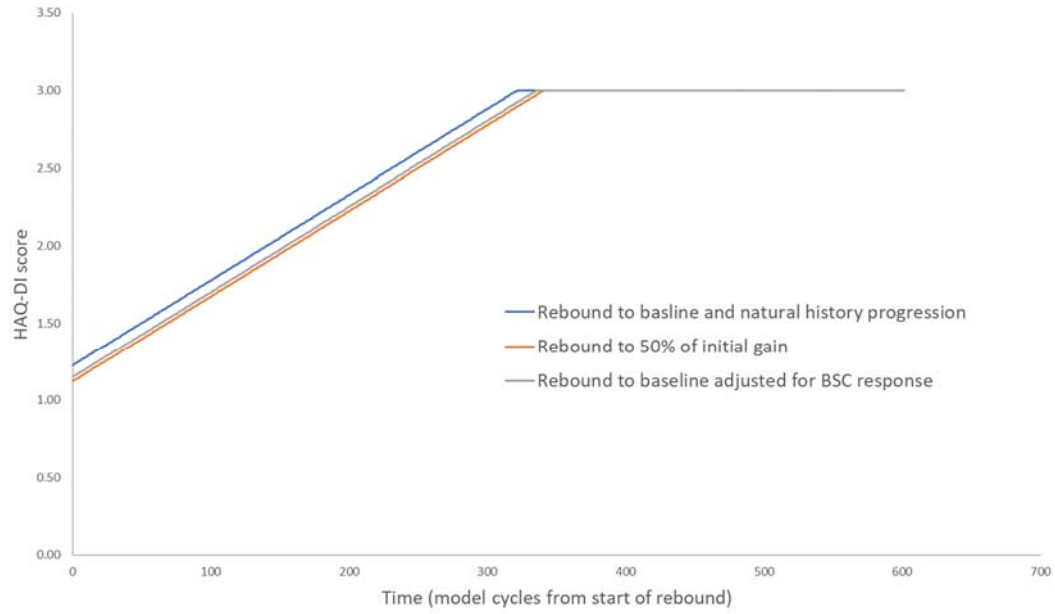
Figure 2: Alternative rebound assumptions



Based on your query, my understanding is that the company submission for upadacitinib for psoriatic arthritis states that the approach outlined in Figure 1 above has been implemented in the model (as per previous appraisals), but the ERG disagrees.

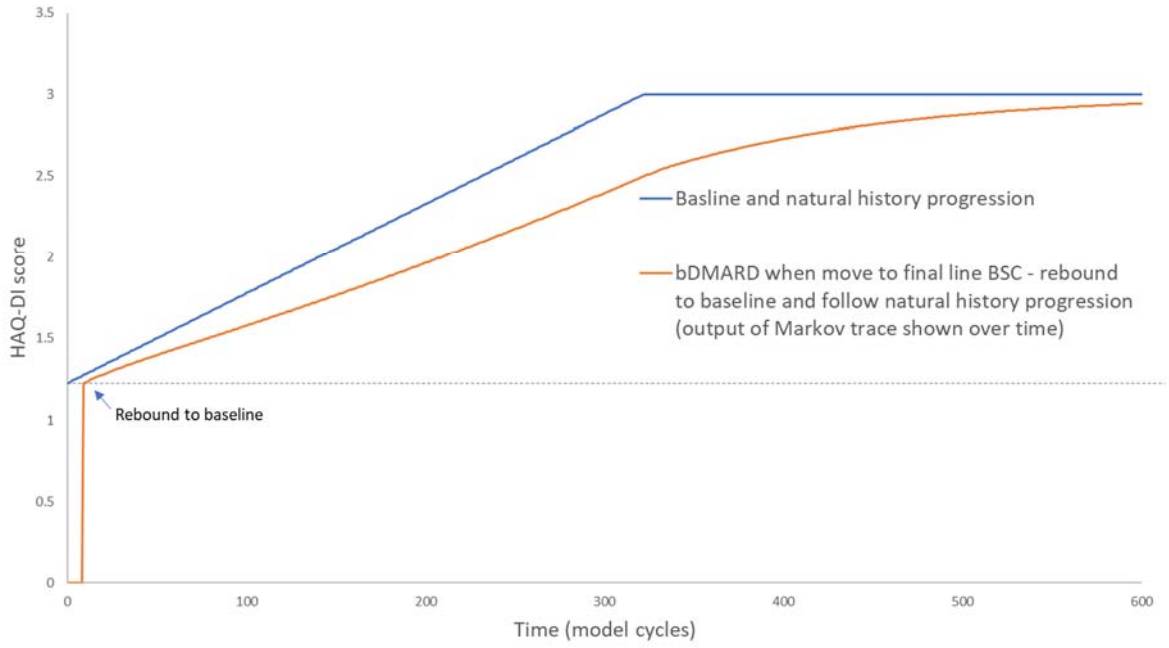
I've looked further at this in relation to TA711, where the model was developed in Excel (original York model was in R) and all previous models are Markov cohort models. Figure 3 shows that HAQ-DI progression over time (from rebound) was modelled appropriately in TA711 (in line with Figures 1 and 2 above).

Figure 3: HAQ-DI progression over time from rebound [TA711 model]



In terms of how this translates into HAQ-DI scores over time for the cohort of patients who initially started a bDMARD treatment and then moved to final line BSC, Figure 4 shows the output of the Markov trace for HAQ-DI score over time at final line therapy (i.e., non-responders to bDMARD treatments).

Figure 4: HAQ-DI scores over time for cohort on final line BSC therapy



There are a couple of points to note from Figure 4:

1. The bDMARD curve when moved to final line BSC (orange line in Figure 4) does not follow the straight line of natural history progression because patients are entering final line therapy (BSC) at different time points in the model, i.e., the proportion of the cohort starting final line therapy is different in each model cycle. Therefore, the rebound to baseline and natural history progression occurs for different proportions of the cohort at each time point of the model.
2. The bDMARD curve also reflects the proportion of patients alive at each time point (i.e. deaths at each model cycle are removed).
3. The bDMARD curve depends on the rebound assumption (in Figure 4, this is rebound to baseline).

In terms of how this relates to the query for upadacitinib, I suspect that the company's approach may be appropriate and consistent with previous models in PsA but I haven't seen the model to validate implementation. The convergence identified by the ERG may be related to point 1 noted above in relation to Figure 4 (i.e. the proportion of the cohort starting final line therapy is different in each model cycle and therefore rebounding at different time points). However, there is a discrepancy between the wording in the company submission (CS) and implementation in Excel in relation to the rebound assumption (point 3 above). The CS suggests a rebound to baseline, but the ERG's description suggests that the rebound assumption is 'rebound to somewhere between baseline and natural history progression'.

Hope this is helpful and doesn't cause additional confusion!

Best wishes,

[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs

Date 25 August 2021

Dear [redacted],

At the first meeting for this topic on 12 August 2021 the appraisal committee were unable to come to a decision. The committee were concerned that the modelling of HAQ-DI progression in the company's economic model was not correctly implemented and not consistent with previous technology appraisals in psoriatic arthritis. The committee did not consider the results of the economic model to be robust and therefore no decision could be made. In addition, there were scenario analyses on the effect of HAQ-DI increases for patients who respond to a biological DMARD whilst receiving treatment that the ERG had requested during clarification and technical engagement that the committee considered would be informative.

For the appraisal committee to make any conclusions on the cost effectiveness of upadacitinib for psoriatic arthritis the company needs to correct the identified errors of HAQ-DI progression and perform the scenario analyses requested. Full details of these requests are outlined below.

NICE requests that a response to this request be submitted by 5 pm on 8 September 2021.

Yours sincerely,

Jasdeep Hayre, Associate Director, Technology Appraisals & HST

Professor Gary McVeigh, Chair, Technology Appraisal Committee D

1) **HAQ-DI progression for people who have responded to a bDMARD and stopped treatment**

Overview of issue**:**

- In the company's current model when a responder to a biological DMARD stops treatment, their HAQ-DI score increases instantaneously to a value that lies between their baseline value and the HAQ-DI score for non-responders to a biological DMARD.

- The HAQ-DI score then converges with the rate of increase for non-responders, rather than progressing in parallel to that rate.

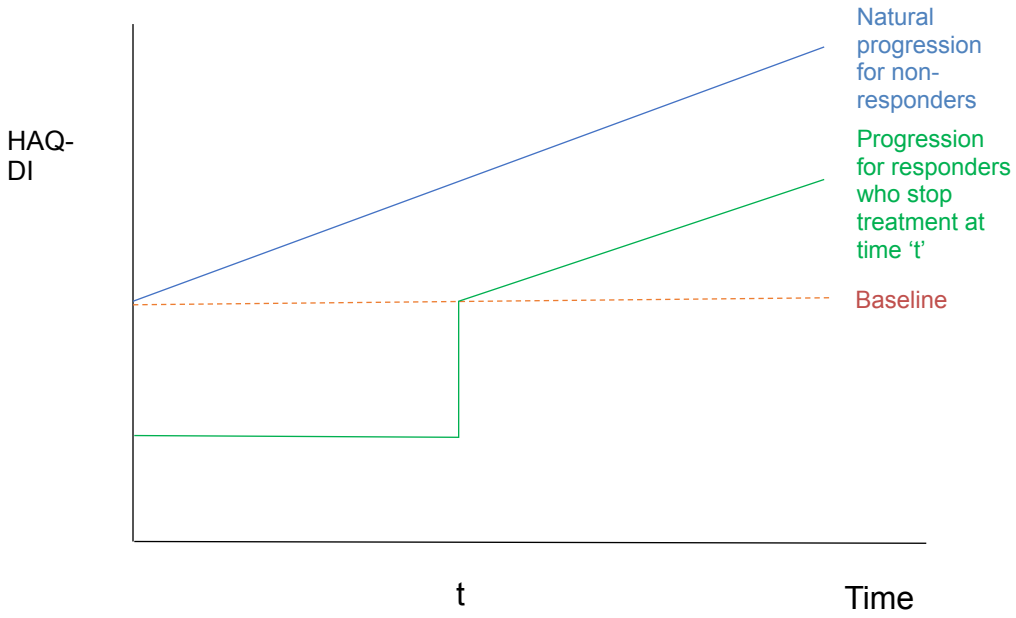
- This is not consistent with previous models in psoriatic arthritis. In previous models when a responder to a biological DMARD stops treatment, their HAQ-DI score increases to baseline value.

- The committee suggested that by rebounding to a point higher than baseline, the company's implementation of HAQ-DI over time for responders who stop active treatment (and move to best supportive care) implies higher levels of disability and associated healthcare costs that are carried forward throughout the model timeline.

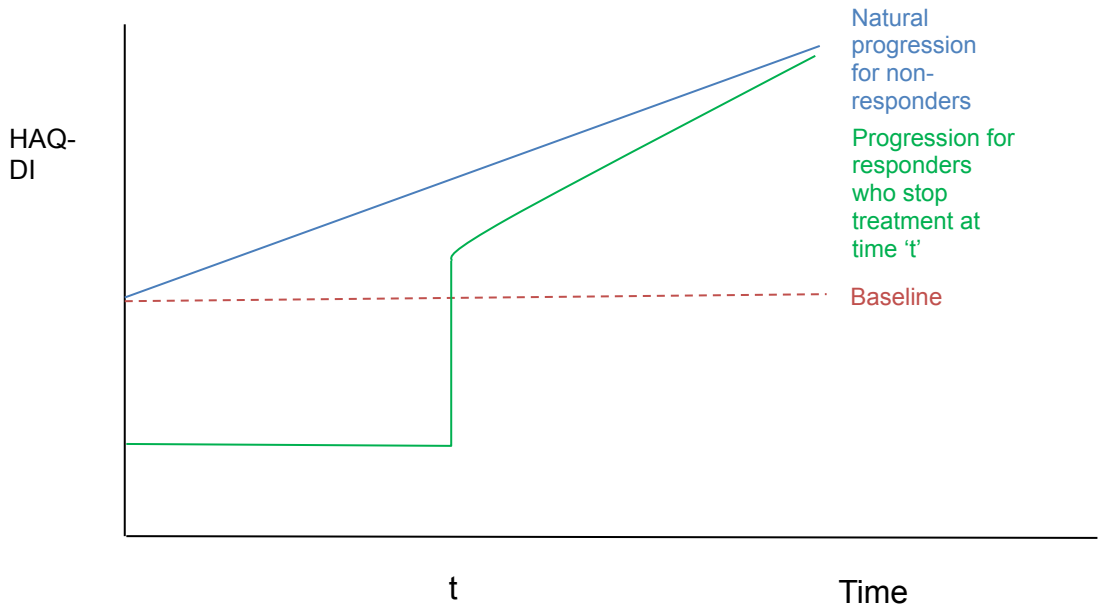
- The committee were concerned to hear that when applying a different discontinuation rate in a scenario analysis the company's ICERs did not change. The committee felt this was a 'red flag' which suggested an error in the company's model as all previous economic models for psoriatic arthritis were highly sensitive to this assumption

- Further details including Markov traces of how HAQ-DI progression was implemented in previous models was supplied to the company in a separate document.

- Company's current description of HAQ-DI progression:

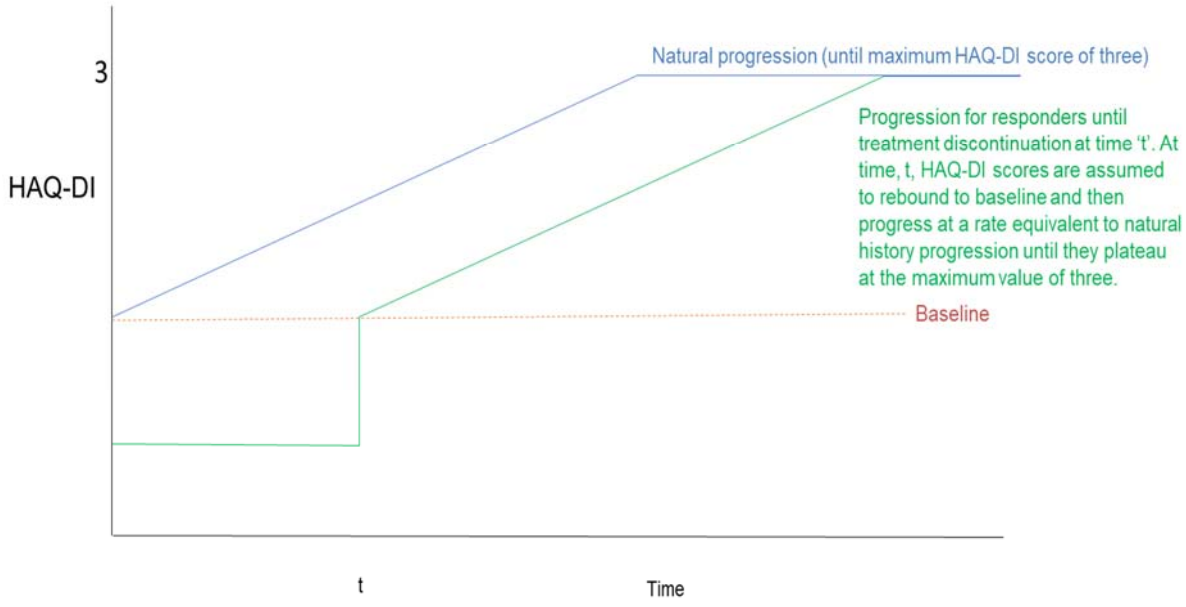


- How HAQ-DI progression is implemented in company's current model



- How HAQ-DI was implemented in TA711

Figure 1



Appraisal committee request:

The appraisal committee requests that the company update its economic model to correctly implement HAQ-DI progression in people who responded to bDMARDs that stop treatment in line with models used in previously published technology appraisals. In your response, please ensure that you present:

i. a graphical representation of the output of the Markov trace for HAQ-DI scores over time (as shown in the examples above)

ii. full details on how the model changes have been implemented

iii. Updated base case results including probabilistic results for all populations

2) Scenario analyses to explore effect of increases in HAQ-DI whilst responding to treatment.

The company model assumes that the HAQ-DI benefit for responders to a specific bDMARD/tsDMARD is maintained until patients stop taking the

treatment. The ERG highlighted at the appraisal committee meeting and in their original report that the evidence submitted by the company to suggest this scenario is not relevant was lacking. The committee were aware that the evidence from the select PSA trials were only available up to 56 weeks. The experts suggested at the meeting that HAQ-DI is likely to increase in the general population over time. The committee considered this was an important assumption to test in a scenario analysis. Therefore, the appraisal committee requests the company:

I. Provide results from a scenario in which the HAQ-DI score for responders increases overtime.

II. Provide full details of how these model changes have been implemented.

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Wednesday 8th September 2021

Dear Jasdeep and Prof. McVeigh,

Thank you for the opportunity to respond to these queries, our responses are included below.

In relation to question 1, we have provided updated base-case results in which patients discontinuing active treatment rebound to their starting HAQ-DI score, the results of which do not change the interpretation of the analyses – upadacitinib remains cost-effective against all comparators for biologic-naïve, biologic-experienced, and contraindicated populations. We have also demonstrated how our model implements HAQ-DI progression, and calculates costs and QALYs, for non-responders in the same way as in TA711 and previous iterations of the York model.

For question 2, we have provided the results of the requested scenario, in which an annual HAQ-DI progression rate of 0.01 is applied to patients responding to active treatment. While this scenario is not reflective of clinical practice and is inconsistent with decision-making in previous psoriatic arthritis appraisals recommended by this committee, the results are consistent with the base-case with upadacitinib remaining cost-effective against all comparators in all treatment lines.

When applying the rebound effect as requested, there is an increase of less than 2% for the ICERs (upadacitinib vs adalimumab) in the biologic naïve population. A reduction of ICERs was seen in the contra-indicated population when looking at upadacitinib vs BSC comparison. In terms of the “HAQ-DI progression while on treatment” scenario, minimal variation was also observed. All these analyses indicate consistency and robustness of the results provided in the company submission.

We hope that these analyses and results alleviate any concerns the committee has, and we hope to be able to move forward with a decision and FAD in a timely manner.

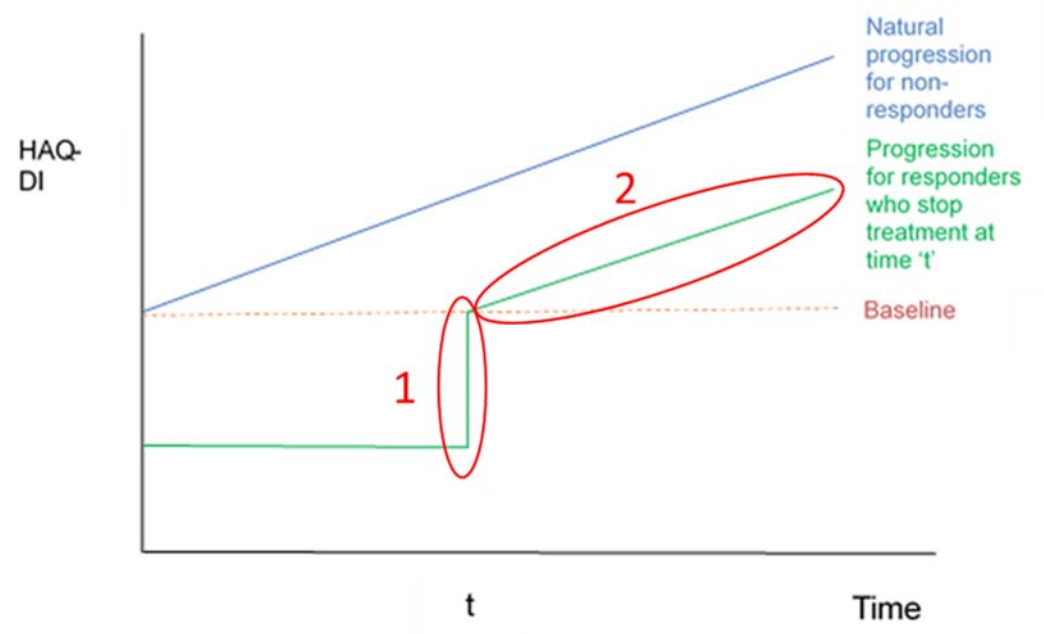
Best wishes,

Gabriela Ramirez-Guevara

1. HAQ-DI progression for people who have responded to a bDMARD and stopped treatment

There are two issues that require addressing here. Firstly, the instantaneous rebound to baseline in HAQ-DI score that occurs when patients discontinue treatment with a bDMARD and revert to BSC (issue 1). Secondly, the rate of progression that is applied upon discontinuation when patients are receiving BSC (issue 2). These issues are highlighted in Figure 1 below.

Figure 1. HAQ-DI progression upon discontinuing active treatment and starting BSC



1: Instantaneous rebound of HAQ-DI score to baseline; 2: HAQ-DI progression rate applied upon discontinuation.

Issue 1

In our submitted model, it was assumed that all patients' HAQ-DI score would revert to baseline when moving to BSC. For patients who have progressed on a biologic, the HAQ-DI baseline score was that for the biologic-experienced population (as they are in 2nd line treatment – ustekinumab – values are taken from the biologic-experienced network, this approach is aligned to previous appraisals, where second line treatment effects in the biologic naive population were input with biologic experience networks). This assumption was used to reflect the fact that once patients enter the BSC state after discontinuing active treatment, these patients would no longer be biologic-naïve and therefore their HAQ-DI score was representative of the biologic-experienced population. This results in a slightly higher HAQ-DI baseline score.

To address concerns, we have provided results for the scenario in which patients' HAQ-DI score reverts to the baseline assigned to the biologic-naïve population (i.e., the baseline values that the patients in the biologic-naïve population started with) after discontinuing active treatment and entering the BSC state. This analysis is only

relevant for the biologic-naïve and TNF inhibitor contraindicated populations because biologic-experienced population rebounds already to the same baseline.

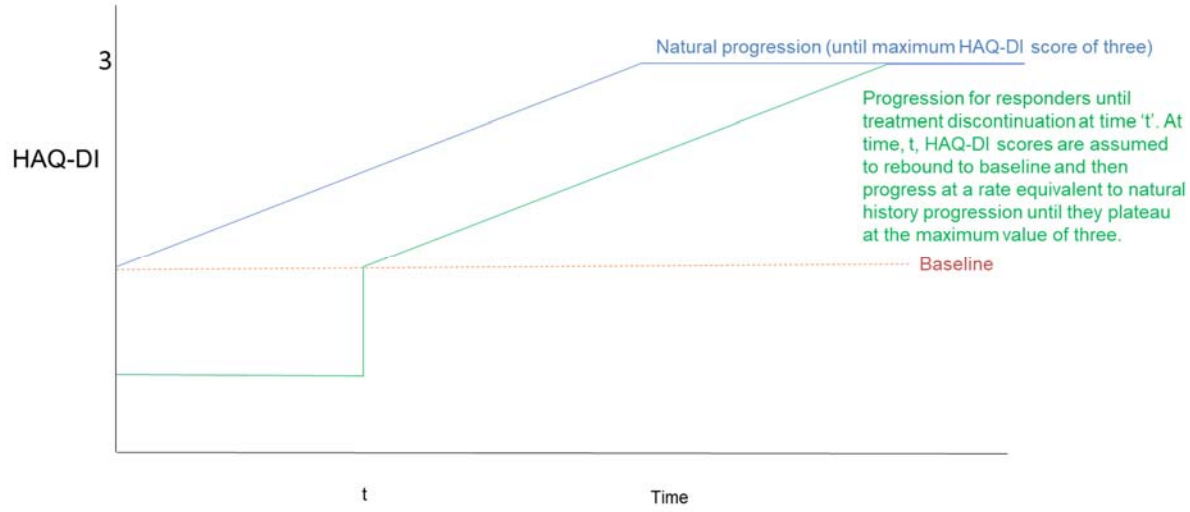
The results of this analysis are included later in this response and demonstrate a minimal impact on the ICERs; upadacitinib remains cost-effective against all comparators.

Issue 2

In relation to issue 2, the NICE clarification letter states that '*the HAQ-DI score converges with the rate of increase for non-responders, rather than progressing in parallel to that rate*'. This is indeed correct, but this reflects an issue that is common to all models based on the York model, including the recent guselkumab appraisal [TA711]. To explore this, we refer to the letter from the York group ('ID2690 upadacitinib York response to NICE query 050821 GK [noACIC]') that was referenced in the appraisal committee meeting on 12th August and subsequently provided to us.

The letter states that '*in TA711 and the previous York model, HAQ-DI score for bDMARD treatment responders is assumed to be constant and maintained throughout the duration of treatment. When patients move to final line therapy of BSC (non-responders to bDMARDs), HAQ-DI scores are assumed to rebound to baseline scores and then progress at a rate equivalent to natural history progression until they plateau at the maximum HAQ-DI value of three*'. To illustrate this, the below figure (Figure 1 from the York letter) was used, which is identical to the graph provided in our Document B. This illustrative figure is not used to calculate costs and QALYs, and it is a mere representation of the theoretical framework for economic modelling of psoriatic arthritis.

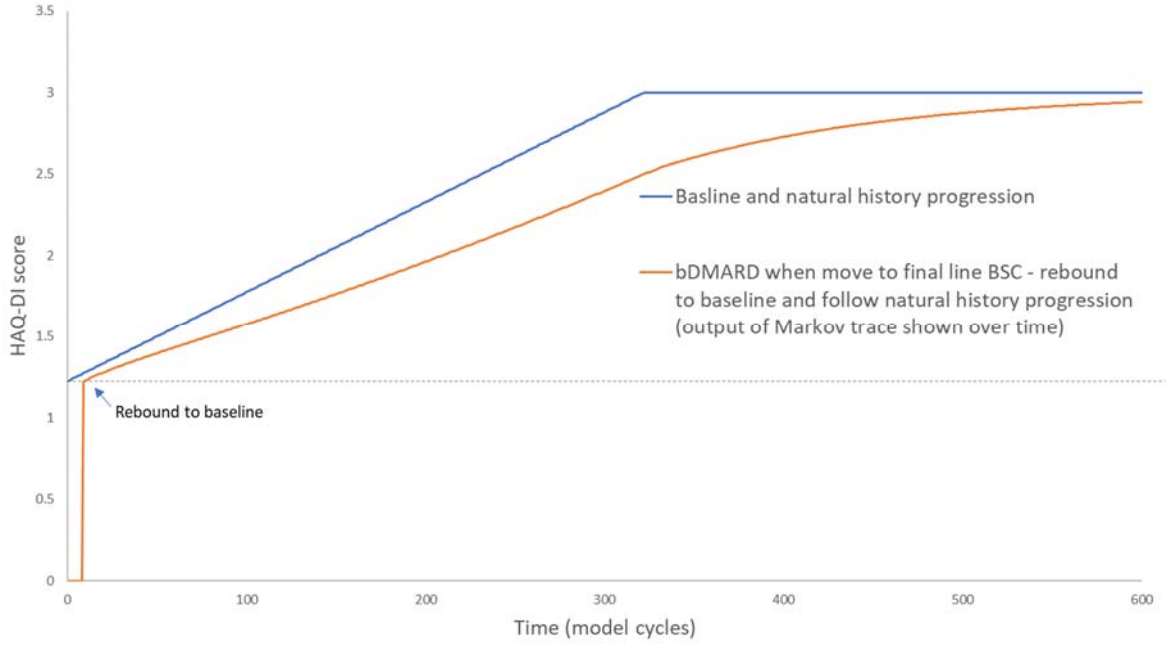
Figure 2. HAQ-DI progression from the York model and TA711, reproduced from York letter



Reproduced from letter sent to AbbVie on 20th August 2021 titled 'ID2690 upadacitinib York response to NICE query 050821 GK [noACIC]'

The York letter then goes on to provide a figure demonstrating how this translates into real HAQ-DI scores over time for the cohort of patients who initially started a bDMARD treatment and then moved to final line BSC, showing the output of the Markov trace for HAQ-DI score over time at final line therapy in TA711 (i.e., non-responders to bDMARD treatments). This is replicated in Figure 3 below (Figure 4 from the York letter).

Figure 3. HAQ-DI scores over time for cohort on final line BSC therapy in TA711, reproduced from the York letter

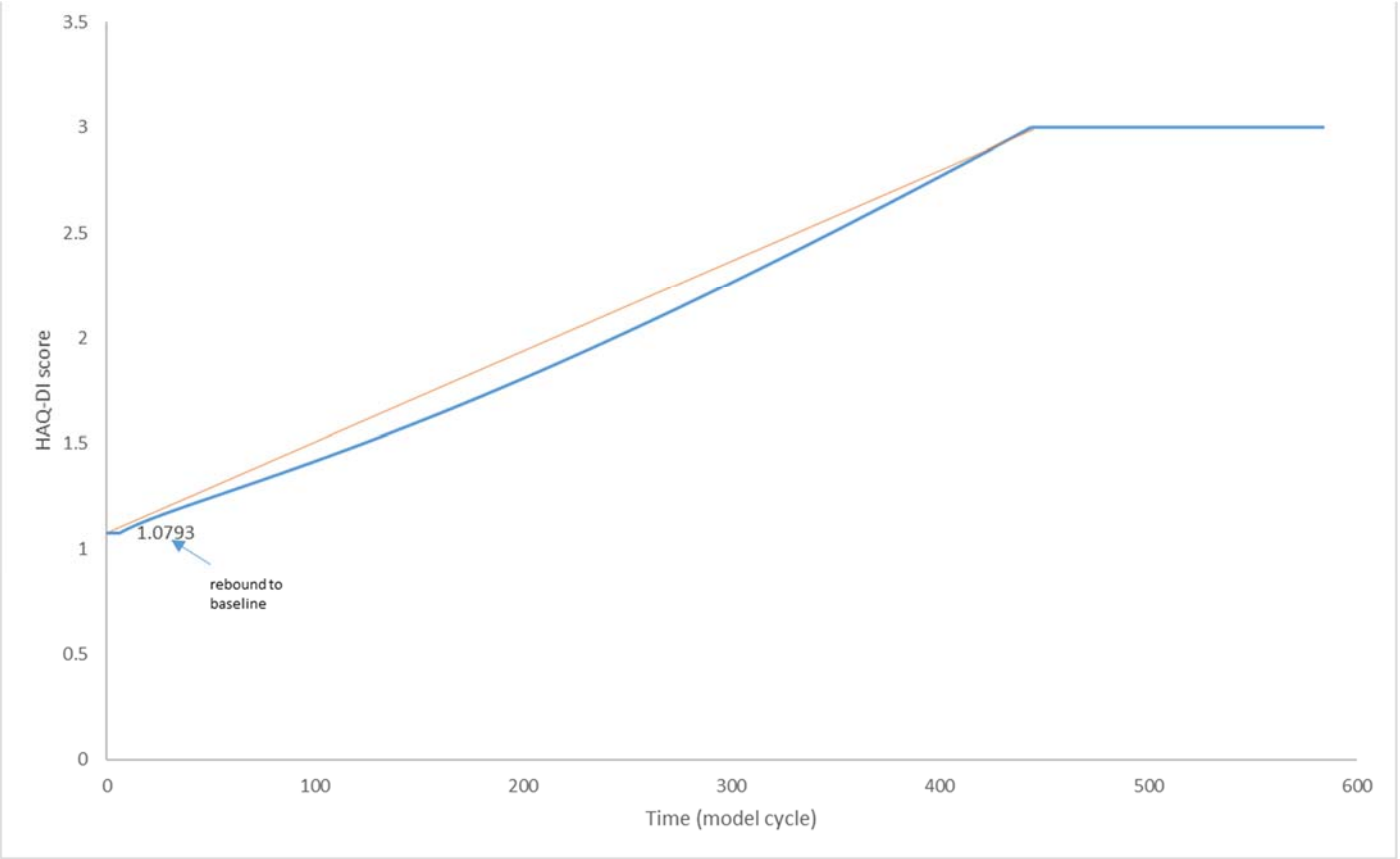


Reproduced from letter sent to AbbVie on 20th August 2021 titled 'ID2690 upadacitinib York response to NICE query 050821 GK [noACIC]'

This clearly illustrates the same issue that was raised by the ERG in our appraisal; namely, that it is not possible within a Markov framework to model HAQ-DI progression linearly even when the progression rate applied is identical (i.e., 0.072 until the maximum HAQ-DI score of 3 is reached, as reported in Rodgers et al. 2011). As stated in the York letter, this is because '*patients are entering final line therapy (BSC) at different time points in the model, i.e., the proportion of the cohort starting final line therapy is different in each model cycle. Therefore, the rebound to baseline and natural history progression occurs for different proportions of the cohort at each time point of the model.*' We have checked the guselkumab model and we have identified the column in the engines (as an example "Comp3" Excel sheet, DE column 26 row to 627, column's label is "HAQ-DI score") York is referring to, and we agree with the description stated in the York letter.

This is identical to the way in which we have modelled HAQ-DI progression. Indeed, the York letter further states that '*I suspect that the company's approach may be appropriate and consistent with previous models*'. Figure 4 below provides evidence of this trend from our Markov trace. We observe that the shape of the curve differs slightly to TA711, as this reflects the different proportion of patients entering BSC in each cycle, but clearly demonstrates the same pattern in which it converges non-linearly with the natural history progression rate to a maximum HAQ-DI score of 3.

Figure 4. HAQ-DI scores over time for cohort on final line BSC therapy - upadacitinib model



Note: the rebound baseline value is for the no psoriasis subgroup

Discontinuation rates

Finally, we wish to address a comment in the letter, which stated that 'The committee were concerned to hear that when applying a different discontinuation rate in a scenario analysis the company's ICERs did not change. The committee felt this was a 'red flag' which suggested an error in the company's model as all previous economic models for psoriatic arthritis were highly sensitive to this assumption.'

The lack of impact on the ICERs when applying different discontinuation rates is consistent with trends observed in previous psoriatic arthritis appraisals, bar TA711. In the base-case we modelled discontinuation in line with previous appraisals with an annual rate of 16.5% applied to all active treatments equally. Two scenarios were performed: 1) a rate of 13.8% for all treatments, and 2) varying the discontinuation rate applied between the biologic-naïve and biologic-experienced treatment lines, again to all treatments equally. This is consistent with the approach in in the MTA (TA445) where two scenarios for discontinuation rates were tested with the same discontinuation rate applied to all treatments equally. The results of these scenario analyses did not vary considerably from the base-case, which is consistent with the results we obtained when varying discontinuation rates in scenario analyses in the upadacitinib model.

This is in contrast with the guselkumab appraisal (TA711) that modelled treatment-specific discontinuation rates and different treatment sequences, which is an approach inconsistent with previous appraisals, leading to variations in the ICERs. The combination of these two variations in this approach could potentially explain the differences between the guselkumab model and upadacitinib model outputs.

Updated base-case results

This section presents updated results to demonstrate the impact of the assumption around the HAQ-DI rebound effect for patients discontinuing active treatment and moving to BSC.

This change is only relevant for the biologic-naïve and TNFα inhibitor-contraindicated populations. For the biologic-experienced population, the baseline HAQ-DI score used in the original submitted model was the same score assumed at model entry and on entering the BSC state (i.e., the baseline HAQ-DI score assigned to the biologic-experienced population). Therefore, only the updated results for the biologic-naïve and TNFα inhibitor-contraindicated populations are provided below.

Biologic-naïve population

The updated results for the biologic-naïve population are very similar to the original results, and do not change the interpretation of the results; from the base-case deterministic results, upadacitinib is still cost-effective against all comparators, across treatment lines, and in all psoriasis severity subgroups. This is expected because the model change is applied to all treatment arms equally.

Furthermore, as expected, the updated analysis results in slightly lower total costs and slightly higher total QALYs for each of the treatment sequences. This reflects the fact that the baseline HAQ-DI score that patients revert to when entering the BSC state is lower (better) than the baseline score used previously (i.e., the baseline value for biologic-naïve patients is better than the baseline value for biologic-experienced patients). A lower HAQ-DI score is associated with lower healthcare costs and reduced disability (improved quality of life).

We have provided below deterministic results as well as probabilistic sensitivity analysis, scenario analyses and one-way sensitivity analyses are provided in Appendix (section 3). Table 1 includes results included in the company submission, which are aligned with results shown in the ACM.

Table 1: Base case results for biologic-naïve population

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - Pairwise ICER of UPA VS comparator (£/QALY)
No psoriasis								
Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£19,889	£19,322
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£19,889	N/A	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£58,392*	£58,392*	£57,118*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£246,988*	£229,092*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£370,615*	£115,943*	£113,594*
Mild-to-moderate psoriasis								
Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£18,003	£17,980
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£18,003	N/A	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant

Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£64,640*	£64,640*	£64,577*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£275,589*	£274,601*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£271,714*	£113,004*	£112,907*
Moderate-to-severe psoriasis								
Adalimumab sequence	[redacted]	31.91	[redacted]	-	-	-	£12,887	£12,701
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£12,887	N/A	N/A
Apremilast sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£88,012*	£88,012*	£86,662*
Golimumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	£374,483*	£353,052*
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£111,114*	£98,305*	£97,333*

Key: bDMARD, biological disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; QALYs, quality-adjusted life years; UPA, upadacitinib; vs, versus.
Note: Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence.

Probabilistic sensitivity analysis

Table 2: Mean PSA base case results – biologic naïve population

Technologies	Total costs (£)	Total QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - Probabilistic pairwise ICER of UPA vs comparator (£/QALY)
Biologic-naïve; no psoriasis						
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£20,387	£19,731
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£58,538*	£56,930*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£246,340*	£223,360*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£115,269*	£112,315*
Biologic-naïve; mild-to-moderate psoriasis						
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£18,473	£18,379
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£64,496*	£64,260*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£272,508*	£267,164*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant

Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£112,295*	£111,810*
Biologic-naïve; moderate-to- severe psoriasis						
Adalimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£13,318	£13,067
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£86,665*	£84,598*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£365,104*	£336,155*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£97,395*	£95,997*

Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; TNFα, tumour necrosis factor alpha; vs, versus.

Notes: South-west ICERs are denoted by an asterisk (*) and indicate that the UPA sequence is estimated to be both less costly and less effective than the specified comparator sequence. South-west ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs the UPA sequence.

TNFα inhibitor-contraindicated population

Base case results

Compared to the original submitted model, the updated results for the TNFα inhibitor-contraindicated population are very similar and do not change the interpretation of the results; from the base-case deterministic results, upadacitinib is still associated with an ICER of below £20,000/QALY in all psoriasis severity subgroups when compared with the cheapest option, BSC.

The largest difference is observed when comparing upadacitinib against BSC. This is because in the BSC sequence, patients enter BSC straight away (before any active treatment options) and therefore in the original submitted model, these patients were still considered biologic-naïve and thus received the baseline HAQ-DI score for the biologic population. This meant that in the model update, the change to the baseline HAQ-DI score that patients reverted to on entering the BSC state only impacted the active treatment sequences.

Table 3: Base case results for people in whom TNFα inhibitors are contraindicated or not tolerated

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - Pairwise ICER of UPA VS comparator (£/QALY)
No psoriasis								
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£12,290	£16,931
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£12,290	N/A	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	£10,151,112*
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant

Mild-to-moderate psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£10,363	£10,492
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£10,363	N/A	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£6,525,710*	£6,525,710*	£6,330,422
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Moderate-to-severe psoriasis							
BSC sequence	[redacted]	31.91	[redacted]	-	-	-	£7,245	£8,809
Upadacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	£7,245	N/A	N/A
Tofacitinib sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ustekinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	31.91	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALYs, quality-adjusted life years; TNFα, tumour necrosis factor alpha; UPA, upadacitinib; vs, versus. **Note:** South-west ICERs are denoted by an asterisk (*) and indicate that the UPA sequence is estimated to be both less costly and less effective than the specified comparator sequence. South-west ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs the UPA sequence.							

Probabilistic sensitivity analysis

Table 4: Mean PSA base case results - TNFα inhibitors are contraindicated or not tolerated

Technologies	Total costs (£)	Total QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - Probabilistic pairwise ICER of UPA vs comparator (£/QALY)
TNFα inhibitor contraindicated or not tolerated; no psoriasis						
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£12,353	£17,057

Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
TNFα inhibitor contraindicated or not tolerated; mild-to-moderate psoriasis						
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£10,424	£10,496
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
TNFα inhibitor contraindicated or not tolerated; moderate-to-severe psoriasis						
BSC sequence	[redacted]	[redacted]	[redacted]	[redacted]	£7,333	£8,774
Upadacitinib sequence	[redacted]	[redacted]	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	UPA is dominant	UPA is dominant

Key: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; TNFα, tumour necrosis factor alpha; vs, versus.
Notes: South-west ICERs are denoted by an asterisk (*) and indicate that the UPA sequence is estimated to be both less costly and less effective than the specified comparator sequence. South-west ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs the UPA sequence.

Methods to implement updated base-case results

To implement the model change described in our response to Issue 1, the model Trace sheets for the biologic-naïve population ("Trace_Seq_Xbn") were updated such that the starting HAQ-DI score used when patients enter the BSC state after discontinuing active treatment was the baseline HAQ-DI score for biologic-naïve patients.

Specifically, this was done by changing the value in cell AH4 of the Trace sheets to equal the baseline HAQ-DI score for the biologic-naïve population ("base_HAQ_bn" rather than "base_HAQ_be"). This then selects the baseline HAQ-DI score from the Specifications sheet, cell H33.

It is this value in cell AH4 of the Trace sheets (now the biologic-naïve baseline HAQ-DI score rather than the biologic-experienced HAQ-DI score) that is then used in the calculations to determine the mean HAQ-DI score in the BSC state.

As described above in response to Issue 2, this mean HAQ-DI score consists of patients rebounding to baseline on initial entry into the BSC state, and patients who progress at the rate of natural history.

2. Scenario analysis to explore effect of increases in HAQ-DI while responding to treatment

In line with our technical engagement response, we maintain that a scenario in which the HAQ-DI score for active treatment responders increases over time is not appropriate in a PsA population. Clinical opinion is that increases in HAQ-DI are largely age-related and that this is only observed in patients older than 70.[1] Given that the typical PsA cohort is younger than this, age-related HAQ-DI progression is unlikely to be a significant factor. Furthermore, the assumption of no HAQ-DI progression on-treatment has been consistently applied in all recent PsA appraisals accepted by this committee; therefore, implementing such a change in this appraisal would represent an unjustified divergence from precedence.

Nonetheless, we have provided the requested scenario in which a HAQ-DI progression rate for responders who remain on treatment of 0.01 per year is applied. This is based on clinical advice, represents the maximum age-related HAQ-DI progression that would be expected in the general population. Again, we wish to highlight that given the age of the modelled cohort and the expected time patients

[1] Sokka, T., et al. (2006) Changes in Health Assessment Questionnaire Disability Scores Over Five Years in Patients with Rheumatoid Arthritis Compared With the General Population. *Arthritis & Rheumatism*, 54(10), 3113-3118.

remain on active treatment in the model, this is likely to be a substantial overestimate.

Results of the scenario analysis are provided in the next section. Please note that the scenario has been performed using the updated base-case provided in response to question 1 above for consistency. Details of how this scenario was implemented are provided in below.

Scenario analysis: effects of increasing HAQ-DI whilst responding to treatment

Results for the scenario analysis in which patients responding to treatment experience HAQ-DI progression at a rate of 0.01 per year, applied to the updated base-case analysis provided in response to question 1 above. Results are presented as discounted, pairwise comparisons of upadacitinib vs. comparator. To ease comparison, initial base case results are included in Table 7.

The results are consistent with the updated base-case, with upadacitinib remaining cost-effective against all comparators, in all treatment lines, and irrespective of psoriasis severity. Our results are also aligned to the findings in TA543 that also explored this hypothesis with minimal impact on ICERs.

Subgroup: no psoriasis

Table 5. Biologic-naive population

Incremental outcomes vs upadacitinib	Adalimumab sequence	Apremilast sequence	Certolizumab pegol sequence	Etanercept sequence	Golimumab sequence	Infliximab sequence	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£21,490	Dominant	Dominant	£61,911*	£308,542*	£122,408*	Dominant	Dominant	Dominant
ICER (£/QALY) - included in company submission	£19,322	Dominant	Dominant	£57,118*	£229,092*	£113,594*	Dominant	Dominant	Dominant

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 6. Biologic-experienced population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	£181,501*	£437,200*	£341,999*	Dominant	£13,204
ICER (£/QALY) - included in company submission	£194,345*	£416,712*	£424,592*	Dominant	£11,513

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 7. TNF alpha inhibitor contraindicated population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant	£14,305
ICER (£/QALY) - included in company submission	Dominant	£10,151,112*	Dominant	Dominant	£16,931

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Subgroup: mild-to-moderate psoriasis

Table 8. Biologic-naive population

Incremental outcomes vs upadacitinib	Adalimumab sequence	Apremilast sequence	Certolizumab pegol sequence	Etanercept sequence	Golimumab sequence	Infliximab sequence	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£19,439	Dominant	Dominant	£68,717*	£352,105*	£119,204*	Dominant	Dominant	Dominant
ICER (£/QALY) - included in company submission	£17,980	Dominant	Dominant	£64,577*	£274,601*	£112,907*	Dominant	Dominant	Dominant

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 9. Biologic-experienced population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£179,254*	£402,394*	£556,225*	Dominant	£11,217
ICER (£/QALY) - included in company submission	£191,874*	£384,703*	£788,986*	Dominant	£9,775

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 10. TNF alpha inhibitor contraindicated population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant	£12,048
ICER (£/QALY) - included in company submission	Dominant	£6,330,422	Dominant	Dominant	£10,492

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Subgroup: moderate-to-severe psoriasis

Table 11. Biologic-naive population

Incremental outcomes vs upadacitinib	Adalimumab sequence	Apremilast sequence	Certolizumab pegol sequence	Etanercept sequence	Golimumab sequence	Infliximab sequence	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£13,814	Dominant	Dominant	£94,876*	£521,767*	£103,092*	Dominant	Dominant	Dominant
ICER (£/QALY) - included in company submission	£12,701	Dominant	Dominant	£86,662*	£353,052*	£97,333*	Dominant	Dominant	Dominant

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 12. Biologic-experienced population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£166,869*	£278,104*	Dominant	Dominant	£7,033

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
ICER (£/QALY) - included in company submission	£177,669*	£269,436*	Dominant	Dominant	£6,165

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Table 13. TNF alpha inhibitor contraindicated population

Incremental outcomes vs upadacitinib	Ixekizumab sequence	Secukinumab sequence	Tofacitinib sequence	Ustekinumab sequence	BSC sequence
Incremental costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant	£8,577
ICER (£/QALY) - included in company submission	Dominant	Dominant	Dominant	Dominant	£8,809

Note: Dominant: upadacitinib dominates the comparator. Southwest ICERs are denoted by an asterisk (*) and indicate that the upadacitinib sequence is estimated to be both less costly and less effective than the specified comparator sequence. Southwest ICERs can be interpreted as the incremental costs per QALY gained for the comparator vs. the UPA sequence; therefore, higher values of a southwest ICER imply better cost-effectiveness for the upadacitinib sequence. Dominant: upadacitinib dominates the comparator.

Methods

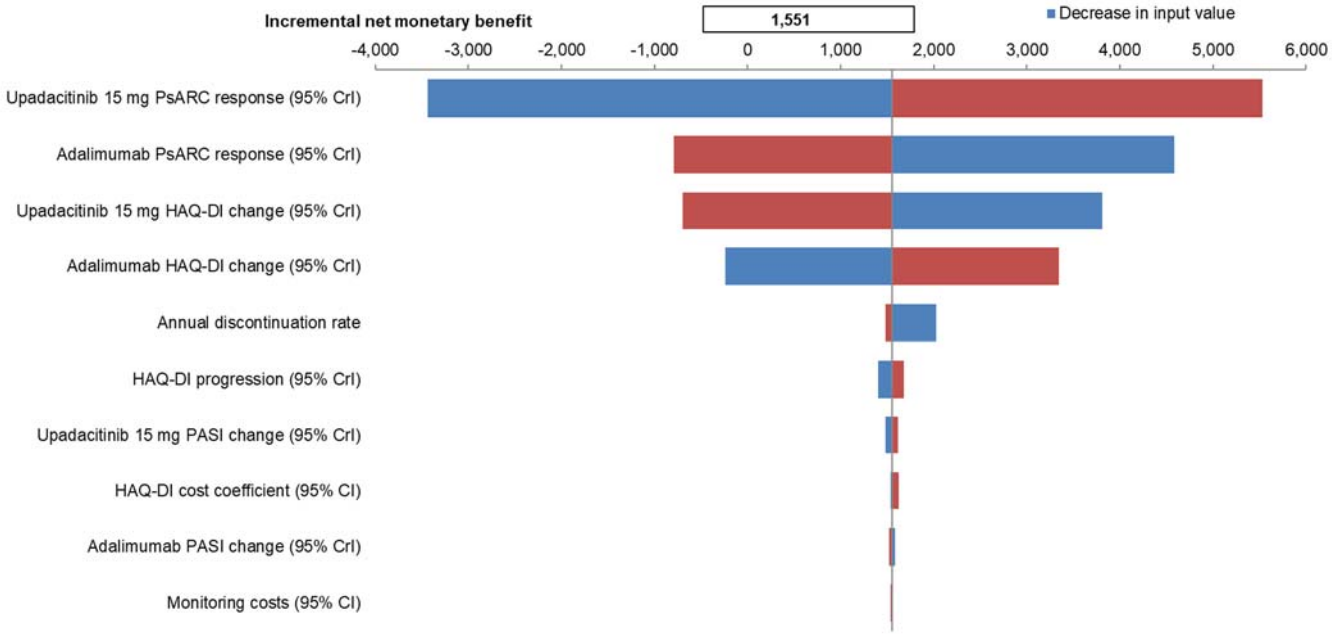
To implement this scenario, in which patients on active treatment experience HAQ-DI progression at a rate of 0.01 per year, a new column was added to the model engines. This column adds a background HAQ-DI deterioration rate during active treatment, which is used to calculate costs and QALYs during active treatment. To implement this, the HAQ-DI progression rate was broken down to a per-cycle rate of 0.00077. This results in increasing costs and decreasing QALYs during active treatment, which previously remained stable while on treatment. In the updated base-case presented above, total QALYs for upadacitinib are 8.84 in the biologic-naïve, no psoriasis population (Table 1); in this scenario total QALYs are 8.62, a reduction of 0.22 QALYs.

3. APPENDICES

APPENDIX 1: Additional analyses - Issue 1

Deterministic sensitivity analysis: biologic-naïve population with no psoriasis

Figure 1: Tornado diagrams: upadacitinib sequence versus adalimumab sequence – biologic-naïve population with no psoriasis



Key: CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Scenario analyses

Table1: Scenario analysis summary: biologic-naïve population

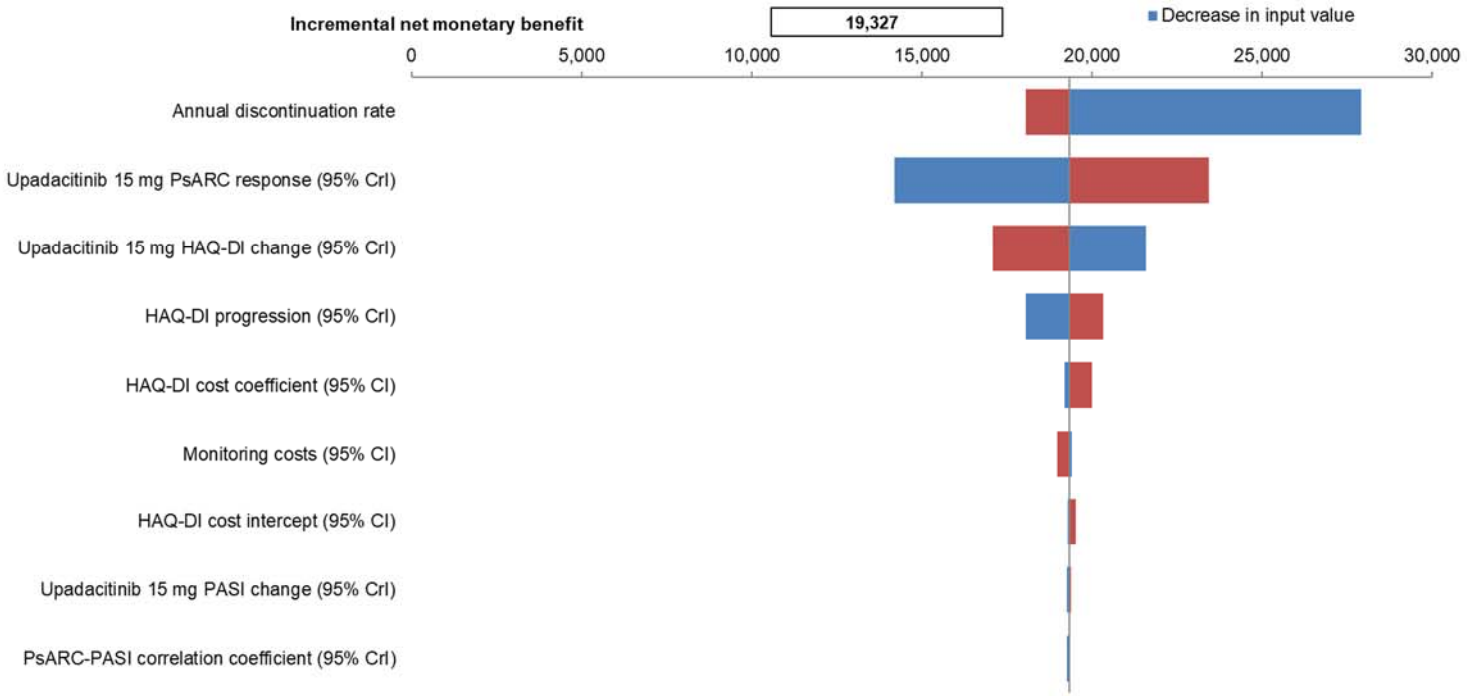
Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case
Base case	£19,889	-	£18,003	-	£12,887	-
Time horizon						
Time horizon: 5 years	£28,238	42.0%	£25,664	42.6%	£17,182	33.3%
Time horizon: 15 years	£25,795	29.7%	£23,200	28.9%	£16,060	24.6%
Annual discount rate						
Annual discount rate for costs 0%; QALYs 0%	£16,584	-16.6%	£15,109	-16.1%	£11,068	-14.1%
Annual discount rate for costs 6.0%; QALYs 6.0%	£21,736	9.3%	£19,631	9.0%	£13,866	7.6%
Model assumptions						
PsARC assessment time point: 24 weeks	£12,512	-37.1%	£11,498	-36.1%	£8,720	-32.3%
Excess mortality: SMR = 1.36	£20,209	1.6%	£18,273	1.5%	£13,050	1.3%
Adjust for perceived expectation effect	£20,843	4.8%	£18,862	4.8%	£13,445	4.3%
Treatment discontinuation						
Annual discontinuation based on Fagerli 2018	£19,858	-0.2%	£17,978	-0.1%	£12,853	-0.3%
Different treatment discontinuation rates applied for different lines of therapy	£19,936	0.2%	£18,035	0.2%	£12,912	0.2%
Trial period response assumptions						

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case
Assume no improvement of utility and disease management costs during the trial period	£20,224	1.7%	£18,345	1.9%	£13,199	2.4%
Assume immediate improvement of utility and disease management costs during the trial period	£19,565	-1.6%	£17,671	-1.8%	£12,584	-2.4%
Utility source						
Utility regression source: pooled SELECT-PsA 1 and 2	£20,281	2.0%	£18,392	2.2%	£13,252	2.8%
Utility regression source: coefficients obtained from TA445	£16,050	-19.3%	£14,716	-18.3%	£11,325	-12.1%
Cost assumptions						
Proportion of patients receiving concomitant methotrexate: 58%	£19,878	-0.1%	£17,992	-0.1%	£12,877	-0.1%
Treatment monitoring frequency source: TA445	£19,391	-2.5%	£17,511	-2.7%	£12,456	-3.3%
Proportion of patients receiving concomitant methotrexate: 0%	£19,871	-0.1%	£17,985	-0.1%	£12,871	-0.1%
Allow vial sharing for infliximab	£19,889	0.0%	£18,003	0.0%	£12,887	0.0%
Include cost of dermatologist visit for moderate-to-severe psoriasis patients	£19,889	0.0%	£18,003	0.0%	£13,236	2.7%

Key: ICER, incremental cost effectiveness ratio; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio

Deterministic sensitivity analysis: TNFα inhibitor contraindicated population with no psoriasis

Figure 2: Tornado diagrams: upadacitinib sequence versus BSC sequence – TNFα inhibitor contraindicated population with no psoriasis



Key: BSC, best supportive care; CrI, credible interval; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area Severity Index; PsARC, Modified Psoriatic Arthritis Response Criteria.

Scenario analyses

Table 2: Scenario analysis summary: TNFα inhibitor contraindicated population

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case
Base case	£12,290	-	£10,363	-	£7,245	-
Time horizon						
Time horizon: 5 years	£29,114	136.9%	£24,146	133.0%	£14,649	102.2%
Time horizon: 15 years	£17,067	38.9%	£14,193	37.0%	£9,246	27.6%
Annual discount rate						
Annual discount rate for costs 0%; QALYs 0%	£9,461	-23.0%	£8,026	-22.5%	£5,884	-18.8%
Annual discount rate for costs 6.0%; QALYs 6.0%	£14,301	16.4%	£12,024	16.0%	£8,219	13.4%
Model assumptions						
PsARC assessment time point: 24 weeks	£11,065	-10.0%	£9,218	-11.0%	£5,941	-18.0%
Excess mortality: SMR = 1.36	£12,445	1.3%	£10,483	1.2%	£7,277	0.4%
Adjust for perceived expectation effect	£13,473	9.6%	£11,370	9.7%	£8,047	11.1%
Treatment discontinuation						
Annual discontinuation based on Fagerli 2018	£11,980	-2.5%	£10,094	-2.6%	£6,815	-5.9%
Different treatment discontinuation rates applied for different lines of therapy	£12,290	0.0%	£10,363	0.0%	£7,245	0.0%
Trial period response assumptions						

Scenario	No psoriasis		Mild-to-moderate psoriasis		Moderate-to-severe psoriasis	
	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case	ICER vs adalimumab	% change from base case
Assume no improvement of utility and disease management costs during the trial period	£12,437	1.2%	£10,542	1.7%	£7,525	3.9%
Assume immediate improvement of utility and disease management costs during the trial period	£12,145	-1.2%	£10,188	-1.7%	£6,973	-3.8%
Utility source						
Utility regression source: pooled SELECT-PsA 1 and 2	£10,229	-16.8%	£8,466	-18.3%	£5,294	-26.9%
Utility regression source: coefficients obtained from TA445	£8,062	-34.4%	£6,848	-33.9%	£4,573	-36.9%
Cost assumptions						
Proportion of patients receiving concomitant methotrexate: 58%	£12,287	0.0%	£10,360	0.0%	£7,242	0.0%
Treatment monitoring frequency source: TA445	£11,071	-9.9%	£9,164	-11.6%	£5,976	-17.5%
Proportion of patients receiving concomitant methotrexate: 0%	£12,274	-0.1%	£10,347	-0.2%	£7,228	-0.2%
Allow vial sharing for infliximab	£12,290	0.0%	£10,363	0.0%	£7,245	0.0%
Include cost of dermatologist visit for moderate-to-severe psoriasis patients	£12,290	0.0%	£10,363	0.0%	£8,258	14.0%

Key: ICER, incremental cost effectiveness ratio; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality adjusted life year; SMR, standardised mortality ratio

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

ERG response to company's response to two queries raised by NICE

Query 1: HAQ-DI progression for people who have responded to a bDMARD and stopped treatment

In the original CS, the company described the progression of HAQ-DI for people who have responded to a bDMARD and stopped treatment as being a rebound to baseline followed by progression in line with natural history of non-responders. This is shown in Figure 1.

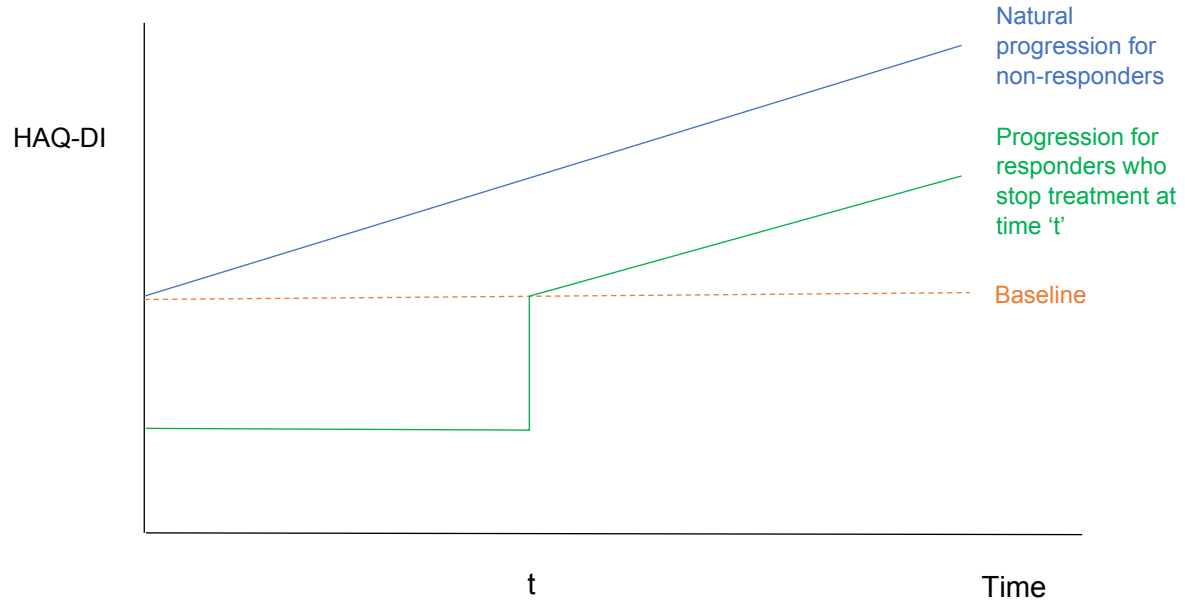


Figure 1 ERG's visual representation of company description of HAD-QI progression for responders and non-responders
Source: Original ERG report, Figure 3

In the company model, HAQ-DI for responders on progression followed a different path from the path described by the company in the CS, with a rebound on (or more accurately one cycle after) progression to somewhere above baseline HAQ-DI and then increasing tangentially to the natural progression of non-responders. This is shown in Figure 2.

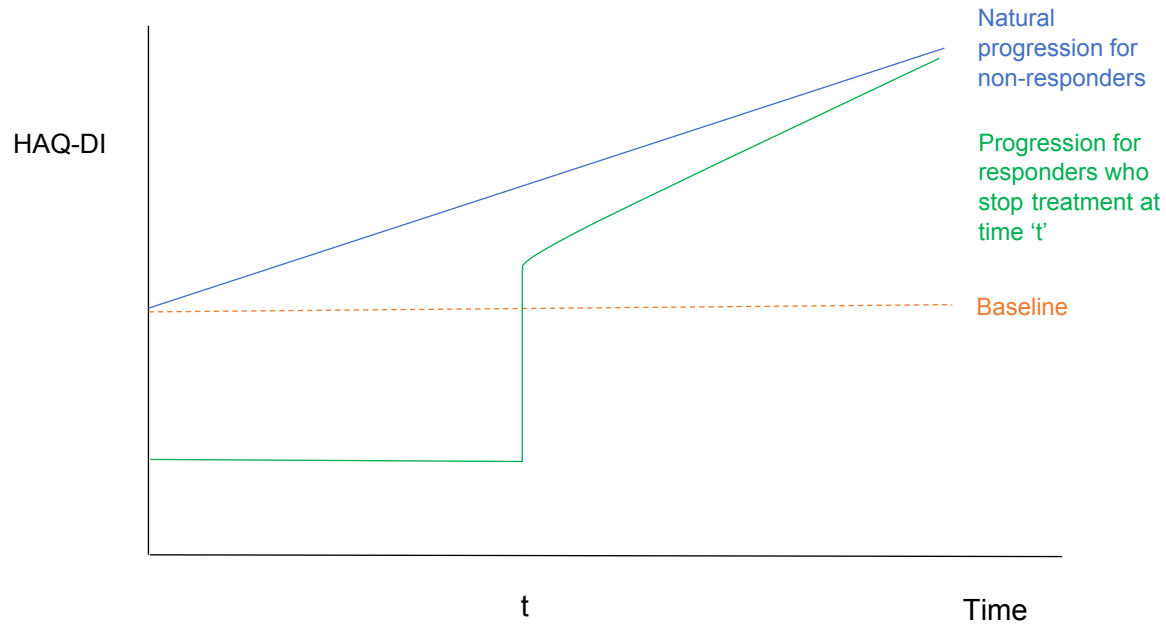


Figure 2 ERG's visual representation of company model HAD-QI progression for responders and non-responders
Source: Original ERG report, Figure 4

In their response to ACM1, the company did not address the stepped jump in HAQ-DI when (or more accurately, the cycle after) responders stop treatment, a jump that becomes larger over time. The company provided a scenario whereby biologic-experienced patients return to the baseline HAQ-DI assigned to biologic-naïve patients, but this scenario addresses an issue that was neither raised by the ERG or the Committee and does not address the rebound issue highlighted above.

The company has not tried to correct the progression of HAQ-DI over time for responders who stop treatment. The company acknowledges in their response to ACM1 that this is an error and that it is not possible in a Markov structure to model HAQ-DI progression as outlined in the CS. The company's justification for not using a model structure that could accommodate HAQ-DI progression as outlined in the CS is that they state that the way they have modelled HAQ-DI is in line with previous submissions to NICE in this disease area, and therefore these models are likely to have had the same error that is in their model. Without access to company models previously submitted to NICE, the ERG cannot comment on the accuracy of this assertion and can only reiterate that the progression of HAQ-DI in the company model does not match that described in the CS (or as described in previous submissions to NICE for active psoriatic arthritis appraisals).

Query 2: Scenario analysis to explore effect of increases in HAQ-DI while responding to treatment

The company has provided a scenario analysis exploring the impact of increasing HAQ-DI for responders. A decline in HAQ-DI of 0.01 per year for responders was included in the scenario analysis based upon clinical advice to the company as being the maximum increase in HAQ-DI that would be seen in the general population. Whilst not stated in the company response to ACM1, the company has also assumed that the baseline HAQ-DI for non-responders would also increase by an additional 0.01 per year. The ERG considers that

this is reasonable. The ERG can confirm that the scenario has been correctly implemented in the company model and whilst the scenario results in some changes to ICERs per QALY gained, the relative cost effectiveness of upadacitinib versus all comparators remains unaltered compared to the company base case results.

LRiG

20 September 2021

Sent: 22 October 2021 13:38

Dear [redacted],

I want to update you on the status of this appraisal following discussions between NICE, DSU and ERG.

Having had access to relevant economic models, the ERG and York (via DSU) have confirmed the implementation in Abbvie's upadacitinib is not in line with the most recent appraisal of guselkumab or the York MTA. Both the ERG and York agree on this point.

York have helpfully provided the following explanation:
"The reason is that the upadacitinib model is not keeping track of the timing of when patients move to last-line BSC in order to follow the appropriate rebound trajectory (and corresponding HAQ scores), as noted previously and discussed on our call.
The guselkumab model implemented this correctly through efficient use of the SUMPRODUCT and OFFSET function in Excel. I have tried to illustrate this in the attached excel worksheet."

York suggests that this should be implementable given the example in the attached spreadsheet (attached).

The DSU have indicated that they currently do not have capacity to work on this topic, and likely only available to work on it in several months. Therefore, in the interest of time, NICE's requests that Abbvie implement the changes and submit this to NICE for review. **I would be grateful for a preliminary view of the when you think the company would be able to provide an updated model, and key ICERs.**

Following this, we expect that the ERG will be needed to review this work. The timelines will be confirmed once we understand how long Abbvie want to consider this.

I hope we can discuss this further in our meeting next week.

Kind regards,
[redacted]

[redacted]
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza | Manchester M1 4BT | United Kingdom
Tel [redacted]
Web: http://nice.org.uk

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Updated model results per DSU request 25th October 2021

Dear [redacted],

Please see below, and the associated model, for the updated model results incorporating the DSU's technique for tracking the timing of when patients move to last-line BSC, in order to follow the appropriate rebound trajectory and HAQ scores. We hope that this resolves the issue, but we'd be very happy to discuss our implementation of the methods with yourself and the ERG/DSU if necessary.

Best wishes,

[redacted], Senior HTA Manager

[redacted], Senior HE Manager

Updated base-case results

This section presents updated results to demonstrate the impact of using the method detailed by the Decision Support Unit to track the timing of when patients move to last-line BSC, in order to follow the appropriate rebound trajectory (and corresponding HAQ scores). The methods applied to implement these changes may be observed in the engine sheets of the model ('Trace_Seq_1bn', 'Trace_Seq_2bn'… 'Trace_Seq_BSCbe') in column AI. The results presented herein are based on an update to the original submitted model, as discussed at the first appraisal committee meeting on 12th August 2021.

Fully incremental and pairwise comparisons are presented for the biologic-naïve, biologic-experienced, and TNF-alpha inhibitor contraindicated populations. As per the ERG report, the results for the TNF-alpha inhibitor contraindicated population have been updated to include two lines of treatment with ustekinumab as the 2nd line treatment option.

The updated results are very similar to the original results, and do not change the interpretation of the results; from the base-case deterministic results, upadacitinib is still cost-effective against all comparators, across treatment lines, and in all psoriasis severity subgroups.

Biologic-naïve population

Table 1: Updated results for biologic-naïve population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
Adalimumab sequence	[redacted]	[redacted]	-	-	-	£19,404	£19,322
Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£19,404	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£57,448*	£57,448*	£57,118*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£233,607*	£229,092*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£366,921*	£114,227*	£113,594*
Mild-to-moderate psoriasis							
Adalimumab sequence	[redacted]	[redacted]	-	-	-	£18,060	£17,980
Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£18,060	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant

Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£64,976*	£64,976*	£64,577*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£280,988*	£274,601*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£272,678*	£113,542*	£112,907*
Moderate-to-severe psoriasis							
Adalimumab sequence	[redacted]	[redacted]	-	-	-	£12,742	£12,701
Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£12,742	N/A	N/A
Apremilast sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Certolizumab pegol sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Etanercept sequence	[redacted]	[redacted]	[redacted]	[redacted]	£87,278*	£87,278*	£86,662*
Golimumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£362,780*	£353,052*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Infliximab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£110,984*	£97,800*	£97,333*

*ICER per QALY gained is in the South West quadrant. An ICER per QALY gained in the South West quadrant should be interpreted in the opposite way to the North East quadrant i.e., higher ICERs per QALY gained mean treatments are more cost effective.

Biologic-experienced population

Table 2: Updated results for biologic-experienced population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
BSC sequence	[redacted]	[redacted]	-	-	-	£10,999	£16,931
Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£10,999	N/A	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£435,050*	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£195,835*	£195,835*	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£415,274*	£10,151,112*
Mild-to-moderate psoriasis							
BSC sequence	[redacted]	[redacted]	-	-	-	£9,342	£10,492
Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£9,342	N/A	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£822,320*	£6,330,422*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£193,295*	£193,295*	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£383,499*	UPA is dominant
Moderate-to-severe psoriasis							
BSC sequence	[redacted]	[redacted]	-	-	-	£5,858	£8,809

Upadacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	£5,858	N/A	N/A
Ustekinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	£179,174*	£179,174*	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£268,662*	UPA is dominant

*ICER per QALY gained is in the South West quadrant. An ICER per QALY gained in the South West quadrant should be interpreted in the opposite way to the North East quadrant i.e., higher ICERs per QALY gained mean treatments are more cost effective.

TNFα inhibitor-contraindicated population (updated as per ERG scenario)

Table 3: Updated results for people in whom TNFα inhibitors are contraindicated or not tolerated (ERG scenario)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER fully incremental (£/QALY)	Pairwise ICER of UPA vs comparator (£/QALY)	Included in company submission - pairwise ICER of UPA vs comparator (£/QALY)
No psoriasis							
Upadacitinib sequence	[redacted]	[redacted]	-	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	£10,151,112*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Mild-to-moderate psoriasis							
Upadacitinib sequence	[redacted]	[redacted]	-	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	£6,330,422*
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Moderate-to-severe psoriasis							
Upadacitinib sequence	[redacted]	[redacted]	-	-	-	N/A	N/A
Tofacitinib sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Ixekizumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant
Secukinumab sequence	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	UPA is dominant	UPA is dominant

*ICER per QALY gained is in the South West quadrant. An ICER per QALY gained in the South West quadrant should be interpreted in the opposite way to the North East quadrant i.e., higher ICERs per QALY gained mean treatments are more cost effective.

ERG STA REPORT ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID2690]

Addendum

This report was commissioned by the NIHR HTA Programme as project number NIHR 133071

Completed 5th November 2021

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

As part of the NICE STA process to consider the clinical and cost effectiveness of upadacitinib for treating active psoriatic arthritis after inadequate response to disease-modifying anti-rheumatic drugs, the company (AbbVie) developed an economic model using Microsoft Excel.

The cost effectiveness results presented in Confidential Appendix 5 were generated using the company model dated 25/10/21. The ERG considers that this model may not generate results that are identical to the results that would be generated if the model had been constructed using tunnel states. However, the ERG also considers that the methods now used by the company to model HAQ-DI progression in the BSC state are consistent with the model described in the geselkumab submission (TA711).